Second amended Annual Work Plan and Budget for 2017

In accordance with Article 16 of the Statutes of the IMI2 JU annexed to Council Regulation (EU) No 557/2014 of 6 May 2014 and with Article 31 of the Financial Rules of the IMI2 JU.

The second amended Annual Work Plan will be made publicly available after its adoption by the IMI2 JU Governing Board.

Annex 1 to the Decision of the IMI2 JU Governing Board No. IMI2-GB-DEC-2017-25 adopted on 28.11.2017

Document reference: IMI2/INT/2017-02428

Contents

Chronology and list of reviews

Versions		Date of Governing Board approval	Items
Annual Work Plan and Budget for 2017	Version 1.0	23.12.2016	Annual Work Plan and Budget for 2017
First amended Annual Work Plan and Budget for 2017 (replacing previous version)	Version 2.0	n/a	IMI2 States Representatives Group and Scientific Committee consultation carried out from 22 February 2017 to 13 March 2017 Update of the following sections: ▪ 2.2.2 Scientific priorities for 2017 ▪ 2.2.6 Stakeholders' engagement and external collaborations ▪ 2.3 Call management rules ▪ 2.4.1 Communications and events ▪ 2.4.2 Procurement and contracts ▪ 2.4.5 Administrative budget and finance ▪ 3 Budget 2017 Insertion of Annexes I and II
	Version 3.0	Approved on 11 July 2017	IMI2 States Representatives Group and Scientific Committee consultation carried out from 12 May 2017 to 07 June 2017 Update of the following sections: ▪ 2.2.2 Scientific priorities for 2017 ▪ 2.3 Call management rules ▪ 2.4.2 Procurement and contracts **Insertion of new topics in Annex II**
Second amended Annual Work Plan and Budget for 2017 (replacing previous version)	Version 4.0		IMI2 States Representatives Group and Scientific Committee consultation carried out from 25 September to 16 October 2017 Update of the following sections: ▪ 2.2.2 Scientific priorities for 2017, including Calls for proposals and related budget ▪ 2.2.8 Socio-economic impact study ▪ 2.3 Call management rules ▪ 2.4.1 Communications and events – Table of events **3. Budget 2017** **Annex III**

1 Introduction

Most countries in the world are facing the same immense challenge: How to bring the latest scientific and technological advances that are generated in our excellent research-intensive institutions to application in healthcare delivery systems, in a time efficient and cost-effective manner. By fostering collaboration between the public and private sectors and proactively engaging the most relevant stakeholders, the Innovative Medicines Initiative 2 Joint Undertaking (IMI2 JU) represents a neutral platform for debates to occur and for real innovations to be developed and implemented so that citizens can benefit from the latest health-related innovations. The IMI2 JU represents a unique collaboration model that is emerging as a world class reference of its kind.

In 2017, we will continue to engage with Associated Partners from other industry sectors (e.g. ICT, imaging, medical technology, etc.) and philanthropic organisations and other public funders to invite these players to invest with us on specific projects. We will engage more with small and medium-sized enterprises (SMEs) that are key to the future of a dynamic and thriving health innovation system in Europe. We will also reinforce collaboration with patient groups, regulators and those who pay for healthcare with a view to demonstrating the value that innovation brings.

Within the framework of the Strategic Research Agenda (SRA), we will further develop our existing programme portfolio in areas such as diabetes, infection control, immunology and neurodegeneration, and explore new areas such as advanced therapies, oncology and areas embracing the “one health” concept. We will also continue to develop our “Big Data for Better Outcomes” strategy across all disease areas.

The year 2017 will also mark the completion of the interim evaluation of IMI2 JU. In this context, particular attention will be given to monitoring the impact and added value of IMI’s completed and ongoing projects.

The IMI2 JU will continue to ensure the delivery of high-quality work according to strict ethical standards, under the principle of sound financial management and with appropriate and balanced levels of controls. The organisation of the Programme Office will be reviewed towards more efficiency and cost effectiveness, in a spirit of continuous improvement.

Pierre Meulien

Executive Director

2 Annual Work Plan Year 2017

2.1 Executive Summary

The main goals of f IMI2 JU in 2017 can be set out as follows:

- Launching two new Calls for proposals based on scientific priorities set out in section 2.2.2
- Successfully manage a growing portfolio of projects, under both the Seventh Framework Programme for Research (FP7) and Horizon 2020 (H2020).
- Expand the basis of external collaborations and partnerships to best meet the challenges of the biopharmaceutical environment and optimise the innovation framework
- Implement an ambitious communication strategy to demonstrate, in a spirit of openness and transparency, the added value of the partnership to EU citizens. The results of the socio-economic impact study on completed IMI1 projects will also contribute to meeting this objective.
- Contribute to the interim evaluation of IMI2 JU due to be completed by 30 June 2017, with conclusions and observations reported by the Commission to the European Parliament and to the Council by 31 December 2017.
- Improve and upgrade various aspects of our operating systems, including implementation of the Call management process under Horizon 2020, effective transition to the Horizon 2020 IT tools, review of the risk assessment and internal control framework, and reorganisation of IMI Programme Office towards enhanced efficiency and cost effectiveness.
- Carry out and implement audits and controls over beneficiaries that receive of IMI funding and companies' in kind contributions.

2.2 Operations

2.2.1 Objectives & indicators - risks & mitigations

The key objectives for IMI2 JU operations in 2017 are based on the overall objectives of IMI2 JU as set out in Article 2 of Regulation No 554/2014, and therefore IMI 2 JU operational activity will ensure a smooth and efficient implementation of its objectives.

Key objectives are as follows:

- Efficient management of Calls for proposals, including preparation, evaluation and grant award processes
- Close monitoring of ongoing projects' achievements, in particular the efficient use of resources and the quality of scientific outputs, as well as contributing to the analysis and dissemination of results and outputs
- Reaching out to new stakeholders towards broadening the network of collaboration in the healthcare family
- Optimal use of the internal resources of IMI2 JU Programme Office, supported by efficient IT systems

Key performance indicators (KPIs)

IMI2 JU assesses its performance on the basis of the KPI framework adopted by the Governing Board, notably in accordance with Art. 3(3) (a) of the IMI2 JU Council Regulation. This framework is currently under review. A revised version will be introduced via the first amendment to the Annual Work Plan 2018.

Key Strategic Focus	Annual Objectives 2017	Link to the Council Regulations setting up IMI JU & IMI2 JU		Selected Key Performance Indicator (KPI)	Method	2017 Target
		73/2008 of 20.12.2007[1]	557/2014 of 6.05.2014[2]			
Portfolio	IMI2 JU's new calls for proposals support the implementation of the research priorities as set out in the Strategic Research Agenda and updated by the Governing Board	▪ Article 2(a) and 2(b) ▪ Article 1(c) in Statutes of IMI JU	▪ Article 2(a) ▪ Article 1(b) in Statutes of IMI2 JU	**KPI 1:** Target number of priority areas defined in IMI2 JU's Annual Scientific Priorities for 2017 that are addressed by IMI's calls for proposals launched in 2017	Extent of coverage of priority areas for 2017 as defined in Section 2.2.2	**KPI 1:** ≥4 priority areas from IMI2 JU's Annual Scientific Priorities for 2017
Scientific Output	IMI projects effectively deliver and disseminate high quality outputs	▪ Article 2(a) and 2(b)	▪ Article 2(a) and 2(b)	**KPI 2:** Target estimated percentage of IMI projects that are assessed by the Programme Office as having achieved at least 90% of pre-set deliverables by the last reviewed reporting period by the end of the year	Progress for each project is assessed by the responsible IMI Scientific Officers, on the basis of cumulative achievements reported from the project start date up to the last reviewed reporting period by the end of the year	**KPI 2:** ≥80% of IMI2 JU projects
				KPI 3: Target estimated average number of IMI publications[3] per EUR10 million of total IMI funding requested by the projects **KPI 4:** Target to measure extent to which IMI's average impact factor of journals in which IMI publications[5] have been published is higher than the EU average	The main source of information is the independent bibliometric analysis and results as last compiled and reported to the Programme Office by an external contractor, applying internationally recognised standards and criteria. Latest available information from IT systems will be used for the calculation of the estimated requested IMI2 JU funding by the end of the year under review.	**KPI 3:** ≥20 publications **KPI 4:** ≥10% higher than EU average

[1] OJ L 30 of 4.2.2008
[2] OJ L159 of 7.6.2014
[3] Covering all publications resulting from IMI projects from the start of IMI JU up the end of the year under review.

Key Strategic Focus	Annual Objectives 2017	Link to the Council Regulations setting up IMI JU & IMI2 JU		Selected Key Performance Indicator (KPI)	Method	2017 Target
		73/2008 of 20.12.2007[1]	557/2014 of 6.05.2014[2]			
				KPI 5: Target to measure extent to which the citation impact of IMI publications[5] is higher than the EU average **KPI 6**: Target to measure the extent to which IMIs bibliometric indicators compare with those of other international funding bodies. Target to compare the citation impact of IMI publications[5] with the one of other international funding bodies (**KPI 6.1**), Target to compare the percentage of highly cited papers of IMI programme with the one of other international funding bodies[4] (**KPI 6.2**)	The benchmarking analysis with other international funding bodies to be performed by external contractor, applying internationally recognised standards and criteria	**KPI 5:** ≥20% higher than EU average **KPI 6.1:** ≥15% higher than the average of sampled institutions **KPI 6.2** ≥5% higher than the average of sampled institutions
Impact on regulatory framework and standardization	IMI projects translate key scientific discoveries into clinical practice and regulatory framework	▪ Article 2 ▪ Article 1(e) in Statutes of IMI JU	▪ Article 2 ▪ Article 1(b) in Statutes of IMI2 JU	**KPI 7:** Target to measure the number of scientific advice and qualified opinions initiated by the IMI projects at the EMA and FDA **KPI 8:** Target to measure the number of regulatory guidelines derived from IMI projects **KPI 9:** Target to measure new standards and best practices derived from IMI projects	The main source of information is the annual periodic reporting, as well as close follows up of the project by the respective Scientific Officers through attendance of the project annual meetings, and other exchanges Each Scientific Officer will report annually during the preparation of the Annual Activity Report If necessary, additional complementary information may also be collected as part of an annual survey of the consortia	**KPI 7:** ≥ 5 **KPI 8:** Baseline data will be collected in 2017 **KPI 9:** Baseline data will be collected in 2017

[4] Publications that belong to the world's top decile of papers for journal category and year of publication.

Key Strategic Focus	Annual Objectives 2017	Link to the Council Regulations setting up IMI JU & IMI2 JU		Selected Key Performance Indicator (KPI)	Method	2017 Target
		73/2008 of 20.12.2007[1]	557/2014 of 6.05.2014[2]			
					For KPI 8 and KPI 9, the methodology for capturing information and the baseline data for establishing the targets will be determined and compiled in 2017.	
Business development and sustainability	IMI projects increase EU competitiveness and foster innovation	▪ Article 2	▪ Article 2	**KPI 10:** Target to measure, on average, the number of patent applications filed and/or awarded to those IMI projects which have been reimbursed at least for the third year of implementation[5] **KPI 11:** Target to measure impact on EU competitiveness **KPI 12:** Target to measure the number of spin-off companies or foundations created as a result of IMI projects **KPI 13:** Target to measure the estimated number of reported Full-Time Equivalents (FTEs) based in the EU that can be considered as directly related to the IMI programme	The main source of information is the annual periodic reporting, as well as close follows up of the project by the respective Scientific Officers through attendance of the project annual meetings, and other exchanges. Each Scientific Officer will report annually during the preparation of the Annual Activity Report If necessary additional complementary information may also be collected as part of an annual survey of the consortia For KPI 11, the methodology for capturing this information from industry and other sources and the baseline data for establishing the target will be determined and compiled in 2017 The estimated total number of FTEs reported by the projects as being directly related to the IMI programme will be reported for KPI 13. The data will be collected directly from the consortia through SOFIA or via an annual survey	**KPI 10:** ≥2 patent applications per EUR 10 million of costs accepted and reimbursed by IMI JU. [6] **KPI 11:** Baseline data will be collected in 2017 **KPI 12:** 25% of finalised projects **KPI 13: ≥ 1500**

[5] During 2017, initial baseline data will continue to be collected and analysed on the number of patents resulting from IMI JU projects, particularly on the first finalised projects.

[6] The calculation will be based on the total value of interim and final payments made by IMI by the end of the year under review to projects that have completed at least the third year of implementation and the total amount will be divided by the cumulative number of patents filed and/or awarded to these projects.

Key Strategic Focus	Annual Objectives 2017	Link to the Council Regulations setting up IMI JU & IMI2 JU		Selected Key Performance Indicator (KPI)	Method	2017 Target
		73/2008 of 20.12.2007[1]	557/2014 of 6.05.2014[2]			
SME participation	IMI2 JU projects promote the participation of SMEs	▪ Article 2(e)	▪ Article 2(a) ▪ Article 1(c) in Statutes of IMI2 JU	**KPI 14:** Target percentage of participants in signed Grant Agreements that are SMEs **KPI 15:** Target percentage of overall budget for projects that has been allocated to SMEs	Calculation is based on the latest available data extracted from IMI IT applications. Participations in IMI projects may count the same organisation multiple times when the same organisation is involved in several projects in line with current practice All participations from the start of IMI up the end of the year under review are considered in this calculation	**KPI 14:** ≥20% **KPI 15:** ≥20%
Patient participation	IMI2 JU projects promote the involvement of patient organisations	▪ Article 2	▪ Article 2(a) ▪ Article 1(c) in Statutes of IMI2 JU	**KPI 16:** Target percentage of projects involving patients' organisations as consortium partners, members of Advisory Boards, Ethical Advisory Boards or on consultancy basis for topics of relevance as identified in the Call text **KPI 17**: Target to measure impact for patients	Calculation is based on the latest available data extracted from IMI IT applications for the project partners Participations in IMI projects may count the same organisation multiple times when the same organisation is involved in several project in line with current practice If necessary, additional complementary information may also be collected as part of an annual survey of the consortia. For KPI 17**,** the methodology for capturing this information and baseline data for establishing the target will be determined in coordination with the European Commission in Q1 2017	**KPI 16:** 100% **KPI 17:** Baseline data will be collected in Q1 2017
Impact on society	IMI2 JU projects address the unmet healthcare needs, e.g. chronic, emerging or diseases lacking effective treatment	▪ Article 2	▪ Article 2	**KPI 18:** Target to measure additional impact on society	For KPI 18, the evaluation methodology development is in progress and the baseline data for establishing the target will be determined in 2017.	**KPI 18:** Baseline data will be collected in 2017

Key Strategic Focus	Annual Objectives 2017	Link to the Council Regulations setting up IMI JU & IMI2 JU		Selected Key Performance Indicator (KPI)	Method	2017 Target
		73/2008 of 20.12.2007[1]	557/2014 of 6.05.2014[2]			
Information, communication and dissemination	The Programme Office raises the awareness of IMI JU and IMI2 JU among all target groups	▪ Article 1(g) in Statutes of IMI JU	▪ Article 1(i) in Statutes of IMI2 JU	**KPI 19:** Target number of average monthly visitors to the IMI2 JU website **KPI 20:** Target to measure the performance of communication activities	Average number of monthly unique visitors as reported by Google Analytics for the year under review For KPI 20, the methodology for capturing the information and the baseline data for establishing the target will be determined in 2017	**KPI 19:** ≥10 000 **KPI 20:** Baseline data will be collected in 2017 and used to determine the appropriate target
Efficiency of the Programme Office	The Programme Office meets the timeframe for Time to Grant (TTG) established by the EU for Horizon 2020	▪ N/A	▪ Article 17	**KPI 21:** Target timeframe for TTG of 245 days	Comply with the timeframe set out in the Horizon 2020 Rules for Participation (Article 20.2 in Regulation (EU) No 1290/2013) Average Time to Grant (TTG) for a two stage evaluation is defined as the time between the deadline for the submission of a Full Project Proposal and the signature of the grant agreement. This will be calculated annually for each grant agreement signed during the year under review	**KPI 21:** ≤245 days
	The Programme Office achieves high levels of performance in its annual budget execution	▪ Article 1(l) in Statutes of IMI2 JU	▪ Article 1(f) in Statutes of IMI2 JU	**KPI 22:** Annual budget execution target for commitment appropriations of running costs **KPI 23:** Annual budget execution target for commitment appropriations of operational costs **KPI 24:** Annual budget execution target for payment appropriations of operational costs	Extracted from annual figures compiled for IMI JU report on the budgetary and financial management	**KPI 22:** ≥95% **KPI 23:** ≥95% **KPI 24:** ≥95%

Key Strategic Focus	Annual Objectives 2017	Link to the Council Regulations setting up IMI JU & IMI2 JU		Selected Key Performance Indicator (KPI)	Method	2017 Target
		73/2008 of 20.12.2007[1]	557/2014 of 6.05.2014[2]			
	The Programme Office meets the maximum time limits for expenditure operations established by the EU	▪ Article 1(l) in Statutes of IMI2 JU	Article 1(f) in Statutes of IMI2 JU	**KPI 25:** Annual Average Time to Pay (TTP) target for pre-financing payments to beneficiaries **KPI 26:** Annual Average TTP target for interim payments to beneficiaries	Comply with time limits as established in the EU's Financial Regulation (Article 92 in Regulation (EU, EURATOM) No 966/2012) and Article 32 of the IMI Financial Rules	**KPI 25:** ≤30 days **KPI 26:** ≤90 days

Risks & mitigations

Risks are a strategic element of planning activities as their identification enables management to customise their objectives and corresponding actions. This section gives an overview of the corporate risks identified by the Programme Office against the overall objectives of IMI2 JU as set out in Article 2 of Regulation No 554/2014 and the above key objectives for 2017.

These conclusions are based on the outcomes of the **annual risk assessment exercise** 2016-2017 performed by the Internal Control and Risk Manager for IMI2 JU management as a proactive process – adjuvant to the definition of the annual work plan. The goal of the annual risk assessment exercise is to identify and assess events that could pose a threat to the achievement of its objectives and determining how the corresponding risks should be managed.

This exercise has identified a number of possible operational and financial risks that can affect (i) the strategies employed by management to implement corporate policies or (ii) internal administrative processes, IT systems, resources and financial management. Risks are mapped through a risk register which provides information on their nature and the required mitigating actions.

At an operational level each functional area produces and manages an **operating risk register** (ORR) with the risks that they might face when implementing the Annual Work Plan.

At corporate level, management makes an assessment of the major cross-sectional risk factors identified at operational level and merges them with the strategic risks that may challenge the achievement of IMI2 JU objectives. These risks are included in the **strategic risk register** (SRR), directly managed at senior level and complemented by an appropriate risk mitigation plan.

Both registers are monitored by the Programme Office to effectively anticipate and mitigate the risks, ensuring that the work plan remains up to date and effective.

The overall assessment of the exercise 2016-2017 shows that some threats tend to persist within the JU. This is because certain risk factors are correlated with the specific objectives of IMI as public-private partnership established to support activities that carry a high level of uncertainty such as the development and implementation of pre-competitive research and innovation in the pharmaceutical sector, mobilising resources and bringing together dissimilar stakeholders such industry, academia, SMEs, patient organisations and regulators.

At the corporate level, in particular, some risks are typically associated with IMI2 JU's mission and strategic objectives and have therefore to be accepted as such and addressed in a way that allow the JU to reduce or partially transfer their impact where needed.

This is the case of the risks that a project fails to achieve all or part of the research objectives envisaged or lacks the capacity to exploit the results and assets generated.

Similarly, IMI2 JU has to cope with the risk that the programme ends with an imbalance between members' contributions and/or unsatisfactory leverage of private contributions.

Operational risks escalated at corporate level mainly consist of specific threats to the internal processes that may affect the IMI2 JU's effectiveness if not appropriately controlled. In this view, finalising the reorganisation of the Programme Office and providing the necessary human and technical resources will be decisive for reinforcing IMI2 JU's performance.

Among the 12 risks identified at corporate level at the end of the exercise 2016-2017, the following four can be considered as critical and are reported hereafter in line with the requirement of the IMI2 JU Internal Control Standard 6 on risk management:

1. Potential negative external perception of IMI2 JU added value and recurrent criticism might undermine the PPP model

In the context of the H2020 JUs mid-term review process and the path towards the next Framework Programme, IMI2 JU will be exposed to a higher degree of scrutiny from all stakeholders. A potential negative external perception of IMI's added value/impact could undermine the continuity of the PPP model after 2020.

2. Risk of imbalance between the contributions committed by Founding Members at the end of the program

IMI2 JU is a partnership based on the principle that pharmaceutical research is equally funded by EFPIA companies and the EU. This strategic objective might be undermined in case of imbalance between EU funding and industry in-kind contribution and weak participation at the end of the program. A mitigation plan has been part forward with the aim at ensuring optimal industry commitment.

3. The planned leverage of private resources (beyond EFPIA) committed to IMI2 JU might be challenging to achieve.

The PPP model developed by H2020 as a tool for increasing research investment in the biopharmaceutical sector may be challenged in case of limited leverage of private resources committed by Associated Partners, and insufficient external collaboration and partnerships. However, as also indicated in the SWOT analysis agreed by the Governing Board this risk is also an opportunity for the JU and should be tackled by promoting IMI's project achievement and increasing its visibility at international level.

4. Risk of delays and ineffective management of the ex-ante control process and operational expenditure

There is an increasing risk of ineffective performance of the ex-ante controls of cost claims due to the increasing backlog in the treatment of periodic and final reports for IMI1 and IMI2 JU projects, the limited resources available in the IMI2 JU financial team.
These circumstances may generate a significant delay of payments with consequently insufficient budget execution and finally, potential business discontinuity of financial processes undermining the internal effectiveness and the reputation gained by the IMI2 JU.

In this context the Governing Board and the IMI2 JU Programme Office have taken a number of actions and measures to mitigate and manage any possible negative effect. These include the implementation of an ambitious communication strategy to demonstrate, in a spirit of openness and transparency, the added value of the partnership to EU citizens. At the same time, opportunities to enhance international cooperation, with targeted actions by area, are being addressed within the auspices of the Governing Board.

Concerning IMI performance, particular attention will be given to the organisational structure as well as staff allocation and financial management. This is considered crucial by management in order to ensure that the structure and resources of the JU continue to meet evolving organisational objectives and needs. Moreover, management will ensure that annual targets and objectives as well as key performance indicators are updated and coordinated with responsibilities and tasks also revised to reflect changing strategic priorities.

In turn, continuous measures are to be taken to strengthen both IMI2 JU operational procedures, increasing the resources available in some specific areas, improving the approach used for topic development, project monitoring and reporting as well as for IT management.

Finally, an external event such as Brexit should be included in the risk assessment given its potential impact on the strategy and programme implementation of IMI2 JU. UK stakeholders have largely contributed to the success of IMI success so far[7]. The consequences of Brexit are unpredictable at this point in time but will require monitoring and assessment within the EU's broader political agenda.

[7] As at 30/09/2016, in IMI2 JU 27.5% of participating EFPIA companies are based in UK (11 out of 40) as well as the 32.3% of beneficiaries (73 out of 226) while IMI2 funds allocated to those UK beneficiaries represent 40.3% of the total IMI contribution.

2.2.2 Scientific priorities for 2017

The IMI2 JU activities for 2017 are fully in line with the objectives as set out in article 2 of the IMI2 JU Regulation. In particular they aim at the development and implementation of pre-competitive research and innovation activities of strategic importance to the EU's competitiveness and industrial leadership, and address specific H2020 societal challenges, in particular that to improve European citizens' health and well-being.

These activities will be developed within the general framework of the Scientific Research Agenda (SRA) for IMI2 (see http://www.imi.europa.eu/content/research-agenda). The SRA identifies a set of scientific priorities where IMI attempts to pilot new ideas in real life in a safe harbour environment that maximises collaboration and synergies among all stakeholders; drives innovation in business models to support the transition from blockbusters to personalised medicines by testing new approaches across multiple companies and projects simultaneously; and pilots new types of collaboration between companies with different innovation cycles to optimise the success in delivering IMI2 JU objectives. The SRA furthermore identifies data and knowledge management as key enabling technologies, as well as education and training, and excellence in clinical trial implementation as key implementation strategies.

The priorities identified for 2017 are fully aligned with the IMI2 SRA and will help with the achievement of IMI2 JU objectives. They include the development of clinical trial networks; the sharing of data to improve and facilitate more powerful data analysis, insight generation and the creation of better tools, biomarkers and standards that will result in accelerating the clinical development of new treatments. In order to achieve its objectives, the initiative continues to seek the involvement of a broader range of partners from different sectors e.g. biomedical imaging, medical information technology, diagnostics and/or animal health industries among others. The actions that will result from the 2017 priorities will generate results that will have a high impact and facilitate the maximum number of stakeholders to join forces. The outcome and impact of these actions should bring great benefit to patients and society at large. There will also be engagement with regulatory agencies and other health bodies fostering the approval of research outcomes. Involving the wider community in this way should help to advance the development of new approaches and technologies for the prevention, diagnosis and treatment of diseases with an expected high impact on public health.

IMI has identified eight scientific priorities, broken down into several topics, for 2017, taking into account the advice provided by Strategic Governing Groups to the IMI2 JU Governing Board. As described in the following pages, each priority area will be implemented via the launch of one or more topics, which will generate multi-stakeholder actions, potentially including (or even driven by) Associated Partners. Further details regarding the expected multi-stakeholder actions are elaborated under the individual topics. Topics for 2017 have been prioritised based on criteria that include the highest impact on reducing attrition in drug development, speeding up patient access, improving health outcomes and enhancing the biomedical research ecosystem. Additional topics for 2017 might also be considered at a later stage in the case of very urgent public health needs, such as rapid response to emerging diseases. The Annual Work Plan 2017 would then be updated accordingly.

To implement the 2017 priorities, IMI2 JU will initiate three competitive Calls for proposals, each covering several topics (see table at the end of this section), with indicative predefined launch dates of 19 July 2017 (first two Calls) and 30 November 2017 [8].

Topics launched on the basis of this Annual Work Plan 2017 will seek synergies with other ongoing initiatives especially those funded under Horizon 2020 and at the national level, and those identified by the European Strategy Forum on Research Infrastructures (ESFRI), to ensure the consistency of approaches, to leverage other funding initiatives and to avoid duplication of effort and funding.

[8] Please see Article 1 (f) and (g) of the Statutes, annexed to the IMI2 JU Council Regulation

A. Diabetes/Metabolic disorders

The activities in this priority area should seek progress towards novel diagnostic and treatment paradigms for the mechanisms involved in and triggering the early onset and progression of (type 1 and type 2) diabetes/metabolic disorders and their complications.

This should aim to enable an early diagnosis with predictive biomarkers, to allow the development of experimental medicine approaches to safe and efficacious treatments, considering also the sustainability of treatment interventions for health systems.

Activities in 2017 will address the following topics:

1. **Assessment of the pheno-mapping profile of diabetic cardiomyopathy for the discrimination from other forms of heart failure:** Diabetic patients have a 2-4-fold increased risk of suffering from heart disease and their prognosis regarding cardiac failure is much worse compared to non-diabetic individuals. Death from cardiovascular disease (CV) is the leading cause of mortality for diabetic patients. Diabetes itself is an independent risk factor for CV as the risk remains increased even after correcting hypertension and ischemic heart disease. Meta-analyses of large clinical trials with diabetic patients have shown that despite strict glycaemic control there were no significant differences between intensified glucose lowering therapy and standard treatment considering non-fatal stroke and CV and all-cause mortality. Diabetes affects the heart indirectly through the progression and aggravation of CAD (Coronary artey Disease) as well as directly through the development of diabetic cardiomyopathy. The diabetic heart exerts a dramatic shift in energy consumption with a decrease in glucose oxidation and increased reliance on oxidation of free fatty acids. As consequence of the lacking correlation between tight glycaemic control and overall mortality the regulatory guidelines today make for each novel antidiabetic drug candidate a CV outcome e study mandatory to obtain approval. The aim of this topic is to unveil the actual incidence and the underlying mechanisms of diabetic cardiomyopathy and its impact on CV-mortality in diabetic patients and to improve the understanding of the clinical manifestations and diagnosis of diabetic cardiomyopathy.

Expected impact of the topics:

- Options for improved treatment of diabetic patients to decrease their risk for CV morbidity and mortality, via a better understanding of diabetic cardiomyopathy and the identification of reliable markers for its diagnosis and risk.
- Enabling of stratified clinical trials with novel antidiabetic drug candidates to assess their CVD risk
- Potential impact on the criteria for approval of novel antidiabetic drugs (alternative to CV-outcome trials).
- .
- A faster evaluation of the benefit and benefit/risk relationship of novel treatment options.
- .
- Potential high impact on future guidelines to treat diabetic and obese individuals.
- Potential high impact on public health regarding population morbidity and mortality and public healthcare costs.

Type of actions:

Research and Innovation Actions

B. Neurodegeneration and other Neuroscience Priorities

The priority area neurodegeneration aims to address the high unmet medical need for effective disease-modifying and symptomatic interventions, as well as relevant companion diagnostics, for neurodegenerative disorders in general and Alzheimer's disease (AD) in particular. The priority addresses the following themes: 1) increasing disease aetiology understanding for new drug target identification & validation; 2) development of translational model systems and identification/validation of biomarkers; 3) increasing the understanding of the blood/brain barrier in health and disease; 4) improving clinical trials including primary/secondary prevention; 5) better patient access.

Activities in 2017 will address the following topics:

2. **Support and coordination action for the projects of the Neurodegeneration area of the Innovative Medicines Initiative**. The coordination and support action will provide the necessary overall framework and resources to achieve effective and efficient coordination and collaboration among the ongoing and future projects in the IMI strategic area of neurodegeneration. It will also contribute to collaboration and alignment of the many initiatives (including but not limited to IMI-AD platform) devised in the aftermath of the G8 Dementia Summit Declaration[9] focused on advancing the field of dementia research. Collaboration is essential to avoid unnecessary duplication, allow for data and insight sharing, and increase efficiency by making joint priority trade-offs.
3. **Mitochondrial Dysfunction in Neurodegeneration.** Explore mitochondrial deficiency as a potential key factor in the neurodegenerative process underlying Parkinson's disease. The topic will lead to the development of a translational framework for the study of mitochondrial dysfunction *in vitro* and *in vivo* that will provide mechanistic insight into the role of mitochondria on disease pathology progression.
4. **Discovery and characterization of blood-brain barrier (BBB) targets and transport mechanisms** Better understanding of the role and alterations of the BBB and transport mechanisms in health and diseases. Relevant diseases are neurodegenerative diseases (e.g. Alzheimer and Parkinson's diseases, Amyotrophic Lateral Sclerosis (ALS)), vascular dementia, multiple sclerosis and metabolism-related central diseases (diabetes and obesity). It will be also important to understand the mechanisms of neurotropic virus-mediated BBB and CNS penetration, and to be able to apply this knowledge for the development of innovative drug delivery systems, especially for biopharmaceuticals, and the identification of novel drug targets.

Expected impact of the topics:

- Support and coordinate the IMI2 JU projects in the area to achieve higher impact than the individual projects via cross-fertilisation
- The fostering of a global dementia research agenda that most efficiently uses the investments of all stakeholders.
- Validation of tools and platforms for discovery of new biological insights into Parkinson's and Alzheimer's disease understanding
- More efficient, cost-effective and successful use of Parkinson's and Alzheimer's disease model systems in support of the development of novel therapies
- Better understanding of the functioning of the blood-brain barrier in health and disease, and how it may be manipulated to aid therapy
- Modernise and optimise clinical development for CNS therapies.

Type of actions:

Research and Innovation Actions; Coordination and Support Actions

[9] https://www.gov.uk/government/uploads/system/uploads/attachment_data/file/265869/2901668_G8_DementiaSummitDeclaration_acc.pdf.

C. Immunology

Autoimmune diseases cover over 100 distinct diseases and syndromes, together affecting approximately 5% of the population of Europe, with two-thirds of the patients being female. The burden of autoimmune disease crosses medical and scientific boundaries, and requires cross-functional collaboration by scientists and physicians with interests in diseases of widely differing organ systems. The proposed work will focus on a key set of immune mediated disease or disease mechanisms where working in partnership will benefit the knowledge base and accelerate delivery of drug treatments to patients. The proposed work will build on the knowledge base and infrastructure present within Europe from ongoing research-based initiatives e.g. Eumusc.net, EMEUNET, EUSTAR, ERS/ELF, ECCO, BILAG, EUVAS and Euro Lupus OMERACT, BLUEPRINT as well as relevant IMI projects (BTCURE, PRECISESADS, ULTRADD, BioVacsafe), which together have aggregated substantive information on disease phenotypes, biomarkers and other factors associated with disease progression in many autoimmune disorders in order to guide better patient treatments.

Activities in 2017 will address the following topics:

5. **Sjögren's syndrome**.Development of sensitive and validated clinical endpoints in primary Sjögren's Syndrome (pSS). Sjögren's syndrome is one of the more prevalent autoimmune disorders that presents as primary Sjorgen's syndrome (pSS) or secondary (sSS) in association with other autoimmune disorders. Unlike many other autoimmune diseases, Sjögren's syndrome lacks universally accepted classification criteria. Primary Sjögren's syndrome affects exocrine glands leading to sicca symptoms of the eyes and the mouth. Systemic (fatigue) and extraglandular (e.g. arthritis or lung) manifestations also often develop. A negative impact on quality of life is substantial, mainly due to the disabling fatigue. In addition, about 5% of pSS patients develop B cell lymphomas. Besides symptomatic treatments, no effective disease modifying treatment has been approved. Moreover, as there are no industry-sponsored studies that have been able to show a disease-modifying effect, and with the growing interest in conducting clinical trials in pSS, specific, sensitive and validated outcome measures have become a necessity to develop effective therapies. The major scope of this topic will be the development and optimisation of pSS-related outcome measures including sensitive and validated clinical endpoints and laboratory data (biomarkers), patient reported outcomes (PROs) and imaging modalities.
6. **Genome-environment interaction in inflammatory skin disease.** Inflammatory skin diseases and in particular Atopic Dermatitis (AD) and Psoriasis (Pso) represent a significant burden of disease. These diseases remain poorly understood with limited understanding of mechanism, endotypes, ontology and co-morbidities, affecting the quality of effective treatments. Key challenges to be addressed include, but are not limited to, the impact of environmental factors (e.g. via the microbiome) interacting with genomic factors and longitudinal studies that elucidate molecular pathways of disease. The topic aim is to lead to a step change in our understanding of the molecular mechanism and ontology of these two main inflammatory skin diseases. Elucidating the molecular pathways of these inflammatory skin conditions over time will give rise to novel and meaningful therapeutic targets for specific patient populations and help address the complex patterns of co-morbidities. In addition, the topic will identify biomarkers that will enable robust, efficient and meaningful patient management. The overall scope encompasses both a retrospective assessment of Pso and AD patients that can aid in defining key endotypes of disease and the disease commonalities and uniqueness and prospective studies that will embrace novel approaches and hypotheses relating to defining these.

Expected Impact of the topics

- Generation of tools and capabilities required to support precision medicine
- Increase the efficiency of the drug discovery and clinical development process
- Improved methods for recognition and diagnosis of autoimmune and inflammatory disorders and a range of treatment options
- Earlier availability of new, more cost effective therapies to patients most likely to benefit

Type of actions:

Research and Innovation Actions

D. Infection control including vaccines

Antimicrobial resistance (AMR) has been declared a major global public health threat. In Europe 25,000 deaths were reported in 2007 as a result of AMR of which 2/3 being due to gram-negative bacteria. In the US deaths due to AMR is estimated to a minimum of 23 000 deaths per year (2013 CDC report: http://www.cdc.gov/drugresistance/threat-report-2013/). The clinical burden is associated with soaring treatment and societal costs with a cost of AMR being estimated at around 1.5 billion Euros per year only in Europe. Despite the recognised need for new antimicrobials the reality is that as a society we are faced with the potential situation where prescribers could have few, if any, therapeutic options to treat certain bacterial infections. Continued efforts are required if key barriers to the development and delivery of effective antibiotics are to be overcome.

Because of their low unit cost for individuals (albeit high societal cost) and improved clinical outcome, antibiotics were overused in the past century which resulted in the pandemic spread of highly resistant bacterial clones. Because of the increased bacterial resistance we need a paradigm shift in the way we deliver care and prescribe antibiotics. Personalized medicine based on novel and rapid diagnostic strategies should help achieving this paradigm shift by identifying those patients who really need antibiotics, and by helping to select the narrow-spectrum antibiotic of choice.

Vaccination is one of the most valuable and cost-effective public health measures to prevent and control the spread of viral/bacterial infectious diseases responsible for high mortality and morbidity. It saves at least three million lives every year globally. Despite the outstanding progress, a significant number of infectious diseases and chronic disorders are still not preventable by vaccination and remain a major cause of death and morbidity worldwide. In addition, immune- and host-based biomarkers which can predict the response to vaccination are lacking. Research and development is required to address the changing risks associated with vaccination innovative solutions and to better understand drivers underpinning inconsistent utilization of available immunization measures.

Activities in 2017 will address the following topics:

7. **The value of diagnostics to combat antimicrobial resistance by optimizing antibiotic use.** As narrow spectrum anti-infective agents continue to progress into clinical use this must be accompanied by the development and use of rapid, point of care diagnostics. The goal is to facilitate the development and accessibility of novel diagnostics which will enable a more rational, reduced and targeted approach to antimicrobial use. In addition, the aim will also be to develop new innovative evaluation techniques to demonstrate the value of diagnostics for impacting antimicrobial resistance and to develop new economic models to incentivize the discovery, development and use of new diagnostics for use now and in the future.
8. **Analysing the infectious disease burden and the use of vaccines to improve healthy years in aging populations.** Stronger knowledge of the epidemiology of infectious diseases and a deeper understanding of the outcomes of infectious diseases in the elderly (morbidity, mortality, etc.) are needed. The goal is to improve understanding of the epidemiology of infectious diseases in the elderly, the mechanisms behind the immune responsiveness and the contribution of extrinsic factors (such as nutrition, physical exercise, co-morbidities and pharmaceutical treatments, etc.). This should allow to develop cost-benefit predictions based on an extended vaccination program, to better control the burden in that age-group through simulations with advanced disease models, and finally to develop strategies to educate all stakeholders working with the elderly.

Expected impact of the topics:

- Novel and rapid diagnostics and new business models for improved access and use
- Delivery of better vaccines in response to target group-specific needs.
- Major impact on the improvement of public health.

Type of actions:

Research and Innovation Actions

E. Translational safety

Translational safety is a key priority for the IMI2 JU programme. Translational safety activities aim at improving the safety assessment of pharmaceuticals through innovative and more predictive preclinical and clinical evaluations. The goal is to optimise the translatability to the 'real life' situation of the safety assessment paradigms and ultimately to improve the safety profile of drugs delivered to patients. In order to create synergies and avoid redundancies, activities in the translational safety area will connect with any other IMI projects relating to safety (including data management), and other relevant European and global initiatives (e.g. US Critical Path Institute, The Health and Environmental Sciences Institute/International Life Sciences Institute (HESI/ILSI), Innovative Questions (IQ) and National Institutes of Health (NIH)-driven projects). Topics brought forward in 2017 will aim at tackling safety-related attrition during drug development by better bridging preclinical and clinical areas, and as a result, should bring safer medicines to the market. Therefore, the topics planned focus on two extremes of the R&D process: on one side, on the improvement of the toolbox used during early phases of preclinical evaluation; and the other side, on clinical evaluation at late stages. The final idea is still to connect both preclinical and clinical areas through translational, integrative approaches.

Activities in 2017 will address the following topics:

9. **Improving the preclinical prediction of adverse effects of pharmaceuticals on nervous system.** Adverse effects of drugs on the central and peripheral nervous system are not uncommon during clinical development and post-marketing surveillance, in the context of either recommended use or misuse/abuse. However, neurotoxicity is poorly predicted by preclinical studies during R&D process, leading to a substantial attrition rate, including post-marketing surveillance (figures for attrition, though variable according to sources, are typically in the range of 5-25%). It is envisaged to bring forward a topic focused on delivering improved preclinical tools and strategies, at every step of the R&D process, using an integrated approach that would combine in silico, in vitro and in vivo models. Efforts in this area have typically concentrated on new chemical entities. Recent information however suggests that biologics (especially monoclonal antibodies) should be included in approaches undertaken.
10. **Translational Safety Biomarker Pipeline: Enabling development and implementation of novel safety biomarkers in clinical trials and diagnosis of disease.** The early and reliable prediction, detection, monitoring and assessment of adverse events are key to improving patient safety and reducing late-stage attrition in drug development. A major challenge to detecting and managing these toxicities is the lack of sufficiently sensitive and specific biomarkers. The aim of the topic will be to deliver biomarkers that fulfil these criteria. To accelerate the process important starting points will include biomarkers that already have data associated with the aim e.g., biomarkers that have received regulatory Letters of Support, but not yet full qualification from EMA and FDA. The scope of the work will include the generation of data that will allow the full qualification of biomarkers studied.
11. **ConcePTION: continuum of evidence from pregnancy exposures, reproductive toxicology & breastfeeding to improve outcomes now.** Women of childbearing age are often required to take medicines to treat conditions that affect them during pregnancy. While reproductive and embryofetal developmental (EFD) studies are conducted routinely to determine potential teratogenic and/or toxic effects associated with foetal exposure and the presence of medicines in breast milk, the predictivity of these studies has limitations. Alternative ways of characterizing disease and compound mediated embryofetal risks and risks to the new-born and infants during lactation are therefore urgently needed. The overall objective of this priority area will be to bring forward topics that will result in optimised, reliable and timely information on reproductive risks of medications used in women of childbearing age.

Expected Impact of the topics

- Improved preclinical models of toxicity
- Qualified safety biomarkers
- Decrease the risk presented to patients by novel pharmaceuticals
- Better protect volunteers or patients involved in clinical trials with drugs acting on nervous system
- Better understanding of the reproductive risks of medications used in women of childbearing age
- Develop new methodologies to better address the risks of adverse foetal outcomes due to disease and medication during pregnancy and lactation

Types of action:

Research and Innovation Actions

F. Data and Knowledge Management

The increasing volume (terabytes/patient), diversity (clinical, genome-wide association study/RNA sequencing, electronic heath records, 'omic, cytometry, imaging, pharmacology, pharmacovigilance etc.) and velocity (e.g. real time telemetric monitoring of patients, social media feeds, wearable devices in healthy subjects etc.) of biomedical data available creates significant opportunity for healthcare research & development (R&D). However, common data standards, as well as robust, production quality data and knowledge management (KM) solutions and services are essential if the full value of these data sets is to be realised in the development of innovative precision medicines. To respond to the challenges faced in healthcare R&D it will be necessary to collaborate on the development of novel enabling technologies and adaptive methods to facilitate the efficient capture and interrogation of these data sets to ensure effective healthcare practices for patients.

Addressing these challenges will also be facilitated by significantly increasing access to real world evidence; enhancing the involvement and central role of patients - including citizen-controlled data repositories; extensions to the RADAR platform (http://www.radar-cns.org/) to include other diseases (e.g. Alzheimer's disease) and monitoring methodologies; leveraging data management for the better standardization of biomarkers; and finally aligning existing DKM platforms towards more standardised methods of utilising pathways and other network data while ensuring the regulatory requirements of this data is complied with fully.

To ensure a harmonised approach, it is planned that ongoing projects will require coordination/collaboration with European biomedical research infrastructures through the European Strategy Forum on Research Infrastructures (ESFRI).

Activities in 2017 will address the following topics:

12. **FAIRification of IMI and EFPIA data.** Establish a sustainable legacy of the IMI data assets. Develop solutions to make a significant portion of the data from IMI2 JU projects hosted in a sustainable way, accessible and interoperable. The activities include making the wealth of data generated during IMI-1 and IMI-2 JU projects Findable, Accessible, Interoperable, and Re-usable (FAIR).
13. **European Health Data Network (EHDN).** This initiative is a critical enabling component of the BD4BO program and it is responsible for delivering its vision for large scale medical outcomes research. Projects under the BD4BO programme will be required to conclude collaboration agreements[10] with each other. Activities will aim at establishing a core distributed data infrastructure to allow real world evidence data repositories to be combined for overcoming the challenge posed by the sheer volume of data and number of repositories and enable the generation of a body of evidence that will inform policy debates. The overall goal is to address this critical challenge by converting relevant datasets across Europe to a common format and standard so that they can be more efficiently used to their full potential within a federated network to achieve the objectives of the BD4BO programme, while respecting patient privacy, local data provenance, governance and applicable regulations.
14. **Development and validation of technology enabled, quantitative and sensitive measures of functional decline in people with early stage Alzheimer's Disease (RADAR-AD).** Extend the Remote Assessment of Disease and Relapse RADAR programme to other disease areas by leveraging the RADAR platform for central nervous system (RADAR-CNS) to study cohorts of patients who suffer from other conditions such as Alzheimer's disease. A focus will be the development and validation of technology-enabled, quantitative and sensitive measures of functional decline in people with early stage Alzheimer's disease. Projects under the RADAR programme will be required to conclude collaboration agreements with each other.
15. **Linking digital assessment of mobility to clinical endpoints to drive regulatory acceptance and clinical practice (DIAMOND)**. The aim of the topic is to validate digital mobility assessment, focusing on "real world walking speed" (RWS) as a primary endpoint for a more sensitive, objective measurement in patients' (from chronically ill or frail populations) native environment over longer periods of time and with greater granularity than is currently feasible. The topic include activities over two phases. In a first phase activities should cover a technical validation part that will develop an algorithm for quantifying RWS in relevant population of slow walkers. In a second phase activities should cover a validation program that will demonstrate that the algorithm predicts relevant clinical outcomes (e.g., falls, injurious falls, hospitalizations, disability, and mortality).

[10] IMI2 Grant Agreement article 41.4: Relationship with complementary beneficiaries — Collaboration agreement.

Expected impact of the topics:

- Stable legacy: enabling IMI data assets security (time and policy) and accessibility.
- An improved understanding: through maximising the utility of individual studies.
- To allow the development of new scientific insights to support and accelerate medicines development; by fulfilling the ethical responsibility to extract most value for contributing patients and by permitting combined, cross study analyses.
- The improved data sharing and interpretation: by developing and supporting independent, agreed and stable public-private standards; by developing and providing common interfaces reducing the threshold for data access to researchers and system interoperability.
- A strengthened community of informatics and knowledge management professionals.
- Robust KM solutions and operational excellence to allow integration and analysis of diverse datasets, addressing long-term sustainability, accessibility and reuse of generated research data for future studies.
- Innovative IT/KM/analytical solutions required to support new clinical trial paradigms, biomarkers and monitoring devices.
- Increased value and return on biomedical research investment through operational excellence and collaboration and reuse of public research infrastructures.
- More cost effective, improved R&D processes enabled by fit-for-purpose KM infrastructures, leading to improved scientific insight and so downstream healthcare improvements for Europe.
- Faster translation of insights from real world health data to biomedical research and development approaches.
- Impact on the care of frail populations and of the development of drugs to treat them.

Type of actions:

Research and Innovation Actions

G. Oncology

IMI via its strategic area oncology aims to foster a significant progress towards the extension and quality improvement of patients living with advanced cancer.

The mission and vision is to define research initiatives that will aspire to effectively double the following parameters: 1) progression-free survival / overall survival; 2) number of patients able to access innovative personalized medicines; 3) speed of drug development; 4) treatment tolerability, and 5) cost effectiveness in cancer drug development .

Activities in 2017 will address the following topic:

16. **Human Tumour Microenvironment Immunoprofiling.** The aim is to generate a data set sufficient to gain a meaningful view of the tumour micro-environment.. Activities will lead to the creation a database containing integrated cellular and molecular data from the tumour microenvironment of patients treated with both targeted and non-targeted therapy, in particular immunotherapy, as well as key information from patient history and clinical progression.

Expected impact of the topic:

- New approaches in drug development/ combination strategies for drugs in development to facilitate patient access to innovative treatments.
- Novel and better defined clinical and molecular endpoints.
- Better, more robust and higher quality screening tools and methods.
- A large positive impact in treatment outcomes, to support the adequate reimbursement of innovations in this field.
- A better understanding of the microenvironment of tumours and its dynamics, including tumour immunology.

Type of actions:

Research and Innovation Actions

H. Other enablers of innovation

17. **European Screening Centre: unique library for attractive biology.** There is a growing need for a better translation of exciting biology concepts into tangible and refined chemical assets. These assets (e.g. chemical lead structures) are needed as tools for a better understanding of disease mechanisms as well as starting points for the future development of novel medicines. Pharmaceutical companies have their own compound libraries, as well as screening and medicinal chemistry facilities. Major academic centres have also started establishing their own libraries and screening activities: e.g. the European Open Screen initiative (http://cordis.europa.eu/result/rcn/173234_en.html). These distributed activities have nevertheless shown their limitations, calling for a more coordinated approach bringing together public and private expertise in this area. The IMI project European Lead Factory (https://www.europeanleadfactory.eu/) established over the last four years is already showing the value of such a central, coordinated approach. This topic will address the need for suitable chemical assets in complex diseases by designing a unique, high quality compound library for attractive biology. This will be achieved by enlarging and building on the work done in the European Lead Factory project (https://www.europeanleadfactory.eu/) screening facilities, with a strong focus on innovative biology, and a structured approach for qualification of the resulting hits. In particular, a further important value creating step towards tangible chemical assets is envisaged: Hit-to-Lead (H2L) workflow for selected programs enabling participants to jump start lead optimization projects and helping to further boost public private partnerships post the IMI funding period.
18. **A sustainable European induced pluripotent stem cell platform.** The overall objective of the action generated from this topic is to establish a fully self-sustainable European human iPSC banking facility, by seamlessly building on and incorporating existing cell lines, knowledge and infrastructure established within former European wide initiatives (e.g. EBiSC). The bank has to be able from the start to handle and deliver a minimum of approximately 500 quality-controlled, disease-relevant (in particular for neurodegeneration, Alzheimer's disease and other tauopathies, Parkinson's disease), cardiovascular disease, safety, and diabetes), research-grade iPSC lines, with integrated data and cell services which will be further built on as part of the research and technology work of the action. The ultimate goal is to transform significant pre-existing European banking infrastructures into a sustainable resource for European research and development.
19. **Clinical Compound Bank for Repurposing (Pilot programme with four topics):Cardiovascular diseases and diabetes,**
20. **Clinical Compound Bank for Repurposing (Pilot programme with four topics):Respiratory diseases,**
21. **Clinical Compound Bank for Repurposing (Pilot programme with four topics):Neurodegenerative diseases**
22. **Clinical Compound Bank for Repurposing (Pilot programme with four topics): rare/orphan diseases.**
The overall objective of this pilot programme is to take one of ten previously deprioritized clinical compounds- that are identified in the Appendix to the full topic text - and investigate their therapeutic potential in new clinical indications in areas of high unmet need., there are four separate topics, one for each of four identified disease areas. Information on original primary indications, already tested indications, ongoing and/or planned clinical studies for each of these ten compounds can be found in the Appendix to the topic.

Expected impact of the topics

- Generate a central European hub for screening and hit profiling for public and private partners
- Foster the translation of novel biology in disease areas with high unmet medical need into *highly valuable* chemical assets.
- A central European iPSC repository hub to accelerate and facilitate European research and development activities.
- Boosting the discovery and development of therapeutics in the areas of cardiovascular diseases and diabetes, respiratory diseases, neurodegenerative diseases and rare/orphan diseases using a more cost-effective approach to drug development.
- Advancing science and knowledge of disease (patho-)physiology through testing of new hypothesis.

Type of action:

Research and Innovation Actions

I. Exploitation of IMI Project Results

A key challenge of any research funding scheme is to ensure that significant results, outputs and/or data generated during the lifetime of a project remain available to be further exploited for maximum beneficial impact after the project finishes. Often, important scientific results reach the public domain via publication in relevant scientific journals. However, for some important results[11] – which may include databases, biobanks, new tools, important clinical samples, demonstration models, etc. – the route to becoming available to the wider scientific community or being exploited fully, remains a difficult path. Realising the full potential of a project's important results within the timeframe available is not always possible and might sometimes only be achieved through the involvement of additional expertise from outside of the project.

23. **Exploitation of IMI Project Results.** This topic aims at providing a starting/short term support to develop enabling solutions to ensure that significant results from IMI projects become fully exploitable, available to all relevant end users, and/or fully sustainable in the long term and in their own right. This will ensure that the significant outputs, important samples and/or data that have been generated by the large public-private investments are maintained and made available for future research by the whole scientific community and that important findings are integrated in general research and medical practice in support of the objectives of IMI2. The work to be supported will consist mainly of activities and measures to make the results available to the broader scientific community and as such may include measures to enable technology transfer and the analysis of regulatory aspects, as well as the standardisation and transfer of samples, databases, tools, etc. to sustainable infrastructures. In addition, the work may also encompass further activities should novel solutions/tools/methods be required to achieve the objectives of sustaining the results and ensuring their full impact. These could include adaptation of technologies to enable wider engagement, development of novel standardisation and/or interoperability measures, further development of scientific and business solutions, etc., as appropriate.

The full Call for proposals text is set out in Annex II. The IMI project results within the scope of this call are identified in the table annexed to the indicative topic text in Annex I.

The relevant consortia will provide the necessary access rights to any potential applicant in furtherance of the call objectives and according to applicable IMI rules[12].

Expected impact:

- It is expected that proposals selected for award under this topic will lead to a sustainable future and full exploitation for key IMI project results. It is also envisaged that sustaining these results will stimulate the development of an open innovation model in biopharmaceutical research and contribute to the achievement of IMI2 objectives.
- Selected proposals should demonstrate an appreciation of the impact of exploiting the results with respect to long-term sustainability; an impact on R&D, regulatory, clinical and healthcare practice, as relevant; strengthening the competitiveness and industrial leadership and/or addressing specific societal challenges, and improving European citizens' health and wellbeing, when appropriate.

Type of action:

Research and Innovation Actions

[11] Important results are defined as those with maximum potential long-term impacts on research and development, as well as on regulatory, clinical and healthcare practice.

[12] Annex II of the IMI Model Grant Agreement 'Part C – Intellectual Property Rights, Use and Dissemination' and in particlaur articles II.30 and II.31:

http://www.imi.europa.eu/sites/default/files/uploads/documents/Rev_Grant_Agreement_2011/1_WP_2013_GA_Annex%20II_2013%2003%2013.pdf

Calls for Proposals

Call number and topics	Indicative Call launch timing[13]	Indicative IMI2 JU funding (in EUR),[14]	Indicative in-kind contribution (in EUR) from EFPIA entities and Associated Partners	Call process
IMI2 Call 11[15] (postponed from 2016) *Exploitation of IMI Project Results (RIA)*	19 July 2017	5,000,000	-	One-stage Call with predefined submission deadline: 24 October 2017 Research & Innovation Actions (RIA)
IMI2 Call 12 [16] *Neurodegeneration and other Neuroscience Priorities* ▪ Discovery and characterization of blood-brain barrier targets and transport mechanisms for brain delivery of therapeutics to treat neurodegenerative & metabolic diseases (RIA) *Immunology* ▪ Development of sensitive and validated clinical endpoints in primary Sjögren's Syndrome (pSS) (RIA) *Infection control including vaccines* ▪ Analysing the infectious disease burden and the use of vaccines to improve healthy years in aging populations[17]. *Data & Knowledge Management* ▪ FAIRification of IMI and EFPIA data (RIA) ▪ European Health Data Network (RIA)[18]. ▪ Development and validation of technology enabled, quantitative and sensitive measures of functional decline in people with early stage Alzheimer's Disease (RADAR-AD) [19] (RIA)	19 July 2017	64,077,000	62,362,000	Two-stage Call with predefined submission deadline Indicative Call deadline for Short proposals: 24 October 2017 Indicative Call deadline for Full Proposals: 16 May 2018 Research and Innovation Actions (RIA)

[13] The IMI2 JU Executive Director may decide to open the call up to one month prior to or after the envisaged date(s) of launch.

[14] The maximum possible rate of co-financing is 100 %.

[15] The full indicative Call for proposals' text is set out in Annex I.

[16] The full indicative Call for proposals' text is set out in Annex II.

[17] Potential applicants must be aware that this topic, if exceptionally needed, may be subject to a restricted follow-up Call for proposals to be launched by IMI 2 JU at a later stage. This follow-up Call for proposals may be restricted to the consortium already selected under such topic, in order to enhance its results and achievements. The consortium will be entitled to open to other beneficiaries as appropriate. The detailed scope of the restricted Call shall be described in the relevant Annual Work Plan.

[18] Potential applicants must be aware that this topic, if exceptionally needed, may be subject to a restricted follow-up Call for proposals to be launched by IMI 2 JU at a later stage. This follow-up Call for proposals may be restricted to the consortium already selected under such topic, in order to enhance its results and achievements. The consortium will be entitled to open to other beneficiaries as appropriate. The detailed scope of the restricted Call shall be described in the relevant Annual Work Plan.

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Call number and topics	Indicative Call launch timing[13]	Indicative IMI2 JU funding (in EUR),[14]	Indicative in-kind contribution (in EUR) from EFPIA entities and Associated Partners	Call process
Other Enablers of innovation ▪ European Screening Centre: unique library for attractive biology (ESCulab) (RIA)				
IMI2 Call 13 [20] *Diabetes/metabolic disorder* ▪ Diabetes cardiomyopathy (RIA) *Neurodegeneration and other Neuroscience Priorities* ▪ Support and coordination action for the projects of the Neurodegeneration area of the Innovative Medicines Initiative. (CSA) ▪ Mitochondrial Dysfunction in Neurodegeneration (RIA) *Immunology* ▪ Genome-environment interaction in inflammatory skin[21] disease. (RIA) *Infection control including vaccines* ▪ The value of diagnostics to combat antimicrobial resistance by optimizing antibiotic use. (RIA) *Translational safety* ▪ Reduce safety-related attrition during drug development: Improving the preclinical prediction of adverse effects of pharmaceuticals on nervous system. (RIA); ▪ Translational Safety Biomarker Pipeline: Enabling development and implementation of novel safety biomarkers in clinical trials and diagnosis of disease (RIA) ▪ Better protect patients, launch safer medicines: ConcePTION - Continuum of Evidence from Pregnancy Exposures, Reproductive Toxicology & Breastfeeding to Improve Outcomes Now[22] (RIA);	30 November 2017	116 421 000	106 629 000	Two-stage Call with predefined submission deadline Research and Innovation Actions (RIA) & Coordination and Support Actions (CSA) Indicative Call deadline for Short proposals: 28 February 2018 Indicative Call deadline for Full Proposals: 6 September 2018

such topic, in order to enhance its results and achievements. The consortium will be entitled to open to other beneficiaries as appropriate. The detailed scope of the restricted Call shall be described in the relevant Annual Work Plan.

[20] The full indicative Call for proposals' text is set out in Annex Iii.

[21] Potential applicants must be aware that this topic, if exceptionally needed, may be subject to a restricted follow-up Call for proposals to be launched by IMI 2 JU at a later stage. This follow-up Call for proposals may be restricted to the consortium already selected under such topic, in order to enhance its results and achievements. The consortium will be entitled to open to other beneficiaries as appropriate. The detailed scope of the restricted Call shall be described in the relevant Annual Work Plan.

[22] Potential applicants must be aware that this topic, if exceptionally needed, may be subject to a restricted follow-up Call for proposals to be launched by IMI 2 JU at a later stage. This follow-up Call for proposals may be restricted to the consortium already selected under such topic, in order to enhance its results and achievements. The consortium will be entitled to open to other beneficiaries as appropriate. The detailed scope of the restricted Call shall be described in the relevant Annual Work Plan.

Call number and topics	Indicative Call launch timing[13]	Indicative IMI2 JU funding (in EUR),[14]	Indicative in-kind contribution (in EUR) from EFPIA entities and Associated Partners	Call process
Data & Knowledge Management ▪ Linking digital assessment of mobility to clinical endpoints to support regulatory acceptance and clinical practice (DIAMOND). (RIA)[23] .*Oncology* ▪ Human Tumour Microenvironment Immunoprofiling (RIA)[24] *Other Enablers of innovation* ▪ A sustainable European induced pluripotent stem cell platform (RIA) ▪ Clinical Compound Bank for Repurposing (Pilot programme with four topics):Cardiovascular diseases and diabetes (RIA) ▪ Clinical Compound Bank for Repurposing (Pilot programme with four topics):Respiratory diseases (RIA) ▪ Clinical Compound Bank for Repurposing (Pilot programme with four topics):Neurodegenerative diseases (RIA) ▪ Clinical Compound Bank for Repurposing (Pilot programme with four topics): rare/orphan diseases (RIA)				
OVERALL TOTAL		**185,498,000**	**168,991,000**	

[23] Potential applicants must be aware that this topic, if exceptionally needed, may be subject to a restricted follow-up Call for proposals to be launched by IMI 2 JU at a later stage. This follow-up Call for proposals may be restricted to the consortium already selected under such topic, in order to enhance its results and achievements. The consortium will be entitled to open to other beneficiaries as appropriate. The detailed scope of the restricted Call shall be described in the relevant Annual Work Plan.

[24] Potential applicants must be aware that this topic, if exceptionally needed, may be subject to a restricted follow-up Call for proposals to be launched by IMI 2 JU at a later stage. This follow-up Call for proposals may be restricted to the consortium already selected under such topic, in order to enhance its results and achievements. The consortium will be entitled to open to other beneficiaries as appropriate. The detailed scope of the restricted Call shall be described in the relevant Annual Work Plan.

Budget

A table overview of the operational budget for the financial year 2017 is set out below.

Heading Title 3	Financial year 2017						Comments
	Budget 2017.0		Budget 2017 Amendment 1	Budget 2017 Amendment 2	Amended Budget 2017.2		
	Commitment Appropriation (CA)	Payment Appropriation (PA)	*Payment Appropriation (PA)*	*Payment Appropriation (PA)*	Commitment Appropriation (CA)	Payment Appropriation (PA)	
Operational expenditure	178 038 671	196 782 634	-56 000 000	-24 000 000	178 038 671	116 782 634	EC contribution to grant agreements - Payments
Appropriations carried over from 2016	134 467 173		77 282 369		134 467 173	77 282 369	The amount carried over from 2016.
Operational expenditure		2 831 000		-1 831 000	0	1 000 000	EFPIA companies' and Associated Partners' contributions to grant agreements - Payments
Total	**312 505 844**	**199 613 634**	**21 282 369**	**-25 831 000**	**312 505 844**	**195 065 003**	

The difference between the total budget available for Title 3 and the budget available for fresh Calls in 2017 is EUR 118 907 844. This amount represents the unused commitment appropriations carried over to the 2017 budget, to conclude Grant Agreements for IMI2 - Call 7 (EUR 46 794 803), Call 8 (EUR 70 000 000), Call 3 (EUR 2 100 000) and recovered amounts (EUR 13 041).

The payment of EUR 1 831 000 is postponed as requested by the Associated Partner, Bill and Melinda Gates Foundation, due to underspending in the project during 2017.

2.2.3 Call management (planning, evaluation, selection, …)

Activities related to proposals evaluation and grant preparation

Key activities in 2017 will comprise the launch of three competitive Calls for proposals implementing the 2017 scientific priorities with indicative launch dates on 19 July 2017 and 30 November 2017. In addition to the above-mentioned July and November calls, the Call 'Exploitation of IMI Project Results', initially planned for 2016, will be launched in 2017, the indicative launch date being 19 July 2017. As of 2017, all IMI2 JU Calls and evaluations will utilise the H2020 participant portal and Horizon 2020 IT infrastructures.

In a single-stage submission evaluation procedure, the submission deadline will be approximately three months from the publication of the Call for proposals.

In a two stage submission evaluation procedure, from the initial publication of the Call for proposals the submission deadline will be:

- for stage 1 approximately three months from the publication of the calls for proposals
- for stage 2 approximately eight months from the publication of the calls for proposals.

In addition, the evaluation of Short Proposals and Full Proposals submitted to Calls launched under the AWP in 2017 will be held according to the predefined timelines established in the relevant Call for Proposals.

Timelines for completion of the evaluation process and of Grant Agreement preparation will be kept as lean as possible with the aim of completing signature of the Grant Agreements within applicable time to grant (TTG), in compliance with the Horizon 2020 framework, i.e. a maximum of eight months from the final date of submission of the full proposals.[25]

To maximise the efficiency of the calls management, the IMI2 JU will continuously explore and implement simplification and improvement processes while maintaining the highest standards of the evaluation process.

2.2.4 Activities to support and monitor ongoing projects

78 ongoing projects will be running at different stages of their life cycle in 2017 with additional projects coming online during the year when Call 8 Ebola+ (3rd and 4th cut-off), Call 9 and Call 10 (launched in 2016) complete their evaluation cycles. All projects will submit to IMI2 JU a periodic report for the previous year summarising their progress and costs incurred. These reports form the basis for the Programme Office's ex-ante controls.

In addition to periodic reporting and associated feedback, IMI2 JU will continue to provide support and advice to the consortia, including on amendments to Grant Agreements.

IMI will organise 8 mid-term (interim) reviews for projects launched under IMI1 JU (Calls 10 and 11) and IMI2 JU (Calls 1 and 3).

		Project periodic report due in 2017						Of which	
IMI Calls	ongoing in 2017	1st RP in 2017	2nd RP in 2017	3rd RP in 2017	4th RP in 2017	5th to 7th RP in 2017	Total reports	finishing in 2017	Final report due 2017
1	0	0	0	0	0	1	1	0	0
2	1	0	0	0	0	1	1	2	1
3	7	0	0	0	0	7	7	5	5

[25] Article 20 of the Regulation (EU) No 1290/2013 of the European Parliament and of the Council of 11 December 2013 laying down the rules for participation and dissemination in "Horizon 2020"

		Project periodic report due in 2017						Of which	
IMI Calls	ongoing in 2017	1st RP in 2017	2nd RP in 2017	3rd RP in 2017	4th RP in 2017	5th to 7th RP in 2017	Total reports	finishing in 2017	Final report due 2017
4	7	0	0	0	0	7	7	7	6
5	1	0	0	0	0	1	1	1	0
6	2	0	0	0	0	2	2	1	0
7	2	0	0	0	2	0	2	0	1
8	4	0	0	4	0	0	4	0	1
9	4	0	1	3	0	0	4	2	2
10	1	0	1	0	0	0	1	0	0
11	8	0	8	0	0	0	8	0	0
IMI2 C1	1	0	1	0	0	0	1	0	0
IMI2 C2	8	0	8	0	0	0	8	5	1
IMI2 C3	5	1	0	0	0	0	1	0	0
IMI2 C4	1	0	1	0	0	0	1	1	0
IMI2 C5	6	6	0	0	0	0	6	0	0
IMI2 C6	4	0	0	0	0	0	0	0	0
IMI2 C7	8	0	0	0	0	0	0	0	0
IMI2 C8	2	2	0	0	0	0	2	0	0
IMI2 C9	6	0	0	0	0	0	0	0	0
Total	**78**	**9**	**20**	**7**	**2**	**19**	**57**	**24**	**17**

A key task will be to continue maximising efficiency, facilitating, optimising, and monitoring the implementation of all these projects and seeking feedback for continuous improvement to IMI2 JU operations. To this end, further workshops to provide guidance on the management of financial and administrative aspects of the projects will be held for IMI beneficiaries. In addition, the IMI Programme Office will work with consortia on helping to communicate on project progress and achievements.

2.2.5 Monitoring and analysis of projects' results

All ongoing IMI projects will complete a periodic report in 2017 and these reports will be used to track progress against their stated objectives and deliverables as laid out in the description of the action. This reporting will also allow an assessment of project achievements and the impact of results. In addition to these ex-ante controls a combination of internal management information systems, external databases, independent evaluations and, if necessary, commissioned studies and surveys will be used to measure the progress and identify significant achievements of IMI projects. In addition, 24 projects will reach their project end date and finish their IMI funding during 2017. Of these, 17 of these are expected to submit their final reports before the end of 2017. For projects resulting from IMI2 JU calls launched in 2017 onwards this monitoring will be done using the functionalities of the Horizon 2020 IT infrastructures.

In 2017 the analysis of the IMI project scientific outputs in terms of publications and collaboration among IMI researchers will be continued. Where feasible monitoring and analysis approaches will be refined in line with observations from the European Court of Auditors (ECA) to ensure the highest possible standards.

2.2.6 Stakeholders' engagement and external collaborations

In 2017 IMI will continue to develop its relationships and engagement with stakeholders such as patients, regulators, payers and healthcare professions to ensure that its outputs are aligned with and address the needs of society. Given their importance in driving employment and innovation in the European economic area IMI JU will continue its engagement with SMEs and encourage their participation in IMI projects. As the healthcare challenges that face society are global the IMI JU will also explore interactions and seek synergies with non-EU organisations when appropriate. Particularly important will be developing relationships with regulatory agencies outside of Europe and in areas where the setting of internationally accepted standards will benefit progress in healthcare research. When appropriate, collaborations with other non-EU organisations will be sought.

Patients

IMI recognises that patients benefit from research and development and can make a vital contribution to shaping research, making it more effective and more oriented to patient needs. The involvement of patients in research also builds their confidence in the research and development process. In addition, this engagement and interaction may provide IMI additional opportunities to communicate its role and mission. Therefore, IMI's goal is to champion a patient centric-approach at all levels and especially encouraging all the projects that it funds to work in partnership with patients wherever possible.

Patients play an essential role when designing and implementing the IMI Strategic Research Agenda, sitting alongside researchers from public and private sectors, including the pharmaceutical industry, biotech companies, academia and regulators. This is why IMI wishes to embed patients and their advocates at all levels; agenda setting for research in medical innovation, project planning, implementation, evaluation processes and content. Therefore the Programme Office will continue to actively engage with patients and promote patient involvement in its projects and activities. Namely IMI will:

- ensure that patient engagement and the role for patients is considered at the idea generation and topic writing stage;
- communicate on patient engagement needs and opportunities at call launch;
- identify the most effective channels of communicating the call to patients and other relevant organisations;
- identify and communicate on best practices of patient engagement in IMI projects;
- facilitate patient engagement in consortia.

IMI will organise at least one patient focus meeting with an objective to provide patient perspective and input into the potential research topics in IMI. IMI will also be represented at least at 1 specific patient focused event.

The aim of these activities is to raise awareness of IMI's activities among patients and explain what IMI is doing for them, to ensure patient input in all aspects of IMI activities as a research-funding organisation, and particularly to promote their involvement in projects. IMI will continue to produce materials for the promotion of patient involvement in IMI.

Regulators

To advance the vision of delivering the right treatment to the right patient at the right time for priority diseases requires all sectors within the healthcare ecosystem to work together to build the environment and infrastructure that allows the full value of this innovation to be realised.

Since its inception IMI has established collaboration with regulators to create an interface between science and regulation, in particular to explore how the current state of science could support the evolution of the regulatory paradigms as enablers of innovation for the benefits of patients. IMI will therefore continue to develop this framework to engage with all relevant regulatory agencies.

To continue to strengthen relations with regulatory agencies, in particular with EMA and FDA, IMI will continue a regular exchange of information with EMA and FDA on research projects, topics under development and strategic vision for collaborative research conducted under IMI to engage in dialogue with regulators as enablers of innovation. This dialogue will also further discuss the impact of IMI project results on the EU regulatory environment, including how they are enabling the implementation of Medicines Adaptive Pathways to Patients (MAPPs) within the current regulatory framework. In addition, IMI will organise a regulatory science summit with the EMA and FDA.

To ensure that IMI projects benefit from the regulators' input and maximize the impact of IMI project outputs to progress regulatory science, IMI staff will continue to support topic writers at the stage of a topic development. IMI staff will also work with IMI consortia to raise awareness of the regulatory relevance of their activities and the subsequent regulatory processes to follow, particularly with the qualification advice/opinions procedures. IMI will also support early liaison with the regulators.

IMI will develop a framework for dialogue with other decision makers particularly health technology assessment (HTAs), payers and other relevant EU-funded initiatives, taking into consideration experience from the IMI coordination and support action ADAPT-SMART.

SMEs

Small and medium-sized enterprises (SMEs) are the backbone of Europe's economy representing 99% of all businesses in the EU. They play a valuable role in bringing forward innovative solutions to help tackle key societal challenges. IMI recognises this important role of SMEs and will continue to work with its founding members and other stakeholders to increase support to SMEs and increase SME participation in its projects.

In 2017, the IMI SME strategy will be finalised and implemented. The first implementation step will be to encourage increased SME participation in IMI call topics by clearly highlighting activities to be carried out by SMEs in the topic description. Another important step will be the overhaul of the IMI website with better and clearer information targeted to SMEs, particularly relating to the management of IPR and the benefits of participating in IMI projects via testimonies from SMEs already participating. Begun in 2016, it is foreseen that the overhaul of the website and updating of information targeted at SMEs will be concluded in 2017.

Whenever possible IMI will look to partner with other EU, national and regional clusters to host events aimed at encouraging SMEs to apply and participate in IMI projects. The IMI will also explore the avenues available for SMEs from other non-pharmaceutical sectors such as IT, medical devices and nutrition to become more involved in IMI activities and projects.

The impact of these activities can be measured through dedicated SME key performance indicators (KPIs).

External collaborations

Clinical Data Interchange Standards Consortium (CDISC)

In 2016 the memorandum of understanding between IMI and CDISC and IMI's membership of CDISC were renewed, so the collaboration focused on providing information on the implementation of data standards and training in this area will be continued. In particular webinars and when necessary face-to-face trainings will be provided by CDISC staff to IMI projects. It is expected that further activities will be explored to ensure that all IMI projects have access to the benefits of IMI membership. In addition, IMI will continue to participate in the Scientific Advisory Committee of the Coalition For Accelerating Standards and Therapies (CFAST).

C-PATH Institute

IMI will continue to collaborate with C-Path Institute to explore synergies and seek alignment of respective activities with the aim of avoiding duplication of efforts in programmes, particularly in areas of common interest, to advance regulatory science and leverage global biopharmaceutical development, as well as, in specific research areas between IMI & C-Path projects.

Collaboration will have a continued focus on the data standard space with a view to ensuring consistent remapping of respective data sets to enable leveraging the data on both sides. There will be regular exchange of information on topics under development and the results of ongoing projects
Interaction in the coming year will be on enabling a collaborative relationship in paediatrics particularly between the C-Path Global Paediatric Clinical Trials Consortium and the IMI 2 project resulting from a topic launched as part of IMI2 JU Call 10. Furthermore, collaboration in the area of neuroscience and tuberculosis and Type 1 diabetes will continue in 2017. It is envisaged that a Joint IMI and C-PATH face-to-face meeting will be organised in Q3 or Q4 of the coming year.

NIH Institutes and Foundation for NIH (FNIH)

Collaboration will continue between the IMI EU-AIMS project and FNIH Biomarkers Consortium's Autism Initiative to align the two initiatives and achieve harmonized biomarkers qualification by EMA and FDA as well as link biobanking and clinical research initiatives.

In addition opportunities will be explored to align the IMI initiatives in areas such as diabetes and neurodegeneration with parallel initiatives launched as part of Accelerated Medicines Platform (AMP).

The Global CEO initiative for Alzheimer's Disease and the UK Dementia Platform

Collaboration will be continued between the global CEO initiative for Alzheimer's Disease, the medical Research Council-UK Dementia Platform (DPUK) and the IMI Platform for Alzheimer's Disease based upon the Global Alzheimer's Platform (GAP).

Key to facilitating this collaboration will be the organisation of a joint meeting at a major international Alzheimer's conference (AAIC, CTAD or AD/PD) to align planned activities and monitor the implementation of aligned activities in GAP and the IMI project EPAD as well as related actions generated under IMI2 JU.

IMI2 JU will continue to contribute to activities developed as part of the Global Action against Dementia (https://worlddementiacouncil.wordpress.com/) of the World Dementia Council.

Cross project interactions

In order to share best practice between the projects and develop potential synergies a series of cross project meetings will be organised for both IMI funded and other initiatives. Cross project interactions are planned for but not restricted to the following areas:

Neurodegeneration - activities will be organised to facilitate links between projects in the portfolio of neurodegenerative diseases. In particular a cross meeting of actions under the IMI Alzheimer's Platform from IMI (AETIONOMY, EMIF AD, EPAD) and IMI 2 (project from IMI2 JU C3, C5 and C6) including a session with other related EU and national projects (HBP, JPND, DZNE, DPUK) where patients and regulators are invited

Psychiatry – a cross project meeting for IMI1 JU and IMI2 JU projects in neuropsychiatry EU-AIMS (IMI) PRISM and RADAR-CNS (IMI2) will be held including a session with other related National and EU projects where patients are invited.

A cross project meeting is planned for projects in the Ebola programmes aiming to foster collaboration and promote the sharing of information and knowledge in a joint repository. The meeting will also be an opportunity to introduce the new projects launched under IMI2 JU Call 8 and facilitate their integration with the existing Ebola programme projects.

New sectors and priority areas

Several new priority disease areas have emerged since the start of IMI2 and efforts are required to ensure that topics brought forward under IMI are aligned with ongoing international initiatives in these areas and societal needs. Therefore, a number of workshops will be organised in the coming year to further develop topic ideas and other activities. A cross SGG workshop on the microbiome will be organised in May 2017. This workshop will explore the possible development of an IMI programme/topic in this area to be included in the AWP 2018. It is expected that another of these workshops will explore a potential new topic under IMI2 to demonstrate the value of diagnostics for the optimal use of antimicrobials and healthcare resources.

It is also planned to have at least one workshop dedicated to new sectors such as nutrition/ ICT/ imaging and another in oncology/advanced therapies where discussions have already started but the strategy requires refinement.

2.2.7 Dissemination and information about projects results

Although the first and foremost responsibility of maximising the impact of their own research and innovation lies with the project consortium, promoting the successes of IMI projects is a core element of both the IMI2 JU Communications and Dissemination Strategies.

The IMI2 Programme Office identifies results and successes in a variety of ways, including through formal routes (project periodic reports, interim reviews) and informal routes (direct contacts with project participants, monitoring of project websites and social media, etc.). IMI2 JU will continue to support and supplement the dissemination of projects' public deliverables via a variety of channels, including the IMI2 JU website, newsletter, social media (Twitter and LinkedIn), the press, and events. In addition, IMI2 JU will investigate how to make better use of EU specific dissemination channels (e.g. CORDIS, Futuris, Horizon Magazine, and the Enterprise Europe Network (EEN)) and will promote projects through them. In addition, following on from a pilot study performed in 2016 on the impact of IMI2 JU projects on the 3Rs (i.e. the replacement, reduction and refinement of animal use in research), IMI2 JU will undertake a more detailed analysis in 2017 of the contribution of project results to this specific area.

As mentioned above, 24 projects from the first IMI1 Calls will reach their project end date with 17 of these submitting their final reports in 2017. In addition, 5 projects that reached their project end date in 2016 are also expected to submit their reports in 2017 Capturing the outcomes and impacts of these projects presents IMI2 JU with a new challenge. To address it, two new actions will be pursued:

It is expected that up to 21 close-out meetings will be organised around the time of the final report submission. The close out meeting provides an opportunity for the consortium to present to the IMI2 Programme Office how the project has reached its objectives, to highlight tangible results and to put the achievements of the project into context and to discuss the potential impact and legacy management. Part of this objective is to provide the IMI communications unit with the main achievements and impacts of the project in order to facilitate further IMI2 JU dissemination via the channels described above. In addition, members of EFPIA, the EC, IMI2 JU Scientific Committee and relevant SGG will be invited to attend the close out meetings to share not only in the results but also in the learnings and experiences of the project consortia.

IMI2 JU will actively participate in the R&I Family tender for tracking research outcomes, which will have the aim of monitoring projects' outcomes for up to five years after their completion, as several studies have demonstrated that at least 40% of projects outcome are generated during this period.

Lastly, IMI2 JU will continue to fulfil its role/obligation to look after policy conformity, effectiveness and efficiency of the dissemination and exploitation at the level of each project.

2.2.8 Socio-economic impact study

The original IMI socio-economic impact study was described and set up under the AWP 2015 and reported in 2016. The objective of this first socio-economic evaluation was to identify and report on the socio-economic impacts of project outputs from IMI 1's completed or nearly-completed 2008 and 2009 Calls. The evaluation aimed to connect the scientific and technology outputs already identified and previously reported with the longer-term, downstream impact measures of the type of healthcare ecosystem innovation that IMI activities represent. The evaluation was carried out by the IMI2 JU with the assistance of independent external experts. One of the key aims of this study was to establish a methodology for identifying and measuring this type of impact of completed IMI projects.

The planned study will utilise this developed methodology and apply it to the next wave of IMI1 JU projects that have completed or are drawing to a close. As with the original study the new evaluation will look at short-term outcomes (2-3 years) such as improved scientific quality, enhanced knowledge production, network-based R&D capacity building, and human resources development. It will also consider mid-term impacts (4-5 years) and longer term outcomes, known as 'wealth and health' benefits. Mid-term impacts indicators will include concrete results on biomarker validation/toxicology test, big data and shared IT infrastructures, improved knowledge transfer and communication. This study is necessary in order to enhance our performance evaluation framework which is currently under review.

As the majority of the initial expert panel's efforts went into developing the methodology and the intention is to continue to use that methodology, IMI2 will use one expert rather than a panel to analyse data collected from the projects by the IMI2 programme office. The final report will be ready for publication by the end of 2018 and will be disseminated to all stakeholders, including policy makers at the European level. It is expected that this study will cost approximatively 20.000 EUR.

2.3 Call management rules

All proposals must conform to the conditions set out in the H2020 Rules for Participation (http://ec.europa.eu/research/participants/data/ref/h2020/legal_basis/rules_participation/h2020-rules-participation_en.pdf and the Commission Delegated Regulation with regard to IMI2 JU http://eur-lex.europa.eu/legal-content/EN/TXT/PDF/?uri=CELEX:32014R0622&from=EN.

The following general conditions shall apply to the IMI2 JU Calls for Proposals:

LIST OF COUNTRIES AND APPLICABLE RULES FOR FUNDING

By way of derogation[26] from Article 10(1) of Regulation (EU) No 1290/2013, only the following participants shall be eligible for funding from the Innovative Medicines Initiative 2 Joint Undertaking:

(a) legal entities established in a Member State or an associated country, or created under Union law; and

(b) which fall within one of the following categories:

(i) micro, small and medium-sized enterprises and other companies with an annual turnover of EUR 500 million or less, the latter not being affiliated entities of companies with an annual turnover of more than 500 million; the definition of 'affiliated entities' within the meaning of Article 2(1)(2) of Regulation (EU) No 1290/2013 shall apply *mutatis mutandis*;

(ii) secondary and higher education establishments;

(iii) non-profit organisations, including those carrying out research or technological development as one of their main objectives or those that are patient organisations.

(c) the Joint Research Centre;

(d) international European interest organisations.

Participating legal entities listed in (b) above established in a third country may receive funding from the IMI 2 JU provided their participation is deemed essential for carrying out the action by the IMI 2 JU or when such funding is provided for under a bilateral scientific and technological agreement or any other arrangement between the Union and the country in which the legal entity is established[27].

STANDARD ADMISSIBILITY CONDITIONS AND RELATED REQUIREMENTS

Part B of the General Annexes to the Horizon 2020 -Work Programme 2016– 2017[28] shall apply mutatis mutandis for the actions covered by this Work Plan.

In addition, page limits will apply to proposals as follows:

At stage 1 of a two-stage call, the limit for RIA/IA short proposals is 30 pages and for CSA short proposals is 20 pages.

For a single stage call, as well as at stage 2 of a two-stage call, the limit for RIA/IA full proposals is 70 pages and for CSA full proposals is 50 pages.

ELIGIBILITY CONDITIONS

Part C of the General Annexes to the Horizon 2020 - Work Programme 2016– 2017 shall apply mutatis mutandis for the actions covered by this Work Plan.

In addition, under all two-stage submission procedures the following additional condition applies:

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[26] Pursuant to the Commission Delegated Regulation (EU) No 622/2014 of 14 February 2014 establishing a derogation from Regulation (EU) No 1290/2013 of the European Parliament and of the Council laying down the rules for participation and dissemination in 'Horizon 2020 — the Framework Programme for Research and Innovation (2014-2020)' with regard to the Innovative Medicines Initiative 2 Joint Undertaking

[27] In accordance with Article 10(2) of the Regulation (EU) No 1290/2013 and Article 1 of Commission Delegated Regulation (EU) No 622/2014

[28] http://ec.europa.eu/research/participants/data/ref/h2020/other/wp/2016-2017/annexes/h2020-wp1617-annex-ga_en.pdf

The participants from EFPIA constituent entities and affiliated entities and other Associated Partners which are pre-defined in the topics - under the section 'Industry consortium' - of a call for proposals do not apply at the stage 1 of the call. The applicant consortium selected from the stage 1 of the Call for Proposals is merged at the stage 2 with the EFPIA constituent entities or their affiliated entities and other Associated Partners.[29]

TYPES OF ACTION: SPECIFIC PROVISIONS AND FUNDING RATES

Part D of the General Annexes to the Horizon 2020 - Work Programme 2016– 2017 shall apply mutatis mutandis for the actions covered by this Work Plan.

TECHNOLOGY READINESS LEVELS (TRL)

Part G of the General Annexes to Horizon 2020 - Work Programme 2016–2017 shall apply mutatis mutandis for the actions covered by this Work Plan.

EVALUATION RULES

Part H of the General Annexes to the Horizon 2020 - Work Programme 2016– 2017 shall apply *mutatis mutandis* for the actions covered by this Work Plan with the following additions:

The relevant call texts launched under this Work Plan must specify whether the Call for proposals is a single-stage or two-stage Call, and the predefined submission deadline.

Award criteria and scores:

Experts will evaluate the proposals on the basis of criteria of "Excellence", "Impact" and "Quality and efficiency of the implementation" according to the submission stage and type of action, as follows:

Type of action	Excellence	Impact	Quality and efficiency of the implementation*
RIA and IA **1st stage** **evaluation**	The following aspects will be taken into account, to the extent that the proposed work corresponds to the topic description in the call for proposals and referred to in the IMI2 annual work plan: Clarity and pertinence of the proposal to meet all key objectives of the topic; Credibility of the proposed approach; Soundness of the concept, including trans-disciplinary considerations, where relevant;	The following aspects will be taken into account, to the extent to which the outputs of the project should contribute at the European and/or International level: The expected impacts of the proposed approach as mentioned in the call for proposals Added value from the public private partnership approach on R&D, regulatory, clinical and healthcare practice as relevant; Strengthening the competitiveness and industrial leadership and/or addressing specific societal challenges;	The following aspects will be taken into account: Coherence and effectiveness of the outline of the project work plan, including appropriateness of the roles and allocation of tasks, resources, timelines and approximate budget; Complementarity of the participants within the consortium (where relevant) and strategy to create a successful partnership with the industry consortium as mentioned in the topic description in the Call for proposal;

[29] Article 9(5) of the Regulation (EU) No 1290/2013 of the European Parliament and of the Council of 11 December 2013 laying down the rules for participation and dissemination in "Horizon 2020"

Type of action	Excellence	Impact	Quality and efficiency of the implementation*
	Extent that proposed work is ambitious, has innovation potential, and is beyond the state of the art; Mobilisation of the necessary expertise to achieve the objectives of the topic, ensure engagement of all relevant key stakeholders	Improving European citizens' health and wellbeing and contribute to the IMI2 objectives[30].	Appropriateness of the proposed management structures and procedures, including manageability of the consortium.
RIA and IA **Single stage, and 2nd stage** **evaluation**	The following aspects will be taken into account, to the extent that the proposed work corresponds to the topic description in the call for proposals and referred to in the IMI2 annual work plan and is consistent with the stage 1 proposal: Clarity and pertinence of the proposal to meet all key objectives of the topic; Credibility of the proposed approach; Soundness of the concept, including trans-disciplinary considerations, where relevant; Extent that proposed work is ambitious, has innovation potential, and is beyond the state of the art; Mobilisation of the necessary expertise to achieve the objectives of the topic, ensure engagement of all relevant key stakeholders.	The following aspects will be taken into account, to the extent to which the outputs of the project should contribute at the European and/or International level: The expected impacts of the proposed approach as mentioned in the call for proposals; Added value from the public private partnership approach on R&D, regulatory, clinical and healthcare practice as relevant; Enhancing innovation capacity and integration of new knowledge; Strengthening the competitiveness and industrial leadership and/or addressing specific societal challenges; Improving European citizens' health and wellbeing and contribute to the IMI2 objectives;[30] Any other environmental and socially important impacts; Effectiveness of the proposed measures to exploit and disseminate the project results (including management of IPR), to communicate the project, and to manage research data where relevant.	The following aspects will be taken into account: Coherence and effectiveness of the project work plan, including appropriateness of the roles and allocation of tasks, resources, timelines and budget; Complementarity of the participants within the consortium (where relevant); Clearly defined contribution to the project plan of the industrial partners (where relevant); Appropriateness of the management structures and procedures, including manageability of the consortium, risk and innovation management and sustainability plan.

30 Article 2 of the Council Regulation (EU) No 557/2014 of 6 May 2014 establishing the Innovative Medicines Initiative 2 Joint Undertaking (O.J. L169 of 7.6.2014)

Type of action	Excellence	Impact	Quality and efficiency of the implementation*
CSA **1st stage** **evaluation**	The following aspects will be taken into account, to the extent that the proposed work corresponds to the topic description in the Call for proposal and referred to in the IMI2 annual work plan: Clarity and pertinence of the proposal to meet all key objectives of the topic Credibility of the proposed approach; Soundness of the concept, including trans-disciplinary considerations, where relevant; Quality of the proposed coordination and/or support measures. Mobilisation of the necessary expertise to achieve the objectives of the topic, ensure engagement of all relevant key stakeholders.	The following aspects will be taken into account, to the extent to which the outputs of the project should contribute at the European and/or International level: The expected impacts of the proposed approach as mentioned in the Call for proposal; Added value from the public private partnership approach on R&D, regulatory, clinical and healthcare practice as relevant. Strengthening the competitiveness and industrial leadership and/or addressing specific societal challenges; Improving European citizens' health and wellbeing and contribute to the IMI2 objectives[31].	The following aspects will be taken into account: Coherence and effectiveness of the outline of the project work plan, including appropriateness of the roles and allocation of tasks, resources, timelines and approximate budget; Complementarity of the participants within the consortium (where relevant) and strategy to create a successful partnership with the industry consortium as mentioned in the topic description in the Call for proposal. Appropriateness of the proposed management structures and procedures, including manageability of the consortium.
CSA **Single stage and 2nd stage** **evaluation**	The following aspects will be taken into account, to the extent that the proposed work corresponds to the topic description in the Call for proposal and referred to in the IMI2 annual work plan and is consistent with the stage 1 proposal: Clarity and pertinence of the proposal to meet all key objectives of the topic;	The following aspects will be taken into account, to the extent to which the outputs of the project should contribute at the European and/or International level: The expected impacts of the proposed approach as mentioned in the Call for proposal; Added value from the public private partnership approach on R&D, regulatory, clinical and health care practice as relevant	The following aspects will be taken into account: Coherence and effectiveness of the project work plan, including appropriateness of the roles and allocation of tasks, resources, timelines and budget; Complementarity of the participants within the consortium (where relevant);

[31] Article 2 of the Council Regulation (EU) No 557/2014 of 6 May 2014 establishing the Innovative Medicines Initiative 2 Joint Undertaking (O.J. L169 of 7.6.2014)

Type of action	Excellence	Impact	Quality and efficiency of the implementation*
	Credibility of the proposed approach; Soundness of the concept, including trans-disciplinary considerations, where relevant; Quality of the proposed coordination and/or support measures. Mobilisation of the necessary expertise to achieve the objectives of the topic and to ensure engagement of all relevant key stakeholders.	Strengthening the competitiveness and industrial leadership and/or addressing specific societal challenges; Improving European citizens' health and wellbeing and contribute to the IMI2 objectives[32]. Effectiveness of the proposed measures to exploit and disseminate the project results (including management of IPR), to communicate the project, and to manage research data where relevant.	Clearly defined contribution to the project plan of the industrial partners (where relevant); Appropriateness of the management structures and procedures, including manageability of the consortium, risk and innovation management and sustainability plan.

* In a single-stage, or in the second-stage of a two-stage evaluation procedure, experts will also be asked to assess the operational capacity of applicants to carry out the proposed work.

The scheme above is applicable to a proposal in a single-stage submission procedure, as well as in a two-stage submission procedure. At each evaluation stage of the two-stage submission procedure, the relevant evaluation criteria and threshold apply.

These evaluation criteria include scores and thresholds. Evaluation scores will be awarded for the criteria, and not for the different aspects listed in the above table. For all evaluated proposals, each criterion will be scored out of 5. Half marks may be given.

For the evaluation of first-stage proposals under a two-stage submission procedure, the threshold for each one of the two first criteria ('excellence' and 'impact') will be 3. There is no overall threshold. For the evaluation of second-stage proposals under a two-stage submission procedure; the threshold for individual criteria will be 3. The overall threshold, applying to the sum of the three individual scores, will be 10. For the evaluation of proposals under a single-stage submission procedure, the threshold for individual criteria is 3. The overall threshold, applying to the sum of the three individual scores, is 10.

Following each evaluation stage, applicants will receive an ESR (Evaluation Summary Report) regarding the respective evaluated proposal.

The full evaluation procedure is described in the IMI2 JU Manual for submission, evaluation and grant award in line with the H2020 Rules for Participation.[33]

Where appropriate and duly justified, IMI 2 JU calls for proposals may follow a two-stage process.

[32] Article 2 of the Council Regulation (EU) No 557/2014 of 6 May 2014 establishing the Innovative Medicines Initiative 2 Joint Undertaking (O.J. L169 of 7.6.2014)

[33] http://www.imi.europa.eu/apply-funding/call-documents/imi2-call-documents#imi2-call-documents-collapsible-1 *[link to be updated after GB approval]*

Under the single-stage evaluation process, evaluated proposals will be ranked in one single list. The best-ranked proposals, in the framework of the available budget, will be invited to prepare a Grant Agreement.

Under the two-stage evaluation procedure, and on the basis of the outcome of the first stage evaluation, the applicant consortium of the highest ranked short proposal[34] (first stage) for each topic[35] will be invited to discuss with the relevant industry consortium the feasibility of jointly developing a full proposal (second stage). Under the second stage preparation process, the applicant consortia of the second and third-ranked short proposals (first stage) for each topic may be invited for preliminary discussions with the industry consortium if the preliminary discussions with the first ranked proposal and the industry consortium fail. In such a case, the first applicant consortium and the industry consortium shall be responsible for jointly notifying the IMI2 JU if the preparation of a joint full proposal is not feasible. This notification must be accompanied by a joint report clearly stating the reasons why a joint full proposal is considered not feasible. Upon acknowledgement and after consideration of the specific circumstances, the IMI2 JU may decide to invite the next-ranked applicant consortium in priority order, i.e. the second ranked proposal is contacted only after failure of preliminary discussions with the first ranked, and the third ranked after the second ranked.

Under the two-stage evaluation procedure, contacts or discussions about a given topic between potential applicant consortia (or any of their members) and any member of the relevant industry consortium are prohibited throughout the procedure until the results of the first stage evaluation are communicated to the applicants.

As part of the panel deliberations, the IMI2 JU may organise hearings with the applicants to:

- clarify the proposals and help the panel establish their final assessment and scores, or
- improve the experts' understanding of the proposal.

INDICATIVE TIMETABLE FOR EVALUATION AND GRANT AGREEMENT

	Information on the outcome of the evaluation (single stage, or first stage of a two-stages)	Information on the outcome of the evaluation (second stage of a two stages)	Indicative date for the signing of grant agreement
Single-stage	Maximum 5 months from the submission deadline at the single stage.	N/A	Maximum 8 months from the submission deadline.
Two-stages	Maximum 5 months from the submission deadline at the first stage.	Maximum 5 months from the submission deadline at the second stage.	Maximum 8 months from the submission deadline at the second stage.

BUDGET FLEXIBILITY

Part I of the General Annexes to the Horizon 2020 - Work Programme 2016–2017 shall apply mutatis mutandis for the actions covered by this Work Plan.

ACTIONS INVOLVING FINANCIAL SUPPORT TO THIRD PARTIES

[34] Under exceptional circumstances, and subject to objective criteria based on grounds which could not be reasonably expected to be known by the evaluation panel, the IMI2 JU Governing Board may decide by motivated decision to invite the next-ranked applicant consortium in priority order.

[35] In cases clearly identified in the relevant call for proposals where a given topic is composed of two or more sub-topics, one short proposal per sub-topic will be invited

Part K of the General Annexes to the Horizon 2020 - Work Programme 2016–2017 shall apply mutatis mutandis for the actions selected under topics covered by this Work Plan.

CONDITIONS RELATED TO OPEN ACCESS TO RESEARCH DATA

Part L of the General Annexes to the Horizon 2020 - Work Programme 2016–2017 shall apply mutatis mutandis for the actions covered by this Work Plan.

However, should a project "opt-out" of these provisions, a Data Management Plan must still be prepared. Guidelines for the Data Management Plan including a template are available on the H2020 Participant portal.[36]

SUBMISSION TOOL

Proposals in response to a topic of the IMI2 JU Call for proposals must be submitted on-line, before the call deadline, by the coordinator via the Electronic Submission Service of the Participant Portal:

http://ec.europa.eu/research/participants/portal/desktop/en/home.html

No other means of submission will be accepted.

OTHERS

For proposals including clinical trials/studies/investigations, a specific template to help applicants to provide essential information on clinical studies in a standardised format is available under:

http://www.imi.europa.eu/sites/default/files/uploads/documents/IMI2_CallDocs/ClinicalTrialInfoTemplateIMI_v201602.docx.

In the first stage of a two-stage evaluation procedure, this template should not be submitted. However, applicants may integrate relevant aspects of this information in their short proposal (within the page limit). In the second stage of two-stage evaluation procedure involving clinical studies, the use of this template is mandatory in order to provide experts with the necessary information to evaluate the proposals. The template may be submitted as a separate document.

Ethical issues should be duly addressed in each submitted proposal to ensure that the proposed activities comply with ethical principles and relevant national, Union and international legislation. Any proposal that contravenes ethical principles or which does not fulfil the conditions set out in the H2020 Rules for Participation, or in the Annual Work Plan shall not be selected. [37]

In order to ensure excellence in data and knowledge management consortia will be requested to Disseminate scientific publications on the basis of open access[38] (see "Guidelines on Open Access to Scientific Publications and Research Data in Horizon 2020").

Full proposals must contain a draft plan for the exploitation and dissemination of the results.

Applicants intending to submit a proposal in response to the IMI2 JU Calls should also read the topic text, the IMI2 JU Manual for submission, evaluation and grant award, and other relevant documents[39] (e.g. IMI2 JU model Grant Agreement).

CONSORTIUM AGREEMENTS

[36] Additional information and guidance are also available at: https://www.openaire.eu/what-is-the-open-research-data-pilot

[37] Article 19 of Horizon 2020 Framework Programme, and Articles 13 and 14 of the Horizon 2020 Rules for Participation.

[38] Article 43.2 of Regulation (EU) No 1290/2013 of the European Parliament and of the Council laying down the rules for participation and dissemination in "Horizon 2020 - the Framework Programme for Research and Innovation (2014-2020)" and repealing Regulation (EC) No 1906/2006

[39] http://www.imi.europa.eu/content/documents#calls_for_proposals_-_imi_2_programme

In line with the Rules for Participation and Dissemination applicable to IMI2 actions[40] and the IMI2 model grant agreement, participants in IMI2 actions are required to conclude a consortium agreement prior to grant agreement.

[40] Regulation (EU) No 1290/2013 of 11 December 2013 and Commission Delegated Regulation (EU) No 622/2014 of 14 February 2014.

2.4 Support to Operations

2.4.1 Communication and events

Communication objectives

The Communication team will continue to focus on attracting the best researchers from relevant target groups to apply for funding under IMI 2 Calls for proposals and to promote networking between the different target groups. It will do so by outreaching directly to potential applicants (mainly through webinars, the IMI website, the IMI newsletter and social media, workshops and events) and by mobilising multipliers and ambassadors (e.g. providing support and participate in info days in Member States, provide training, info and material to SRG, SC and other multipliers).

After 8 years of the first IMI call launch, the first projects are drawing to a close providing unique results that will allow IMI to demonstrate how IMI projects are delivering excellent science that is already having a real impact on the way medicines are developed. Therefore, in the context of IMI's mid-term evaluation, the IMI Communication and External Relations Strategy for 2017 will concentrate on raising the awareness levels and perception of IMI's added value among all target groups, with a particular focus on policymakers and opinion leaders, patients, SMEs, and other industries.

Communication support to IMI stakeholder strategies: patients and SMEs

As the IMI patient strategy keeps evolving with patients and carers reaching new ways of meaningful involvement in IMI projects, the Communications team will continue to support awareness-raising activities and to encourage patients to get involved in both IMI's projects and its broader activities.

Under IMI2, in line with Horizon 2020, IMI2 JU will be expected to ensure 20% of its budget goes to SMEs. Yet IMI is competing with other funding programmes to attract SME participation, some of them SME tailored. The Communications team will focus on a comprehensive outreach and support strategy by (i) improving communication on IMI through SRGs/regional contact points/clusters, (ii) by participating in partnering events and investor conferences and (iii) by designing specific tools for SMEs, such as a comprehensive dedicated webpage in the revamped IMI webpage or a toolkit on IPR specifically developed for SMEs.

Redesign the IMI website

The current IMI website was launched in autumn 2010. Although the information in it is up to date and the number of visitors continues to rise, IMI has evolved and outgrown the motivations behind the current website.

Following suggestions from a survey among our main stakeholders and IMI's 2017 communication objectives, the revamped website will be designed following three main drivers: (i) it will be tailored to IMI's different stakeholders, (ii) it will give a stronger voice to our projects, and (iii) it will be more visual.

Further develop IMI success stories

The incorporation of a writer to the communications team in 2016 will allow IMI to reinforce contacts with its projects to ensure a steady flow of success stories that will be used to illustrate IMI's key messages through the different communication channels.

Increase synergies with regional research and innovation activities

Even though IMI funds are granted on the sole criterion of scientific excellence, IMI can contribute to regional strategies by providing a rich collaborative environment where open innovation can flourish. During 2017, regional events will be fostered in order to raise awareness on IMI among potential participants, but also to strengthen national and regional support to excellent scientist and SMEs, in particular among those countries with a lower participation in IMI.

Media outreach

In recent years, IMI has enjoyed increased positive visibility in key general and specialist media. In 2017, IMI will work to ensure this trend continues by maintaining links with key journalists, issuing regular press releases, organising press interviews, and inviting media to IMI events.

As described above, one of the four critical risks identified at corporate level is the generation of a negative external perception of IMI2 JU's added value and the publication of inaccurate comments in the press and other public fora. As a consequence, the Programme Office will remain alert to issues that could damage IMI's reputation, and respond accordingly by proactively reaching out to opinion leaders, for example by preparing briefings or sets of questions and answers.

Communication channels

IMI will continue to develop the following channels in support of its communication goals:

- Events (both IMI and external);
- Website;
- Newsletter;
- Social media (LinkedIn, Twitter);

Multipliers: IMI founding members / Governing Board, members of advisory bodies (States Representatives Group, Scientific Committee), National Contact Points, relevant scientific, patient, business umbrella groups / associations, IMI projects, organisations partnered by IMI, e.g. through a Memorandum of Understanding;

- Media (general and specialist, mainly in Europe but also international);
- Direct mailings;
- Publications;
- Videos;
- Direct contacts with opinion leaders.

Preparation of IMI 10th anniversary

In 2018, IMI will celebrate its 10th birthday, and this will represent an excellent opportunity to showcase what IMI has achieved in that time (and its plans for the future) through a year-long programme of events and activities. Due to the timelines involved the communications team will have to start planning and organising these activities in 2017.

Events planned in 2017

Activity	Timeline
Promote Calls for proposals (webinars, info-days, website, etc.)	all year round
Create IMI new website	Q2, Q3
Promote projects	all year round
IMI presence at relevant large conferences: BIO, PSWC2017, BioVision, BIOEurope	Q2 and Q4
IMI presence in the European Parliament	Ongoing activity
IMI Stakeholder Forum 2017, including a Patient's Engagement Session	18-19 October

2.4.2 Procurement and contracts

In order to reach its objectives and adequately support its operations and infrastructures, IMI2 JU will allocate funds to procure the necessary services and supplies. To make tender and contract management as effective and cost-efficient as possible, IMI2 JU makes use as much as possible of multi-annual framework contracts and EU inter-institutional tenders. Most essential framework contracts IMI is currently using will be running beyond 2017.

The framework contract for the provision of meeting and event facilities and the framework contract for audio-visual technology and related support services expired in 2016. New tender procedures for framework contracts will be launched at the beginning of 2017.

Additionally, IMI will launch a low-value procedure to procure the necessary services for implementing its communication activities. This concerns in particular the creation of a short corporate video on IMI for dissemination via the internet, social media, events and other relevant channels.

IMI2 JU is planning to cover other needs for communication activities (event organisation support, graphic design, printing services) through the use of inter-institutional procurement procedures or service level agreements.

IMI2 JU will earmark a total budgetary envelope of EUR 1 335 000 for procurement needs in 2017. The table below provides a summary of the tenders planned for 2017 and related procurement procedure expected to be used, the estimated budget and expected timing for publication.

IMI2 JU is planning an important refurbishment of its premises inter-alia to accommodate new staff.

Subject	Expected procedure	Estimated total amount (EUR)	Indicative timing of publication
Meeting and event facilities	Multiannual Framework Contract (FWC)	1 000 000	Q3-4
Meeting premises for Stakeholder Forum 2017	Middle-value single contract	100 000	Q2
Meeting premises for evaluation of Call 10, 11, 12	Middle-value single contract	60 000	Q1-Q2
Rental of audio-visual technology and related support services	Middle-value single FWC	125 000	Q3-4
IMI office refurbishment	Middle-value single contract	Up to 130 000	Q3
Total		**1 465 000**	

2.4.3 IT and logistics

The IMI information and communications technologies (ICT) strategic objective is to deliver value to the business and to be a key enabler of new business initiatives with the goal of supporting and shaping the present and future of IMI. Operations and administration information systems and infrastructure aim at making all IMI processes simpler and more efficient.

A strong element in achieving this goal will be the use of the full suite of Horizon 2020 IT tools (SEP, EMI, SyGMa/COMPASS) for the management of IMI2 JU operations, from the launch of calls for proposals and selection of evaluation experts, to the follow-up of the grants. The transition to H2020 IT tools started in December 2016 with the launch of the IMI2 JU Call 10 in SEP (Submission & Evaluation of Proposals) and will continue with the gradual transfer of existing IMI2 JU grants from Calls 1 to 9 to SyGMa (Q1-Q3 2017). It will be completed with the transfer to SyGMa of the winning proposals of Call 10 in Q3/4 2017. In addition, all IMI2 data that currently exist in SOFIA will be transferred automatically to CORDA.

In order to achieve the aforementioned goal, IMI IT will focus its 2017 activities on three main areas:

i. business operations information systems,
ii. collaboration, communication and administration management information systems and
iii. infrastructure, security and office automation support.

2.4.3.1 Business operations information systems

In order to support IMI core business two applications have been until now available to end-users and IMI staff and stakeholders; the Submission of Information Application (SOFIA) tool for the management of IMI calls, projects and related processes, and Qlikview, which is a reporting tool with a variety of tailor-made dashboards, enabling the analysis of scientific and financial data regarding IMI calls and project.

In 2016, IMI started using European Commission's IT tools related to Horizon 2020, such as SEP, EMI, COMPASS and SyGMA. Although the maintenance and new developments of the IT tools related to H2020 fall under the responsibility of European Commission, since IMI1 projects will continue running until at least 2021, the following developments are foreseen for the SOFIA application:

- Enhancement of the application regarding performance, usability and user interface in order to improve the end-user experience and facilitate IMI staff work (Q1 – Q4 2017)
- Maintenance (continuous) of the application with helpdesk support, bug fixes and implementation of service requests (Q1 – Q4 2017)

Moreover, in order for IMI to be fully operational regarding IMI2 JU projects, the following developments are necessary:

- Extraction of IMI2 JU data from SEP and CORDA and other potentially sources and import to Qlikview, which is expected to take place in Q1-Q2 2017
- With the migration to H2020 IT Tools, the EFPIA Operations reporting views in SOFIA will no longer contain accurate data. Therefore, the particular views will be implemented in QlikView. Although this development already started in Q4 2016, it is expected to be completed in Q1 2017 with the migration of QlikView application to a dedicated server and the purchase of additional QlikView licenses to cover the needs of EFPIA operations
- Addition of QlikView reports based on the needs of external groups, for example SRG, and internal stakeholders, and improvement of currently available dashboards (Q1 – Q4 2017)

2.4.3.2 Collaboration, communication and administration management information systems

IMI has well established collaborative platforms to provide support to the governance bodies, namely the Governing Board, the Scientific Committee, the States Representatives Group and the Strategic Governing Groups. These platforms will be maintained and updated both from a content and operations point of view.

Furthermore, IMI uses a number of web-based applications related to human resources management, time management, mission management, document management, incident management and internal communications. Alongside other Joint Undertakings, IMI2 JU will investigate the possibility to access and use

European Commission related applications, in case those provide enhanced functionalities compared to those in place.

The following developments are foreseen in 2017 in order to safeguard the continuous improvement and increase of scope of the afore-mentioned systems:

- Enhancement of the applications regarding performance, usability and user interface in order to improve the end-user experience and facilitate IMI staff work (Q1 – Q4 2017)
- Maintenance (continuous) of the applications with helpdesk support, bug fixes and implementation of service requests (Q1 – Q4 2017)
- Reengineering of IMI's website in order to use up-to-date technologies, which are expected to improve the interaction with the site, potentially reduce the need for custom-made software components and increase security. This project, with the close collaboration of IMI's Communication team, started in 2016 with the gathering and analysis of the business requirements and it is expected to be completed in 2017 (Q3/4 2017)
- Assessment of the practicality of the current document repository application to support the automation of IMI's administrative processes compared to commercial off-the-shelf products with applied workflows. This initiative is driven by the concept of a paperless office, towards which IMI would like to move in 2018 (Q4 2017).

2.4.3.3 Infrastructure, security and office automation support

IMI shares IT infrastructure, related IT operations and office automation support with other JUs that are also located in the same premises. In the context of the common infrastructure the following activities are foreseen for 2017, which are expected to provide with efficiency gains in the operation of the organisation:

- Replacement of the end of life of currently used hardware of common data centre, based on the strategy and architecture related to common IT infrastructure study that was concluded in 2016 (Q2 – Q3 2017)
- Maintenance (continuous) of the common infrastructure and networks and end-user office-automation support covering incidents, service requests and improvements (Q1 – Q4 2017)
- Migration of IMI's laptops to Windows 10 and Office 2016 (Q2/3 2017)

Moreover, IMI utilises an online infrastructure in order to host its business operations information systems, and the collaboration, communication and administration information systems mentioned above. The following activities are anticipated to take place in 2017 in the context of the dedicated infrastructure:

- A cyber-capability security assessment took place in Q4 2016. The proposed actions necessary for the improvement of IMI's cloud cyber-security will be implemented in 2017 (Q1-Q2 2017)
- Maintenance (continuous) of the online infrastructure (Q1 – Q4 2017).

2.4.4 Human Ressources

The 2017 objective for HR shall be: recruit, train, assess, motivate and retain highly qualified staff with a view to ensure effective and efficient operation of the JU as well as ensuring equal opportunities. This objective will be implemented through four main themes:

Staffing

The staffing needs of IMI2 JU will be addressed in line with the growth projection set out in IMI2 JU Legislative Financial Statement, as well as the Governing Board decision amending the Staff Establishment Plan (of 10 November 2016, reference IMI2-GB-DEC-2016-27), which altogether foresee a total staff level of 54 people (temporary and contract agents) by the end of 2017. The additional two posts already foreseen in IMI multiannual staff plan will be assigned to reinforce project management tasks, given the sharp increase in volume of work, with IMI2 JU project portfolio to grow from 75 to more than 100 projects by early 2018.

In addition, two seconded national experts will be recruited to provide expertise to the IMI2 JU. This is aimed at bringing specific expertise where there may be a gap and to help with a strategy around regional clusters in health innovation in Europe where IMI2 JU may play an important role in future.

The Human Resources team will implement the selection and recruitment actions.

Organisation development

Human resources will advise management on means and actions to enhance operational efficiency and effectiveness. Main actions planned shall be:

- Assignment of duties and responsibilities to best achieve fulfilment of objectives and tasks, in the particular context of the corporate reorganisation
- Establishment of clear and efficient reporting lines and set up necessary delegations of authority.
- Enhancement of co-ordination between the different activity cluster areas.

HR management

HR will deal with core functions such as day-to-day management of administrative workflows and process, performance management and assessment, safety and wellbeing at work, salary, compensation and benefits, employee motivation, communication, and training. In 2017, the first staff reclassification (promotion) exercise will take place.

Inter-JU cooperation

The efficiency and cost effective management of IMI2 JU resources is also based on a close collaboration with other Joint Undertakings through arrangements and mechanisms of pooling expertise for specific time-bound tasks. In 2017, the JUs will continue to share human resources IT tools, common calls for tender as well as a common approach to implementing rules of the EU Staff regulation.

2.4.5 Administrative budget and finance

Budget 2017

A table overview of the administrative budget for the financial year 2017 is set out below.

	Heading Title 1	Financial year 2017		
Chapter		Commitment Appropriation (CA)	Payment Appropriation (PA)	C2 - Payment Appropriation (PA)
11	Staff in active employment	5 242 000	5 242 000	
12	Staff recruitments - miscellaneous expenditure	20 000	20 000	5 982
13	Missions and duty travels	190 000	190 000	8 000
14	Socio-medical structure	230 000	230 000	103 807
17	Representation	20 000	20 000	6 786
	Title 1 - Total	**5 702 000**	**5 702 000**	**124 575**

	Heading Title 2	Financial year 2017		
Chapter		Commitment Appropriations (CA)	Payment Appropriations (PA)	C2 - Payment Appropriation (PA)
20	Office building and associated costs	679 000	679 000	102 917
21	Information technology purchases	592 000	592 000	445 237
22	Office equipment (movable property and associated costs)	153 000	153 000	
23	Current administrative expenditure	123 000	123 000	11 368
24	Telecommunication and postal expenses	68 000	68 000	20 980
25	Expenditure on formal meetings	158 000	158 000	30 201
26	Running costs in connection with operational activities	300 000	300 000	35 860
27	External communication, information and publicity	625 000	625 000	180 301
28	Service contracts	729 000	729 000	458 924
29	Expert contracts and cost of evaluations	700 000	700 000	6 347
	Title 2 - Total	**4 127 000**	**4 127 000**	**1 292 135**
	Total running costs Title 1 + Title 2	***9 829 000***	***9 829 000***	***1 416 710***

The payment appropriations carried over to the 2017 budget are related to the commitments carried forward from 2016 to 2017.

The operational budget is covered under section 2.2.2. Calls for proposals.

A table overview of the 2017 budget is set out in Chapter 3 of this Annual Work Plan.

Financial Management

During 2017, the finance team will continue with its day to day activities of initiation, verification and payments of invoices and cost claims, creation of commitments, recovery orders, and analysis of periodic reports and negotiations of financial and administrative parts of projects. These activities will be conducted in a timely manner that will be monitored through corporate KPIs, in particular payment times and budget execution.

Best practice and highest quality standards will be ensured through the availability of a Manual of Financial Procedures that is under regular revision. In addition, knowledge dissemination will be further developed through the development of further guidance and the tenure of several financial workshops, in particular targeting beneficiaries, with the aim to reduce errors in financial reporting. 2016 Financial Year accounts will be for the first time audited by an external audit firm (see also Section 2.6.3).

2.4.6 Data protection

Objectives	To prepare the implementation of the General Data Protection Regulation To promote a culture of data protection at IMI2 JU To support projects in establishing common minimum requirements for protecting and sharing personal data
Planned Activities	To prepare the implementation of the General Data Protection Regulation and in particular: ▪ increased accountability: advise controller and data processors on their upcoming responsibility and liability for further processing ▪ higher data handling standards: re-define the Data Protection Officer role (e.g. performance of data protection impact assessments, further recording of processing activities and collection of evidence for obtaining consent); ▪ data security: establish internal procedures in relation to the use of technologies ▪ transparency: analyse the implications of changes in consent and the shifting of the burden of proof for compliance. To promote a culture of data protection at IMI2 JU: ▪ training and advising ▪ continue to implement the internal procedure for handling notifications and, where applicable, prior checking notifications to the European Data Protection Supervisor (EDPS) ▪ participate on the EU network for Data Protection Officers and implement best practices ▪ follow-up progress and analyse potential impact of the new EU framework for data protection To support projects in establishing common minimum requirements for protecting and sharing data: ▪ advising ▪ follow-up on recommendations addressed to IMI by the European Data Protection Supervisor
Expected results	To ensure that personal data is protected, that Regulation (EC) 45/2001 is complied with and that the transition to the application of the General Data Protection Regulation is handled smoothly. Actions: ▪ train newcomers ▪ inform IMI staff on data protection matters during internal meetings ▪ provide advise upon request ▪ support the preparation of internal notifications ▪ prepare prior-checking notifications and/or their updates ▪ attend EDPS and Data Protection Officers meetings ▪ prepare standard operating procedures

Access to documents

IMI will continue to address requests for access to IMI documents according to Regulation (EC) No 1049/2001, in a spirit of openness and transparency in order to bring its activities and output closer to the public.

The objectives of actions in this field will continue, as a means to keep high level of public confidence in IMI2 JU by giving the opportunity to the public to monitor its work. In addition, this will bring additional benefits such as:

- Improving public awareness of IMI activities and processes;
- Stimulating the interaction on key issues.

2.5 Governance

Key objectives

- Further develop an IMI strategic orientation and related objectives.
- Ensure that activities are in line with and support IMI strategic orientation.
- Further improve the efficiency and effectiveness of the IMI's governance activities.
- Promote and maintain a positive reputation among stakeholders and partners as a key facilitator of healthcare research.

Planned activities

- Support to the Governing Board, Scientific Committee, States Representatives Group and management.
- Align planning activities (strategy, annual work plans and related budget) and the following monitoring and reporting activities.
- Improve responsibilities and accountability.
- Enhance communication and transparency.

IMI will continue to provide support to the Governing Board, the Scientific Committee, the States Representatives Group, and the Stakeholders' Forum and their working groups.

The **Governing Board** gathers representatives of IMI2 JU members. It has the responsibility for overseeing the operations of the IMI2 JU and the implementation of its activities. It will meet at least twice.

The **Scientific Committee** is an advisory body to the Governing Board of the IMI2 JU providing its advice in written form. The specific tasks of the Scientific Committee are outlined in Article 10 of the Statutes of the IMI2 JU and include advising on the scientific priorities to be included in the SRA taking into account related activities in Horizon 2020; advising on the scientific priorities to be addressed in the annual work plans and advising on the scientific achievements described in the annual activity report. The Chair will participate in Governing Board meetings as observer.

It is planned that the Scientific Committee shall meet at least twice in 2017 at dates to be proposed by the Chair of the committee. Additional meetings in 2017 may be convened at the request of the Chair or Vice-Chair of the Scientific Committee, the Governing Board or the Executive Director.

The **States Representatives Group** will be consulted on the Annual Work Plans and will receive information on Calls and proposals, evaluation process. At least two meetings of the States Representatives Group are planned for 2017. The Chair will participate in Governing Board meetings as observer.

In order to cover all areas of life science research and innovation of public health interest and to further develop the IMI2 JU objectives, IMI2 JU will pursue its action to attract a wide range of legal entities, notably offering the possibility to become **Associated Partners** at programme or topic level.

The **Strategic Governing Groups** (SGGs) ensure the coordination of IMI 2 JU's work in certain strategic areas and work to make the development of new topics more transparent and effective. As such, the SGGs are made up of representatives of companies active or interested in the area covered by the scope of the SGG as well as representatives from the European Commission, the IMI Programme Office and the IMI Scientific Committee. Currently, the seven established SGGs focus on the following areas: Immunology; Diabetes / metabolic disorders; Neurodegeneration; Translational safety; Data and knowledge management; Infections control, and Oncology.

In 2017 the SGGs will continue to develop comprehensive strategies for future projects for their specific areas. Each SGG will meet on a regular basis to discuss their portfolio of projects and ensure synergy with ongoing projects, both IMI 2 JU and non-IMI2 JU. They may engage with external parties to consult on topic development or key challenges in specific areas as required. Efforts will be made to enhance communication with these bodies as well as seek and feedback on any significant IMI activities and developments. In addition, they will be called upon to advise on how best to exploit IMI projects outputs, enhance cross-projects' collaboration as well as explore synergies with similar or complementary activities at national and global level.

In line with article 13.3 (b) of IMI2 JU Regulation, costs of activities related to allowing the SGGs perform these tasks and achieve their objectives are considered as eligible in-kind contributions under the conditions set out in the SGG charter[41].

Expected results

- Streamlined governance activities

Actions:

- Preparation of plans, reports, briefings, decisions.
- Organisation of consultations and assessment of the input.
- Organisation of meetings and presentations.
- Implementation of decisions and recommendations.
- Coordinate information across governance structures.

[41] http://www.imi.europa.eu/sites/default/files/uploads/documents/IMI2_GB_DEC_2016_21_Decision_on_new_SGGs_Charter_SIGNED_30SEP2016.pdf

2.6 Internal Control framework

Internal control

The overarching objective of the IMI2 JU internal control system is to ensure the adequate management of the risks relating to the legality and regularity of the underlying transactions. In this view, the internal control framework is designed to ensure that operational activities are implemented in an effective and efficient way; that legal and regulatory requirements are met, that financial and other management reporting is reliable, and that assets and information are safeguarded.

This is achieved through a combination of processes, procedures and supervision, notably including ex ante and ex post controls and the monitoring of financial performance and transaction checks. The implementation of recommendations from audits by the European Court of Auditors and the Commission's Internal Audit Service (IAS) also play a key role in this area.

The priority objective is to implement and maintain an effective internal control system so that reasonable assurance can be drawn that (1) resources assigned to the activities are used according to the principles of sound financial management (2) risk of errors in operations is minimised and (3) the control procedures put in place give the necessary assurance concerning the legality and regularity of the underlying transactions.

A particular challenge for 2017 will also be to assess the Internal Control Standards (ICSs) capability to better meet the expectations of IMI2 JU's Members and stakeholders in terms of efficiency, effectiveness and flexibility. In this context, a revision of the standards may be considered and planned on a multiannual basis, in order to develop for IMI2 JU a quality management system.

2.6.1 Financial procedures

The IMI2 JU Financial Rules are the point of reference for the principles and procedures governing the establishment and implementation of the IMI2 JU budget and the control of its finances. Alignment of internal procedures involves also a continous process.

The objective for 2017 will be the optimisation of internal procedures in order to increase simplification (cutting red tape, speeding up procedures, in particular the time-to-grant, and shifting the focus from paperwork to performance) reduce cost of operations ensuring enhanced sound financial management. Actions taken and further planned will then contribute to:

- Continue the adoption and implementation of revised internal control strategies, procedures and workflows;
- Improve efficiency of ex-ante controls, especially of operational expenditure,to reduce the risk of undue payments and administrative errors;
- complete the implementation of harmonized reporting and payment workflows which incorporate the automated financial circuits and are supported by the common grant management IT system (SyGMa-Compass with full integration with ABAC).

2.6.2 Ex-ante and ex-post controls

For projects running under the IMI1 programme, the Programme Office will carry on with the implementation of its ex-post audits strategy as a means to ensure the legality and regularity of operational expenditure. This strategy complements ex-ante controls embedded in IMI's management processes and includes the correction of any amounts found to have been paid in excess. Errors of a systematic nature will also continue to be extended to cover unaudited financial statements ('Form C') of the same participants.

Representative and, if necessary, risk-based audits of beneficiaries will be launched during the year to cover new cost claims received and validated by IMI since the last audited period. In parallel, independent reviews of submitted certificates of in-kind methodology as well as risk-based audits of accepted declarations of in-kind contributions by EFPIA companies will also be continued and followed-up.

As regards the IMI2 JU programme, the Commission Common Audit Service (CAS) will carry out the H2020 audits in accordance with its common audit strategy, as part of the harmonisation effort of the Horizon 2020 Framework. IMI2 JU contributes to the development and implementation of the audit programme in close cooperation with CAS. The harmonised legal framework will enable IMI2 JU to draw an additional element of assurance from extension of audit results on shared beneficiaries across the H2020 programme.

In line with the IMI2 JU Regulation, controls of in-kind contributions by EFPIA companies will be based essentially on review of audit certificates provided annually by independent auditors.

2.6.3 Internal and External audits

The audit environment is an assurance and accountability pillar within the IMI2 JU internal control framework since it provides reasonable assurance about the state of effectiveness of risk management and control processes and serves as a building block for the annual Declaration of Assurance of the Executive Director.

The Audit Manager will coordinate audits carried out by IMI2 JU's internal and external auditors and will follow up and asses the implementation of the Internal Audit Service of the European Commission (IAS) and the European Court of Auditors (ECA) audit recommendations with the objective to confirm the effective implementation.

The IAS will continue performing internal audit function and implement the Strategic Internal Audit Plan 2015-2017.

In 2017, the Audit manager will contribute to the overall corporate objective of receiving an unqualified ('clean') ECA audit opinion and positive statement of assurance.

The ECA will audit and issue opinion on the legality and regularity of the underlying transactions. In accordance with the revised IMI2 JU Financial rules, IMI2 JU's 2016 annual accounts will be audited by external audit company while the Court will draw opinion on the basis of their work.

The Audit Manager will continue to examine and evaluate risk management, control and governance processes of the IMI2 Joint Undertaking to provide independent assessment and consulting aimed at adding value and improving IMI2 JU's operations.

2.6.4 Anti-Fraud strategy

Anti-fraud measures are an essential part of sound financial management required under the EU Financial Regulation. They also safeguard the financial interests of the Joint Undertaking and contribute to its reputation. Based on its Anti-Fraud Strategy (AFS) - adopted in 2016 in line with the Research Anti-Fraud Strategy (RAFS) - the IMI2 JU activities will implement throughout 2017 its Action Plan focusing on specific objectives and pro-active actions for fraud protection, early detection and immediate correction taking into account the specific needs and nature of the JU as a Public-Private Partnership.

IMI actions will cover the following four elements:

- Minimising the opportunities for internal and external fraud ensuring that effective counter-fraud measures are in place and provide an appropriate response when fraud occurs;
- Training the staff (especially agents involved in direct grant management) and raising awareness about fraud risk across the JU as well as among partners and beneficiaries;
- Conducting fraud risk analysis and reviews especially in areas considered vulnerable to fraud;
- Coordination with the research family members in the field of anti-fraud maintaining operational contacts with the Fraud and Irregularity Committee for Research (FAIR) ant the European Anti-fraud Office (OLAF). All cases of suspected fraud are reported to OLAF, there is no target. Official cases shall be regularly monitored and reported in the annual activity report, as well as the number of cases relevant to IMI initiated directly by OLAF.

3 Budget 2017

An overview of the 2017 budget per chapters is set out below.

STATEMENT OF REVENUE

	Heading Revenue	Financial year 2017						Comments
		Budget 2017.0		*Budget 2017 Amendment 1*	*Budget 2017 Amendment 2*	Amended Budget 2017.2		
Chap		Commitment Appropriation (CA)	Payment Appropriation (PA)	*Payment Appropriation (PA)*	*Payment Appropriation (PA*	Commitment Appropriation (CA)	Payment Appropriation (PA)	
10	European Commission contribution (including EFTA contribution)	182 953 171	201 697 134	*-56 000 000*	-24 000 000	182 953 171	121 697 134	Commitment appropriations include EUR 4,914,500 for running costs and EUR 178,038,671 for operational costs. Payment appropriations include running costs of EUR 4,914,500 and operational costs of EUR 116,782,634.
C2	Appropriations carried over from 2016	134 467 173		*78 699 079*		134 467 173	78 699 079	The amount carried over from 2016. Administrative expenditure - payment appropriation. Operational expenditure - commitment and payment appropriation.
	Title 1 - Total	**317 420 344**	**201 697 134**	***22 699 079***	**-24 000 000**	**317 420 344**	**200 396 213**	
20	EFPIA contribution	4 914 500	4 914 500			4 914 500	4 914 500	EFPIA contribution to IMI JU running costs.
21	Subsidy from other Members other than the Union and the Associated Partners, or their constituent entities or their affiliated entities	-	1 000 000			-	1 000 000	Four EFPIA companies ((Sanofi Pasteur SA, Abbott Biologicals BV, Seqirus UK Limited, GlaxoSmithKline Biologicals S) contribution to operational payment appropriations
	Title 2 - Total	**4 914 500**	**5 914 500**			**4 914 500**	**5 914 500**	
30	Associated Partners contributions	-	1 831 000		-1 831 000	-	-	Bill and Melinda Gates Foundation contribution to operational payment appropriations
	Title 2 - Total	**-**	**1 831 000**		**-1 831 000**	**-**	**-**	

	Total contributions	**322 334 844**	**209 442 634**	***22 699 079***	**-25 831 000**	**322 334 844**	**206 310 713**	

STATEMENT OF EXPENDITURE

Heading Title 1		**Financial year 2017**					**Comments**
Chap		Commitment Appropriation (CA)	Payment Appropriation (PA)	*Payment Appropriation (PA) C2*	Commitment Appropriation (CA)	Payment Appropriation (PA)	
11	Staff in active employment	5 242 000	5 242 000		5 242 000	5 242 000	Salaries
12	Staff recruitments - miscellaneous expenditure	20 000	20 000	*5 982*	20 000	25 982	Miscellaneous expenditure on staff recruitment: travel expenses, etc.
13	Missions and duty travels	190 000	190 000	*8 000*	190 000	198 000	Mission expenses
14	Socio-medical structure	230 000	230 000	*103 807*	230 000	333 807	Other staff costs: training, language classes, medical service, interim staff
17	Representation	20 000	20 000	*6 786*	20 000	26 786	Representation, receptions and internal meetings
	Title 1 - Total	**5 702 000**	**5 702 000**	***124 575***	**5 702 000**	**5 826 575**	

	Heading Title 2	Financial year 2017					Comments
Chapter		Commitment Appropriations (CA)	Payment Appropriations (PA)	*Payment Appropriation (PA) C2*	Commitment Appropriation (CA)	Payment Appropriation (PA)	
20	Office building and associated costs	679 000	679 000	*102 917*	679 000	781 917	Rent, works, common/IMI charges and parking. Additional costs: indexation, insurance, water/gas, electricity, heating, maintenance + repairs, security and surveillance.
21	Information technology purchases	592 000	592 000	*445 237*	592 000	1 037 237	IT purchases, software licences, software development, IMI website.
22	Office equipment (movable property and associated costs)	153 000	153 000		153 000	153 000	Purchases and rental of office equipment, maintenance and repair.
23	Current administrative expenditure	123 000	123 000	*11 368*	123 000	134 368	Office supply. Literature, subscriptions, translation services, bank charges and miscellaneous office expenditure.
24	Telecommunication and postal expenses	68 000	68 000	*20 980*	68 000	88 980	Data communication such as telephone, video conferences and postal services.
25	Expenditure on formal meetings	158 000	158 000	*30 201*	158 000	188 201	Official meetings such as SRG, Scientific committee, Governing Board and working groups created by GB.
26	Running costs in connection with operational activities	300 000	300 000	*35 860*	300 000	335 860	Expenditure in connection with research activities and objectives of IMI (workshops, meetings and events targeting IMI projects).
27	External communication, information and publicity	625 000	625 000	*180 301*	625 000	805 301	External communication and events such as Info Days, stakeholder forums.
28	Service contracts	729 000	729 000	*458 924*	729 000	1 187 924	Studies, consultancy, accounting services, audits.
29	Expert contracts and cost of evaluations	700 000	700 000	*6 347*	700 000	706 347	Costs linked to evaluations, expert contracts.
	Title 2 - Total	**4 127 000**	**4 127 000**	***1 292 135***	**4 127 000**	**5 419 135**	
	Total running costs Title 1 + Title 2	***9 829 000***	***9 829 000***	***1 416 710***	***9 829 000***	***11 245 710***	

	Heading Title 3	Financial year 2017						Comments
Chap		Commitment Appropriation (CA)	Payment Appropriation (PA)	*Payment Appropriation (PA)*	*Payment Appropriation (PA)*	Commitment Appropriation (CA)	Payment Appropriation (PA)	
30	Implementing the research agenda of IMI JU	178 038 671	199 613 634	*-56 000 000*	-25 831 000	178 038 671	117 782 634	Grant agreements - Payments: EU- EUR 116,782,634; Other Members- EUR 1,000,000; Associated Partners- 1,831,000.
C2	Appropriations carried over from 2016	134 467 173		*77 282 369*		134 467 173	77 282 369	The amount carried over from 2016.
	Total operational costs Title 3	***312 505 844***	***199 613 634***	***21 282 369***	***-25 831 000***	***312 505 844***	***195 065 003***	
	Total contributions	**322 334 844**	**209 442 634**	***22 699 079***	**-25 831 000**	**322 334 844**	**206 310 713**	

An overview of the 2017 budget and structure per budget lines is set out in the table below.

Expense budget line	Description	Commitment appropriations	Payment appropriations	C2 - Payment Appropriation (PA)
A01100	Staff in active employment and costs linked to employment	3 576 000	3 576 000	
A01101	Family Allowances	361 000	361 000	
A01102	Transfer and expatriation allowance	391 000	391 000	
A01110	Contract Agents	576 000	576 000	
A01111	Seconded National Experts	0	0	
A01130	Insurance against sickness	95 000	95 000	
A01131	Insurance against accidents and occupational diseases	14 000	14 000	
A01132	Unemployment insurance for temporary staff	38 000	38 000	
A01133	Pension	0	0	
A01140	Birth and death allowance	10 000	10 000	
A01141	Annual travel costs from the place of employment to place of origins	57 000	57 000	
A01144	Fixed local travel allowances	3 000	3 000	
A01149	Other allowances	0	0	
A01172	Cost of organizing traineeships within IMI	16 000	16 000	
A01175	Translation and typing services and work to be contracted	0	0	
A01177	Other services rendered	5 000	5 000	
A01178	PMO fees	41 000	41 000	
A01180	Sundry recruitment expenses	0	0	
A01181	Travelling expenses (taking up duty)	5 000	5 000	
A01182	Installation allowance	42 000	42 000	
A01183	Moving expenses	0	0	
A01184	Temporary daily allowance	10 000	10 000	
A01190	Weightings (correction coefficient)	2 000	2 000	
A01191	Salaries adaptation	0	0	
11	**Staff in active employment**	**5 242 000**	**5 242 000**	**-**
A01200	Miscellaneous expenditure on staff recruitment	20 000	20 000	5 982
12	**Staff recruitments - miscellaneous expenditure**	**20 000**	**20 000**	**5 982**
A01300	Mission expenses	190 000	190 000	8 000
13	**Missions and duty travels**	**190 000**	**190 000**	**8 000**

Expense budget line	Description	Commitment appropriations	Payment appropriations	C2 - Payment Appropriation (PA)
A01401	Socio-medical structure	0	0	
A01410	Other trainings	60 000	60 000	2 595
A01430	Medical service	5 000	5 000	2 770
A01440	Trainings covered by the SLA	6 000	6 000	3 659
A01490	Other interventions	159 000	159 000	94 783
14	**Socio-medical structure**	**230 000**	**230 000**	**103 807**
A01700	Representation expenses	20 000	20 000	6 786
17	**Representation**	**20 000**	**20 000**	**6 786**
	Title 1 - Total	**5 702 000**	**5 702 000**	**124 575**
A02000	Rentals	570 000	570 000	88 289
A02001	Guarantees	0	0	
A02002	Contributions	0	0	
A02010	Insurance	0	0	
A02020	Water gas electricity and charges	80 000	80 000	2 439
A02030	Cleaning and maintenance	0	0	
A02040	Furnishing of premises (works)	10 000	10 000	
A02050	Security and surveillance	19 000	19 000	12 189
A02090	Other expenditure on buildings	0	0	
20	**Office building and associated costs**	**679 000**	**679 000**	**102 917**
A02101	Hardware, infrastructure and related services	168 000	168 000	130 140
A02102	Software development, licenses and related services	424 000	424 000	315 097
A02103	Other expenses maintenance and repair	0	0	
21	**Information technology purchases**	**592 000**	**592 000**	**445 237**
A02200	Purchase	123 000	123 000	
A02201	Rentals	10 000	10 000	
A02202	Maintenance utilisation and repair	20 000	20 000	
A02203	Other office equipment	0	0	
22	**Office equipment (movable property and associated costs)**	**153 000**	**153 000**	**-**
A02300	Stationery and office supply	40 000	40 000	6 805
A02320	Bank charges	0	0	
A02321	Exchange rate losses	0	0	
A02329	Other financial charges	0	0	
A02330	Legal expenses	0	0	

Expense budget line	Description	Commitment appropriations	Payment appropriations	C2 - Payment Appropriation (PA)
A02350	Other operating expenditure	13 000	13 000	2 000
A02351	Petty expenses	0	0	
A02360	Library stocks purchase of books and subscriptions	44 000	44 000	80
A02370	Translation interpretation	26 000	26 000	2 484
23	**Current administrative expenditure**	**123 000**	**123 000**	**11 368**
A02400	Correspondence and communication expenses	68 000	68 000	20 980
24	**Telecommunication and postal expenses**	**68 000**	**68 000**	**20 980**
A02500	Formal meetings	158 000	158 000	30 201
25	**Expenditure on formal meetings**	**158 000**	**158 000**	**30 201**
A02600	Running costs in connection with operational activities	24 000	24 000	310
A02601	Events	0	0	
A02602	Workshops	270 000	270 000	35 050
A02603	Knowledge Management	6 000	6 000	500
26	**Running costs in connection with operational activities**	**300 000**	**300 000**	**35 860**
A02700	External communication	225 000	225 000	118 505
A02701	Events	300 000	300 000	31 902
A02702	Material	100 000	100 000	29 893
27	**External communication, information and publicity**	**625 000**	**625 000**	**180 301**
A02800	Ex-post Audits	615 000	615 000	380 090
A02801	Studies, consultancy	114 000	114 000	78 834
A02802	Audit services	0	0	
28	**Service contracts**	**729 000**	**729 000**	**458 924**
A02900	Evaluation Experts meetings	600 000	600 000	5 618
A02901	Evaluation Facilities	100 000	100 000	729
A02902	Evaluations ENSO	0	0	
29	**Expert contracts and cost of evaluations**	**700 000**	**700 000**	**6 347**
	Title 2 - Total	**4 127 000**	**4 127 000**	**1 292 135**
B03000	Implementing the research agenda of IMI1 JU	0	108 000 000	
B03020	Implementing the research agenda of IMI2 JU	178 038 671	9 782 634	
B03020 - C2	Implementing the research agenda of IMI2 JU	134 467 173		77 282 369

Expense budget line	Description	Commitment appropriations	Payment appropriations	C2 - Payment Appropriation (PA)
30	Implementing the research agenda of IMI JU	312 505 844	117 782 634	77 282 369
	Total expenditures	322 334 844	127 611 634	78 699 079

3.1 Staff Establishment Plan

Grade	Establishment Plan 2016			Year 2017											
				Posts evolution						Organisational evolution			Establishment Plan 2017		
				Promotion / Career advancement			Turn-over (departures/arrivals)			New posts (per grade)			Requested (Budget)		
	PERM	TEMP	TOTAL	Officials	TA - LT	TA - ST	Officials	TA - LT	TA - ST	Perm	TA - LT	TA - ST	Perm	TA	Total
AD16															
AD15															
AD14		1	1											1	1
AD13															
AD12		2	2											2	2
AD11		2	2											2	2
AD10															
AD9		3	3											3	3
AD8		7	7											7	7
AD7		6	6											6	6
AD6															
AD5		11	11											12	12
Total AD		32	32											33	33
AST11															

Grade	Establishment Plan 2016			Year 2017											
				Posts evolution						Organisational evolution			Establishment Plan 2017		
				Promotion / Career advancement			Turn-over (departures/arrivals)			New posts (per grade)			Requested (Budget)		
	PERM	TEMP	TOTAL	Officials	TA - LT	TA - ST	Officials	TA - LT	TA - ST	Perm	TA - LT	TA - ST	Perm	TA	Total
AST10															
AST9															
AST8		1	1											1	1
AST7															
AST6															
AST5															
AST4															
AST3		4	4											4	4
AST2															
AST1		1	1											1	1
Total AST		**6**	**6**											**6**	**6**
SC6															
SC5															
SC4															
SC3															
SC2															
SC1															
Total SC		**0**	**0**											**0**	**0**
Overall Total		**38**	**38**											**39**	**39**

Contract Agents Grade	2016	2017
FG IV	2	2
FG III	11	12
FG II	1	1
FG I	0	0
Total CA	**14**	**15**

Seconded National Experts	2016	2017
	0	**2**

Annex I - IMI2 Call 11 topics text

Introduction

The Innovative Medicines Initiative is a jointly funded partnership between the European Union, represented by the European Commission, and the European Federation of Pharmaceutical Industries and Associations (EFPIA).

The Innovative Medicines Initiative 2 Joint Undertaking (IMI2 JU) has been created[42] following the principles below:

- Research related to the future of medicine should be undertaken in areas where societal, public health and biomedical industry competitiveness goals are aligned and require the pooling of resources and greater collaboration between the public and private sectors, with the involvement of small and medium-sized enterprises (SMEs).
- The scope of the initiative should be expanded to all areas of life science research and innovation.
- The areas should be of public health interest, as identified by the World Health Organisation (WHO) report on priority medicines for Europe and the World[43].

The IMI2 JU objectives are usually implemented through Research and Innovation Actions (RIAs), and Coordination and Support Actions (CSAs) where public and private partners collaborate, joining their expertise, knowledge and resources.

The initiative should therefore seek to involve a broader range of partners, including mid-sized companies[44], from different sectors e.g. biomedical imaging, medical information technology, diagnostic and/or animal health industries. Involving the wider community in this way should help to advance the development of new approaches and technologies for the prevention, diagnosis and treatment of diseases with high impact on public health.

The IMI2 Strategic Research Agenda (SRA)[45] is the main reference for the implementation of research priorities for IMI2 JU. The scientific priorities for 2017 for IMI2 JU have been prepared based on the SRA.

Applicant consortia are invited to submit a proposal for each of the topics that are relevant for them. These proposals should address all aspects of the topic to which the applicant consortia are applying. The size and composition of each consortium should be adapted so as to respond to the scientific goals and the expected key deliverables.

Applicants consortia, during all stages of the evaluation process, must consider the nature and dimension of the IMI2 JU programme as a public-private collaboration.

While preparing their proposals, applicant consortia should ensure that the needs of patients are adequately addressed and, where appropriate, patient involvement is encouraged. Applicants should ensure that gender dimensions are also considered. Synergies and complementarities with other national and international projects and initiatives should be explored in order to avoid duplication of efforts and to create collaboration at a global level to maximise European added value in health research. Where appropriate, the involvement of regulators is also strongly encouraged.

Applicant consortia shall ensure that where relevant their proposals abide by the EU legal framework on data protection[46].

Before submitting a proposal, applicant consortia should familiarise themselves with all Call documents such as the IMI2 Manual for evaluation, submission and grant award[47], and the IMI2 evaluation criteria. Applicants

[42] Council Regulation (EU) No 557/2014 of 6 May 2014 establishing the Innovative Medicines Initiative 2 Joint Undertaking (IMI2 JU).
[43] http://www.who.int/medicines/areas/priority_medicines/en/
[44] Under IMI2 JU, mid-sized companies having an annual turnover of EUR 500 million or less not being affiliated entities of companies with an annual turnover of more than 500 million; the definition of 'affiliated entities' within the meaning of Article 2(1)(2) of Regulation (EU) No 1290/2013 applies mutatis mutandis. Where established in an EU Member State or an associated country, are eligible for funding.
[45] http://www.imi.europa.eu/sites/default/files/uploads/documents/IMI2_SRA_March2014.pdf
[46] Directive 95/46/EC on the protection of individuals with regard to the processing of personal data and the free movement of such data and implementing national laws: http://eur-lex.europa.eu/legal-content/EN/TXT/?uri=celex:31995L0046
[47] http://www.imi.europa.eu/sites/default/files/uploads/documents/IMI2_CallDocs/Manual_SubEvalAward_IMI2_v1.4_Oct2016.pdf

should refer to the specific templates and evaluation procedures associated with the topic type: Research and Innovation Actions (RIA), Coordination and Support Action (CSA).

Exploitation of IMI project results

Topic details

Topic code	IMI2-2017-11-01
Action type	Research and Innovation Action (RIA)
Submission & evaluation process	Single stage

Background and problem statement

A key challenge of any research funding scheme is to ensure that significant results, outputs and/or data generated during the lifetime of a project remain available and can be further exploited and valorised for maximum and long-term impact after the project finishes. Often, important scientific results reach the public domain via publication in relevant scientific journals. However, for some important results, the route to becoming available to the wider scientific community, or being fully exploited, remains a difficult path. Important results are defined as those with maximum potential long-term impacts on research and development, as well as on regulatory, clinical and healthcare practice.

Realising the full potential of project results within the timeframe available to the project is not always possible and sometimes may only be achieved through the involvement of additional expertise beyond the project.

In order for important results[48]from IMI JU projects to be integrated into general research and medical practice, significant outputs, important samples and/or data that have been generated by the large public-private investments need to be maintained and made available for future research by the whole scientific community. This might mean that new solutions paving the way to long term sustainability have to be identified.

This Call for proposals aims to provide initial/short term support so that significant results from IMI JU projects that have finished or are nearing completion become fully exploitable, available to all relevant end users, and fully sustainable.

Need and opportunity for public-private collaborative research

IMI JU projects are public-private partnerships between industrial members of EFPIA and other private and public stakeholders with a focus on tackling challenging bottlenecks in pharmaceutical research and development (R&D) and improving the delivery of healthcare to patients. Important project results have been developed based upon collaboration between public and private stakeholders. In order to ensure that these results are exploited fully and eventually benefit end users, the collaboration of public and private stakeholders and additional public and private support may be necessary to ensure that:

- the results are available to the wider scientific community and other relevant end users, and/or
- key industry and societal challenges can be tackled.

Exploitation might often be most successfully achieved via integration in healthcare systems and public research infrastructures.

To enable this exploitation, collaboration between private industries (especially EFPIA members), and different stakeholders such as academic experts, small and medium-sized enterprises (SMEs), regulatory agencies, patient organisations, public health institutes, and potentially public research infrastructures, is necessary. Convergence between innovative SMEs, larger companies, and academic institutions will ensure that the best approaches are sought to ensure the IMI JU results are further exploited in line with IMI2 JU objectives. Cross-country collaboration will bring together competences and facilities which are not available

[48] For the purposes of this Call, results are defined as that foreground generated under a IMI project from IMI Calls launched between 2008-2013.

on a national level, avoid dispersion of the results, and contribute to maintaining European competitiveness in the field of biomedical research and innovation.

Scope

The objective is to ensure the optimal exploitation and sustainability of key results from IMI projects that have finished or are nearing completion, and where relevant activities had not been already included as a funded activity of the project. Results should be those with the greatest chance of significant impact, beyond the original project lifetime. In some cases, this might be best achieved by finding solutions that can be applied to results generated across more than one project, to avoid dispersion and duplication of efforts.

Proposals must be in line with the objectives of IMI2 JU[49], particularly by aiming at sustaining and exploiting key results of previous projects to improve processes for the development of new medicines and/or lead to an improvement of individual and public health.

It is essential that applicants demonstrate that the funding sought will facilitate and foster the exploitation and sustainability of results beyond the original objectives of the project(s) by providing the necessary intermediate solutions and funding for a maximum of two years. It is expected that at the end of this period, further exploitation and sustainability will be achievable.

Thus commercial exploitation is outside the scope of this Call.

Applicants should be aware that only the project results identified in Table A annexed to the Topic Text are within the scope of this Call. As such, applicants must clearly indicate through their proposals which results they are utilising. In furtherance of the Call objectives, in line with Article II.30 and II.31 of the relevant IMI JU Model grant agreement[50], participants from the listed IMI JU projects have formally undertaken to grant potential applicants access to appropriate information in order to enable them to draft a proposal. Furthermore, access to appropriate information for successful applicants will be addressed on a case by case basis in line with Article II.30 and II.31 of the relevant IMI JU Model grant agreement:

The work to be supported will consist mainly of activities and measures to make the results available to the broader scientific community and as such may include measures to enable technology transfer and the analysis of regulatory aspects, as well as the standardisation and transfer of samples, databases, tools, etc. to sustainable infrastructures. In addition, the work may also encompass further activities should novel solutions/tools/methods be required to achieve the objectives of sustaining the results and ensuring their full impact. These could include adaptation of technologies to enable wider engagement, development of novel standardisation and/or interoperability measures, further development of scientific and business solutions, etc., as appropriate.

The applicants must demonstrate that the results to be exploited and sustained are viable for exploitation. A justification has to be included of the importance and value of sustaining these results for biomedical research and/or the delivery of healthcare, and to fulfil an unmet need of the end users, e.g. researchers or patients.

Proposals should clearly demonstrate that the solutions selected for achieving exploitation and sustainability of the results are fit for purpose, including when relevant attention to standardisation and interoperability, and

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[49] http://eur-lex.europa.eu/legal-content/EN/TXT/?uri=uriserv:OJ.L_.2014.169.01.0054.01.ENG
The IMI2 Joint Undertaking shall have the following objectives:
(a) to support, in accordance with Article 25 of Regulation (EU) No 1291/2013, the development and implementation of pre-competitive research and of innovation activities of strategic importance to the Union's competitiveness and industrial leadership or to address specific societal challenges in particular as described in parts II and III of Annex I to Decision 2013/743/EU, and in particular the challenge to improve European citizens' health and well-being;
(b) to contribute to the objectives of the Joint Technology Initiative on Innovative Medicines, in particular to:
(i) increase the success rate in clinical trials of priority medicines identified by the World Health Organisation;
(ii) where possible, reduce the time to reach clinical proof of concept in medicine development, such as for cancer, immunological, respiratory, neurological and neurodegenerative diseases;
(iii) develop new therapies for diseases for which there is a high unmet need, such as Alzheimer's disease and limited market incentives, such as antimicrobial resistance;
(iv) develop diagnostic and treatment biomarkers for diseases clearly linked to clinical relevance and approved by regulators;
(v) reduce the failure rate of vaccine candidates in phase III clinical trials through new biomarkers for initial efficacy and safety checks;
(vi) improve the current drug development process by providing support for the development of tools, standards and approaches to assess efficacy, safety and quality of regulated health products.

[50] http://www.imi.europa.eu/sites/default/files/uploads/documents/Rev_Grant_Agreement_2011/1_WP_2013_GA_Annex%20II_2013%2003%2013.pdf

leveraging the latest knowledge and learning, allowing the results to enable further research beyond the state of the art.

Expected key deliverables

- At the end of the action, plans for the further exploitation and sustainability of results of IMI JU projects will have to be in place. Plans should include a clear value proposition for the end users to be targeted, for example: transfer to a sustainable infrastructure, technology transfer, etc.
- A convincing scientific and business solution that sustains key IMI JU project results without the need for further IMI JU funding beyond the duration of the funding of this Call.
- Measures to make the results available to the broader scientific community (public and private) beyond the duration of the sustainability funding to maximise the impact of the results on biomedical research and/or the delivery of healthcare.

Expected impact

It is expected that proposals selected for award under this Call will result in the future full exploitation of key project results in the scope of this Call (Table A, annexed) and their sustainability, which will stimulate the development of an open innovation model in biopharmaceutical research and contribute to the achievement of the objectives of IMI2 JU.

To ensure the expected impact, it is necessary that the most valuable solutions with maximum potential long-term impacts on research and development, as well as on regulatory, clinical and healthcare practice be identified. Some examples can be, among others, integrated and interlinked (translational) databases linked to biobanks that, when relevant, enable the sustainability of results from multiple projects. Other examples are well validated targets, assays, tools, biomarkers and models that require only limited further refinement for practical applications in drug development, regulatory and healthcare practices.

Thus to ensure the expected impact, applicants should seek out the best solutions to achieve the exploitation and long-term sustainability of the result, and identify relevant end users. Proposals have to include a clear argumentation of how the sustained assets will be effectively applied in future activities that will significantly move the field forward, create socio-economic impact, and bring significant benefits to the wider scientific and R&D community.

Where appropriate, the activities funded should prove the viability of the findings, methodologies, processes, prototypes, models, technologies, clinical trials etc., developed with a potential for application.

Overall, proposals should demonstrate an appreciation of the impact of exploiting the results with respect to:

- their long-term sustainability as a result of the exploitation activities;
- an impact on R&D, regulatory, clinical and healthcare practice as relevant;
- a strengthening of the competitiveness and industrial leadership (demonstrated by the ability to mobilise relevant industrial contributions) and/or addressing specific societal challenges, improving European citizens' health and wellbeing.

The impact of the IMI2 JU action is expected to be generated via mobilizing resources and relevant expertise from the members of the consortium of the IMI2 JU action[51] significant enough to ensure meeting the proposal specific objectives and contribute to the IMI2 JU objectives as a public-private partnership.

[51] Including contributing partners: EFPIA companies or organisations associated to EFPIA, and Associated Partners to IMI2 JU contributing resources to the action may report it as their in-kind or financial contribution to the IMI2 JU. If the contributing entity is not yet an affiliate or a constituent entity of an IMI2 Member other than the Union (i.e. EFPIA), or an Associated Partner at the time of the proposal submission, and the proposal is selected for funding, such a legal entity is invited to become an affiliate or a constituent entity of an IMI2 Member, other than the Union, or an Associated Partner in accordance with the IMI2 JU Statutes prior to the signature of the relevant Grant Agreement.

Potential synergies with existing consortia

While proposals must be based on results included in the table presented in the Annex I to the Topic Text, synergies with existing initiatives should be considered in order to favour solutions maximising the impact while avoiding duplication and fragmentation.

Consortia have to demonstrate that they have developed their proposal taking into consideration and leveraging already available and relevant research infrastructures in Europe.

Indicative duration of the action

Proposals should include an appropriate duration for the action in relation to the activities and action work plan but should be no longer than 24 months.

Indicative budget

The indicative financial contribution from the IMI2 JU will be a maximum of EUR 5 000 000 globally for all selected actions. Within this budgetary envelope it is expected that each proposal will include a sound justification of the budget requested.

Applicant consortium

Applicant consortia are expected to address all of the objectives and have the necessary expertise to produce the deliverables and ensure the expected impact as outlined in the Call text.

The size and composition of each consortium should be adapted so as to respond to the goals and the key deliverables. The consortium participants need to include participants as appropriate to exploit the targeted results in the most logical and efficacious manner.

While preparing their proposals, applicant consortia should ensure that all relevant stakeholders are engaged appropriately and that the needs of patients are adequately addressed and, where appropriate, patient involvement is encouraged.

Applicant consortia will also be required to establish a robust legal/IPR apparatus that can facilitate the management and transfer of project results and sustainability efforts, including relevant ethical considerations, whilst remaining cognisant of, and consistent with, the IMI legal framework and associated project consortium agreements.

Applicants must pay particular attention to harnessing support from different stakeholders, including the mobilisation of funds through the inclusion of contributing partners – not necessarily involved in the original project – to reflect the public-private character of IMI actions. These mobilised contributions must be in addition to those already committed by any contributing partners when the original project(s) began.

Proposal preparation

Given the specific scope of this Call, when preparing their proposals, applicants must ensure the following points are covered in the relevant section of the proposal template:

- Result(s) chosen from those listed as in the scope of this Call have to be highlighted in the section of the proposal ‘1.2 Relation to the Call topic text’.
- A justification of the need and importance of further exploiting these results and expected value to be created, as well as how the funding under the present Call will trigger further long-term, self-standing sustainability. These activities should be confirmed as not being part of the funded activities of the original IMI JU project(s).
- A clear justification of the contributions mobilised to achieve the objectives.
- A description of the intended end-users and how they would benefit from the proposed exploitation and sustainability solution.
- All elements listed in the ‘Expected Impact’ section have to be addressed.
- A detailed explanation of the resources required and alignment with the budget requested.

- For entities that intend to contribute by becoming an Associated Partner of IMI2 JU, a request letter (http://www.imi.europa.eu/content/get-involved) has to be provided as an appendix to the proposal (this letter is not to be counted in the maximum number of pages).

Conditions for this Call for proposals

All proposals must conform to the conditions set out in the H2020 Rules for Participation (https://ec.europa.eu/research/participants/portal/doc/call/h2020/common/1595113-h2020-rules-participation_oj_en.pdf),the Commission Delegated Regulation with regard to IMI2 JU (http://eur-lex.europa.eu/legal-content/EN/TXT/PDF/?uri=CELEX:32014R0622&from=EN) and the relevant general conditions of the IMI2 JU AWP2017.

Applicants intending to submit a proposal in response to this Call for proposals should read in particular this topic text, the IMI 2 JU Annual Work Plan, the IMI2 Manual for submission, evaluation and grant award, the IMI2 RIA evaluation criteria and other relevant documents (e.g. IMI2 model Grant Agreement).

Call Identifier	**H2020-JTI-IMI2-2017-11-single-stage**
Type of action	**Research and Innovation Action (RIA)**
Publication Date	**19 July 2017**
Submission start date	**19 July 2017**
Submission deadline	**24 October 2017 (17:00:00 Brussels time)**
Indicative budget	
From the IMI2 JU	A maximum of EUR 5 000 000

Call Topic

IMI2-2017-11-01	The total indicative financial contribution from the IMI2 JU is a maximum of EUR 5 000 000.	Research and Innovation Action. Single-stage submission and evaluation process.

Table A of project results for IMI2 Call 11 indicative topic text 'Exploitation of projects results'

Project acronym, title & number	Project results (IMI1 project foreground)	Foreground type	Reference to scientific publications / other public sources	Project website and contacts
EMTRAIN **European Medicines Research Training Network** **115015**	▪ on-course®: a unique, independent, searchable, postgraduate course database containing over 7 600 courses for Masters, short courses and PhD programmes with >100 000 users. Now also used for research purposes. ▪ LifeTrain: established the principles for mutually-recognised lifelong learning and developed competency profiles, assessment of competencies and recognition / implementation processes - now part of the European Molecular Biology Laboratory (EMBL) conference series. ▪ Public-private partner (PPP) PhD workshops to increase industry awareness and support the acquisition of critical transferable skills. ▪ Toolkit for trainers: teaching methods for course developers. ▪ Extensive pan-European network including hundreds of thousands of biomedical scientists.	▪ Databases ▪ Learning platforms	1. Payton A, Janko C, Renn O, Hardman M. on-course(®) portal: a tool for in-service training and career development for biomedical scientists. Drug Discovery Today 2013; 18: 803-806. 2. Payton A, Dallakian P, Fitton A, Payton A, Hardman H, Yuille M. Course fees and academic ranking: insights from the IMI EMTRAIN on-course® database. Drug Discovery Today 2013; 19 (7): 830 – 833. 3. Hardman M, Brooksbank C, Johnson C, Janko C, See W, et al. LifeTrain: towards a European framework for continuing professional development in biomedical sciences. Nature Reviews Drug Discovery 2013; 12: 407-408. 4. Aperia A, Dirach J, Hardman M, et al. It pays to promote joint PhD programmes between academia and the private sector. Journal of Medicines Development Sciences 2015; 1 (2): 37–40. 5. Klech H, Brooksbank C, Price S, Verpillat P, Bühler FR, et al. European initiative towards quality standards in education and training for discovery, development and use of medicines. European Journal of Pharmaceutical Sciences 2012; 45: 515-520. 6. www.on-course.eu 7. www.lifetrain.eu	www.emtrain.eu michael.wolzt@meduniwien.ac.at

Project acronym, title & number	Project results (IMI1 project foreground)	Foreground type	Reference to scientific publications / other public sources	Project website and contacts
EUPATI **European Patients' Academy on Therapeutic Innovation** **115334**	▪ Certificate Patient Expert Training Course on medicines research and development (R&D). ▪ 98 certified Patient Experts in two course cycles. ▪ Pan-European workshop series on patient involvement in R&D. ▪ 'EUPATI Toolbox' and 'Internet Library' on medicines R&D in 7 languages, more than 50 000 users, add-on 'mini-course starter-kits' for short–courses. ▪ ~18 supported EUPATI National Platforms: launched: AT, FR, DE, IE, IT, MT, ES, CH, UK, PL; emerging: DK, SL, SR, NL, PT, GR; under construction: BE, LU. ▪ Guidance documents for interaction of patients/patient organisations with industry, regulators, health technology assessment (HTA) and ethics committees. ▪ Spearheaded public debate on patient and public involvement (PPI) in R&D.	▪ Educational material on seven-language toolbox website and on EUPATI Moodle e-learning system ▪ Guidance documents on interaction of patient organisations with 4 stakeholder groups, text ▪ Pan-European network of key contacts in advocacy and PPI, database ▪ Patients involved platform, website	1. Pavitt S. EUPATI: An initiative to provide expertise in patient advocacy and in medicines development processes. Regulatory Rapporteur 2013; 10 (9). 2. Chakradhar S. Training on trials: Patients taught the language of drug development. Nature Medicine 2015; 21 (3): 209-210. 3. Parsons S, Starling B, Mullan-Jensen C, et al. What the public knows and wants to know about medicines research and development: a survey of the general public in six European countries. BMJ Open 2015; 5: e006420. doi: 10.1136/bmjopen-2014-006420. 4. Pushparajah DS, Geissler J, Westergaard N. EUPATI: Collaboration between patients, academia and industry to champion the informed patient in the research and development of medicines. Journal of Medicines Development Sciences 2015; 1(1): 74–80. 5. Parsons S, Starling B, Mullan-Jensen C, et al. What do pharmaceutical industry professionals in Europe believe about involving patients and the public in research and development of medicines? A qualitative interview study. BMJ Open 2016; 6: e008928. doi: 10.1136/bmjopen-2015-008928. 6. Korieth, K. (2016) Three resonating patient-centric initiatives. The CenterWatch Monthly 2016; 23 (7). 7. Organisation for Economic Co-operation and Development (OECD) Global Science Forum. Facilitating international cooperation in non-commercial clinical trials. 2011.	www.eupati.eu jan@patientsacademy.eu walter.atzori@eu-patient.eu

Project acronym, title & number	Project results (IMI1 project foreground)	Foreground type	Reference to scientific publications / other public sources	Project website and contacts
PharmaTrain **Pharmaceutical Medicine Training Programmes** **115013**	▪ Shared content and quality standards for post-graduate diploma and Master programmes in medicines development + implemented course recognition procedure + implementation of post-graduate certification as 'Specialist in Medicines Development' presented in the 'PharmaTrain Manual, Curriculum Standards and Best Practices'. ▪ Shared content and quality standards for post-graduate Master programmes in regulatory affairs. ▪ Clinical investigator certificate (CLIC) position paper on development of a responsibility-based clinical trial management training programme for clinical investigators and their staff.	▪ Course Handbook for post-graduate diploma and Master programmes in pharmaceutical medicine and regulatory affairs ▪ Standard operating procedures (SOPs) and charters for national implementation of the post-graduate certification programme 'Specialist in Medicines Development' ▪ Position paper with syllabus and learning outcomes for the three levels investigator training in clinical trial management	1. Klech H, Brooksbank C, Price S, Verpillat P, Bühler FR, Dubois D, et al. European initiative towards quality standards in education and training for discovery, development and use of medicines. European Journal of Pharmaceutical Sciences 2012; 45: 515-520. 2. Boeynaems J-M, Canivet C, Chan A, Clarke MJ, Cornu C, Daemen E, et al. A European approach to clinical investigator training. Frontiers in Pharmacology 2013; 4: 112.	www.pharmatrain.eu ingrid.klingmann@pharmatrain.eu

Project acronym, title & number	Project results (IMI1 project foreground)	Foreground type	Reference to scientific publications / other public sources	Project website and contacts
Open PHACTS **The Open Pharmacological Concepts Triple Store** **115191**	The Open PHACTS Discovery Platform offers semantically integrated life science data allowing to query across the concepts compounds - targets - pathways - diseases. A well-structured application programming interface (API) allows standardised access and data retrieval.	▪ Semantically integrated life science data	1. Williams AJ, Harland L, Groth P, Pettifer S, Chichester C, Willighagen EL, et al. Open PHACTS: Semantic interoperability for drug discovery. Drug Discovery Today 2012; 17: 1188-98. doi: 10.1016/j.drudis.2012.05.016. 2. www.openphacts.org/news-and-events/publications	www.openphacts.org gerhard.f.ecker@univie.ac.at stefan.x.senger@gsk.com
RAPP-ID **Development of RApid Point-of-Care test Platforms for Infectious Diseases** **115153**	Breath sample technology: this technology is intended for capturing non-volatile components of exhaled breath for patient diagnostic purposes. The device, labelled BESS (Breath ElectroStatic Sampler), is based on electrostatic capture of microbe-containing aerosols present in exhaled breath. The BESS features a liquid capture interface, allowing collection of exhaled breath particles directly into microliters of buffer, the latter being adaptable to any biological assay of interest. The BESS has been designed with disposability in mind, using cost-saving plastics, along with one-time-use collectors to eliminate cross contamination between patients and saving time. Early-stage studies with influenza-infected patients of the usage of BESS versus swab sampling indicate a strong preference for BESS-collected samples, rather than the standard nasopharyngeal swab collection.	▪ Prototype	1. Ladhani L, Pardon G, van der Wijngaart W. A 3D microfluidic cage collector for airborne particles. 19th International Conference on Miniaturized Systems for Chemistry and Life Sciences, October 25-29 2015, Gyeongju, South Korea. www.rsc.org/images/LOC/2015/PDFs/Papers/0079_1B3-4.pdf	www.rapp-id.eu jvillaci@its.jnj.com herman.goossens@uza.be pieter.moons@uantwerpen.be

Project acronym, title & number	Project results (IMI1 project foreground)	Foreground type	Reference to scientific publications / other public sources	Project website and contacts
WEB-RADR **Recognising Adverse Drug Reactions** **115632**	WEB-RADR has delivered a mobile app for adverse drug reaction (ADR) reporting, regulatory news and ADR data. WEB-RADR can make available software code, images, and databases developed through the project. Additionally, the backend connections and rules between the World Health Organization Uppsala Monitoring Centre (WHO-UMC), national authorities and the apps are a shared resource, developed through WEB-RADR. The foreground can be described in sufficient detail to provide a sense of the capabilities. However, data security is paramount because a too detailed public description could expose systems to outside malicious actors. Therefore, the level of information that is transferred must meet the security requirements of each existing country using the app.	▪ Databases ▪ Technology platform	1. https://itunes.apple.com/gb/app/yellow-card-mhra/id990237487?mt=8 2. https://itunes.apple.com/mg/app/bijwerking/id1060529495?mt=8 3. https://itunes.apple.com/us/app/halmed/id1080314179?mt=8 4. https://play.google.com/store/apps/details?id=uk.org.mhra.yellowcard&hl=en_GB 5. https://play.google.com/store/apps/details?id=nl.lareb&hl=en_GB 6. https://play.google.com/store/apps/details?id=hr.halmed&hl=en_GB	www.web-radr.eu phil.tregunno@mhra.gsi.gov.uk
GetReal **Incorporating real-life clinical data into drug development** **115546**[52]	▪ The web-based navigator tool has been designed to: a. guide medicine development/evidence generation strategy: b. provide a methodological platform to provide options for study designs and analytical approaches; c. guide users towards more detailed material, publications and case studies reported by each GetReal work package (WP);	▪ Website ▪ Software tools ▪ Online education and Training programme	Information on all aspects of the project foreground included in this call are publically available at the following sources: 1. General information about GetReal and all relevant publications can be found on the GetReal website https://www.imi-getreal.eu 2. The Navigator can be accessed via: http://rwe-navigator.nice.org.uk 3. Details of the all the deliverables described in this Call can be can be found at: https://www.imi-getreal.eu/Events/Stakeholder-Conference	www.imi-getreal.eu elaine.a.irving@gsk.com d.e.grobbee@umcutrecht.nl p.stolk@umcutrecht.nl

[52] This list is provisional upon finalisation of the inclusion of Foreground from the GetReal project.

	d. direct users to authoritative external guidance and sources. ▪ Research and policy recommendations on the use of real world evidence (RWE) in drug development and stakeholder decision making in addition to recommendations around the use of the research tools, key outputs of simulation studies and methodological recommendations generated in GetReal. ▪ PragMagic: a decision support tool for pragmatic trial design aimed at facilitating the design & planning of pragmatic trials, by providing insights into the consequences of design choices & possible operational challenges to maximise the generalisability of trial findings while ensuring validity and operational feasibility. ▪ ADDIS software: a system that allowed us structured clinical trials data. We support the automated discovery and (meta-) analysis of trial data, as well as benefit-risk assessment. ▪ Education and training materials on a remote e-learning platform intended to simultaneously discover the possibilities of, and the requirements on, a database of ▪ Increase knowledge and skills about topics that are at the core of the GetReal project, with a particular emphasis on the connection between methodology development and its practical applications within companies, regulatory agencies and HTA bodies. ▪ GetReal platform for the engagement of key stakeholders.		4. Additional information regarding all key foreground listed are available via the GetReal website (slides and materials shown at stakeholder meeting of 24 November 2016, Brussels).	

Annex II - IMI2 Call 12 topics text

Introduction

The Innovative Medicines Initiative is a jointly funded partnership between the European Union, represented by the European Commission, and the European Federation of Pharmaceutical Industries and Associations (EFPIA).

The Innovative Medicines Initiative 2 Joint Undertaking (IMI2 JU) has been created[53] following the principles below:

- Research related to the future of medicine should be undertaken in areas where societal, public health and biomedical industry competitiveness goals are aligned and require the pooling of resources and greater collaboration between the public and private sectors, with the involvement of small and medium-sized enterprises (SMEs).
- The scope of the initiative should be expanded to all areas of life science research and innovation.
- The areas should be of public health interest, as identified by the World Health Organisation (WHO) report on priority medicines for Europe and the World[54].

The IMI2 JU objectives are usually implemented through Research and Innovation Actions (RIAs), and Coordination and Support Actions (CSAs) where public and private partners collaborate, joining their expertise, knowledge and resources.

The initiative should therefore seek to involve a broader range of partners, including mid-sized companies[55], from different sectors e.g. biomedical imaging, medical information technology, diagnostic and/or animal health industries. Involving the wider community in this way should help to advance the development of new approaches and technologies for the prevention, diagnosis and treatment of diseases with high impact on public health.

The IMI2 Strategic Research Agenda (SRA)[56] is the main reference for the implementation of research priorities for IMI2 JU. The scientific priorities for 2017 for IMI2 JU have been prepared based on the SRA.

Applicant consortia are invited to submit a proposal for each of the topics that are relevant for them. These proposals should address all aspects of the topic to which the applicant consortia are applying. The size and composition of each consortium should be adapted so as to respond to the scientific goals and the expected key deliverables.

Applicant consortia, during all stages of the evaluation process, must consider the nature and dimension of the IMI2 JU programme as a public-private collaboration.

While preparing their proposals, applicant consortia should ensure that the needs of patients are adequately addressed and, where appropriate, patient involvement is encouraged. Applicants should ensure that gender dimensions are also considered. Synergies and complementarities with other national and international projects and initiatives should be explored in order to avoid duplication of efforts and to create collaboration at a global level to maximise European added value in health research. Where appropriate, the involvement of regulators is also strongly encouraged.

Applicant consortia shall ensure that where relevant their proposals abide by the EU legal framework on data protection[57].

Before submitting a proposal, applicant consortia should familiarise themselves with all Call documents such as the IMI2 Manual for evaluation, submission and grant award[58], and the IMI2 evaluation criteria. Applicants

[53] Council Regulation (EU) No 557/2014 of 6 May 2014 establishing the Innovative Medicines Initiative 2 Joint Undertaking (IMI2 JU).
[54] http://www.who.int/medicines/areas/priority_medicines/en/
[55] Under IMI2 JU, mid-sized companies having an annual turnover of EUR 500 million or less not being affiliated entities of companies with an annual turnover of more than 500 million; the definition of 'affiliated entities' within the meaning of Article 2(1)(2) of Regulation (EU) No 1290/2013 applies mutatis mutandis. Where established in an EU Member State or an associated country, are eligible for funding.
[56] http://www.imi.europa.eu/sites/default/files/uploads/documents/IMI2_SRA_March2014.pdf
[57] Directive 95/46/EC on the protection of individuals with regard to the processing of personal data and the free movement of such data and implementing national laws: http://eur-lex.europa.eu/legal-content/EN/TXT/?uri=celex:31995L0046
[58] http://www.imi.europa.eu/sites/default/files/uploads/documents/IMI2_CallDocs/Manual_SubEvalAward_IMI2_v1.4_Oct2016.pdf

should refer to the specific templates and evaluation procedures associated with the topic type: Research and Innovation Actions (RIA), Coordination and Support Action (CSA).

Topic 1 : Development and validation of technology enabled, quantitative and sensitive measures of functional decline in people with early stage Alzheimer's disease (RADAR-AD)

Topic details

Topic code	IMI2-2017-12-01
Action type	Research and Innovation Actions (RIA)
Submission & evaluation process	2 Stages

Part of the Remote Assessment of Disease and Relapse Programme (RADAR)

Introduction to the RADAR programme and problem statement

With rising healthcare costs, all healthcare stakeholders (payers, physicians, patients) are shifting the onus from a 'pay for intervention' to a 'pay for performance' model. This change in focus towards overall outcomes will drive a paradigm shift towards disease interception, i.e. move from a 'diagnose and treat' to a 'predict and pre-empt' approach. In this model, pre-emption, i.e. intervening early enough in the disease process to prevent serious effects of the disease associated with progression, becomes a critical component of managing chronic disease. Additionally, as the trajectory of chronic diseases is often cyclical, this offers multiple interception opportunities to prevent serious decline — for example, predicting and pre-empting recurrence/suicidality in severe depression, hypoglycaemic events in diabetes, or exacerbations in multiple sclerosis (MS), chronic obstructive pulmonary disease (COPD) or asthma.

Measuring physiological and activity-based parameters remotely and continuously via unobtrusive on-body sensors or smartphones has the potential to revolutionise our ability to predict and pre-empt harmful changes in disease trajectory. Developing methods for real-time identification of behavioural and physiological patterns (bio-signatures) that culminate in relapse is of great importance; early detection and communication of 'red flags' to patients, caregivers and care providers can prompt help-seeking behaviour and deployment of just-in-time interventions that may prevent relapse episodes, effectively altering one's clinical trajectory. A platform to acquire data in a real world setting would also enable the development of measures of real world effectiveness of medicines.

RADAR is a multi-topic programme in IMI2 that aims to overcome three key bottlenecks in developing such methods:

1) a lack of fundamental disease understanding into the signals and fluctuations in disease state;

2) the lack of clear policy, guidelines and pathways to develop and license 'pre-emptive' therapeutic strategies that use such digital monitoring and remote assessment technology;

3) the immaturity of the technology platforms, including sensor technology, data exchange standards, continuous sensor data access and stream processing technology, as well as the analytical methodology, where today research is hampered by ad-hoc solutions that are not suitable to develop healthcare products in the longer term.

Need and opportunity for public-private collaborative research under the RADAR programme

The RADAR programme aims to test if new pre-emptive therapeutic development and clinical care strategies based on remote continuous monitoring are both scientifically feasible and also practically feasible as part of a wider healthcare system.

Scientific feasibility will be performed via the individual topics of the RADAR programme to focus on the specifics of different disease areas. The first topic of the RADAR platform was published as part of IMI2 JU - Call 3, and the action that it generated studies the fluctuation of the chronic diseases of depression, multiple sclerosis and epilepsy, using remote monitoring technology, to provide a foundation for developing a novel paradigm based on prediction and pre-emption. The current topic, launched as part of IMI2 - Call 11 will study the development and validation of technology-enabled, quantitative and sensitive measures of functional decline in people with early stage Alzheimer's disease.

Research in these areas needs to bring together physicians, patient groups, sensor manufactures, ICT (information and communication technology) providers, data management and analyst specialists with the pharmaceutical industry.

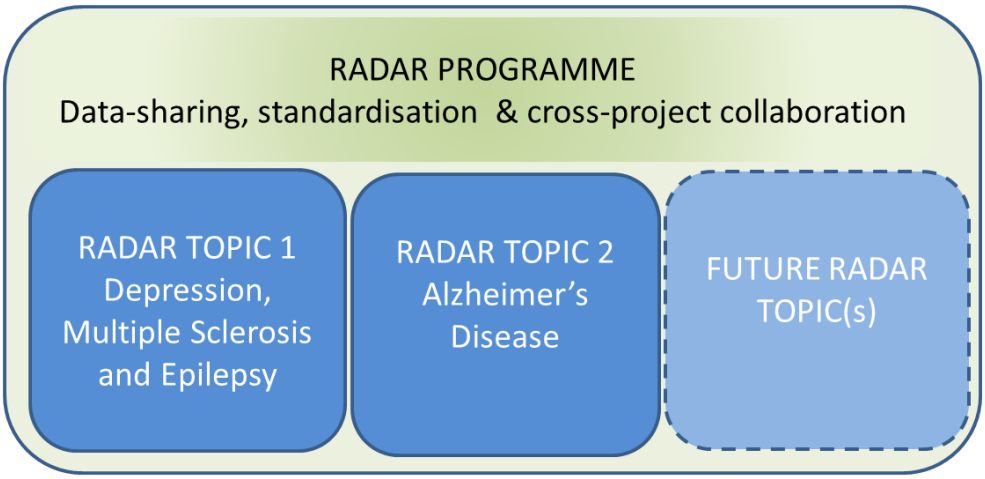
Introducing a drug development and a clinical care strategy based on such science and technology requires a second type of public-private research to be undertaken to: 1) develop policy for the regulatory and licensing pathways to deliver a digital intervention; 2) understand and develop a framework to support new digital-based interactions between patients and health care providers. This will require key stakeholders such as patient groups, regulators, healthcare providers, communications organisations, device manufactures and infrastructure providers to understand and develop a roadmap of how such interventions can be deployed effectively and safely.

Overall objectives of the RADAR programme

The key objective of the RADAR programme is to develop the foundational components of a digital platform to improve patient outcomes through remote assessment. These components will be split into several topics, with some cross-cutting themes co-ordinated across all topics. Considering the overall objective of the RADAR programme, the actions stemming from the different topics will be deemed to be complementary to each other.

RADAR programme architecture

The full RADAR programme will consist of several topics that are resourced and managed independently but will join forces in key areas such as technological approach and data sharing. The RADAR-CNS action covering depression, MS and epilepsy was generated from the topic launched under IMI2 - Call 3. It has developed a key part of the core platform for the collection, transmission, storage, analysis and visualisation of the relevant functional measures for the whole RADAR platform, which can act as the basis for the integration of further modules provided by other RADAR initiatives. The core platform will be extended with new or enhanced capabilities wherever identified as beneficial for the topics at the core of the present project on patients with dementia, hence beyond RADAR-CNS, to make sure the platform can evolve with the state-of-the–art in the field. Applicants must reserve some resources to facilitate these cross-projects activities and consider this key aspect when developing their solutions to ensure interoperability through the horizontal platform. Under IMI2 - Call 12, one additional topic will be launched in Alzheimer's disease (AD).



Future RADAR topics

At a later stage, IMI2 JU may publish additional topics which will become part of the RADAR programme.

In that respect, potential applicants must be aware that all or some of these RADAR topics, if exceptionally needed and so foreseen in the applicable IMI2 JU Annual Work Plan, may be restricted to those consortia already selected under the relevant Calls in order to enhance their results and achievements by extending their duration and funding.

Consortia will be entitled to open to other beneficiaries as they see fit to fill critical skills gaps in the consortia that reflected the extensions in these work plans.

In the case of the RADAR-AD topic, a restricted Call may be launched as part of a future IMI2 JU Annual Work Plan, for further detail see below under 'Future Project Expansion'.

General Principles for all Projects Conducted under the RADAR Programme:

Data Sharing and interoperability

Data sharing and interoperability is paramount to the success of the RADAR programme. The framework supporting this data sharing (i.e., the type of data to be shared and the rules governing the access, (use/ re-use and informed consent) to data as well as the data sharing) must be established prior to the submission of the full proposal in line with IMI2 Intellectual Property (IP) policy and considering the overall approach agreed upon in the other RADAR projects. EFPIA members and consortia partners will be committed to sharing all data (clinical, bio-sensor, etc.) available to, or generated by the RADAR program amongst all members of a RADAR topic, and across topics as required. In addition to data, RADAR constituents will also share, among others, domain practices and expertise developed with respect to data management procedures, usability, regulatory and policy pathways etc. across the RADAR program and externally as required by IMI policy and procedures. Please, also see the expectations with regard to data standards, compatibility and interoperability in the impact section of the topic description. It is to be noted that the digital platform in development should be able to interface to different kind of sensors and devices, which, some of them, will be tested in the frame of the present project.

Specific challenges to be addressed

Alzheimer's disease (AD) is today the leading cause of dementia and one of the most common causes of disability and loss of independence among the elderly. The World Health Organization (WHO) estimates the cost of dementia disorders in the European Union alone to be more than € 160 billion per annum. This cost will continue to rise dramatically as the numbers of people with dementia in the European Union are projected to nearly double every 20 years, due to Europe's aging demographic.

The early stages of AD are associated with cognitive decline, overlapping with increasing functional decline (impairments in the ability to perform daily activities), leading to progressive loss of independence and escalation of caregiver burden and medical costs. While much effort has gone into developing sensitive measures of cognition, today there are no similar measures of subtle functional changes in early AD subjects which have a direct impact on disease burden.

Recent data from long-term longitudinal cohorts have begun to delineate cognitive domains and functional tasks that are most affected by AD pathology. These include cognitive domains related to episodic memory, spatial orientation, processing speed and functional read-outs such as changes in ability to perform simple financial calculations, ability to use a phone/computer, gait speed, driving performance, and ability to adhere to medications, among other things. In addition, AD and related co-morbidities also have an effect on stress, mood and sleep. Impairment of these cognitive domains, functional capabilities and mood and sleep can be captured by new technology methods such as wearables, mobile devices and home-based sensor technologies.

The overall goal of the action generated from the RADAR-AD topic would be to measure functional status and some key underlying cognitive abilities of AD patients in order to identify meaningful differences compared to normal status, using a robust, scalable technology-enabled system that can be deployed in real world settings to monitor and improve real world outcomes that are relevant to patients and their caregivers. While the main focus of the topic is to understand functional decline in subjects with mild cognitive impairment (MCI) and in the early stages of AD, nevertheless late-stage AD monitoring should also be considered in order to validate the results and show the relationship of functional measures with all stages of AD.

Need and opportunity for public-private collaborative research

The ability to track and measure functional decline in AD populations to shorten clinical development and generate payer-relevant evidence of real world impact of therapeutic interventions is a precompetitive need in the field of Alzheimer's drug development. The development and validation of technology-enabled functional endpoints in AD will require public-private collaboration between AD clinical sites, home-based caregivers, sensor manufacturers, analytics experts and software developers. In addition, successful implementation will also require a collaborative partnership with AD patient advocacy groups, the caregiver community and privacy and bioethics experts to ensure that the technology solutions developed in the project can be adopted in the real world. The implementation of the project involving all these stakeholders will ensure the sustainability of the results. These stakeholders need to have expertise from diverse fields and different industries, and they need to align with patients and regulators; all these requirements imply that the goals of the RADAR-AD topic are best accomplished in a public-private consortium setting.

Scope

The main goal of the action to be created from this topic is to develop a digital platform to measure a valid and meaningful combination of smartphone, wearable and/or home sensor based parameters that can detect subtle functional deficits in early Alzheimer's patients (mild AD, MCI or earlier), in the context of AD progression. Risk factors and other biomarkers that could identify pre-symptomatic prodromal AD will be also considered as exploratory assessment. Even though the system developed should be suitable for longitudinal assessment of function, in their proposal applicants should come with their suggestions on how the digital platform will generate validity data from a cross-sectional study to demonstrate that function can be measured at baseline in a reliable and sensitive manner. Considering the limited budget and project duration, the solution to be built will have to rely upon already available technology platforms and on available longitudinal datasets. In case of a successful outcome, the results should be discussed with regulatory agencies in order to obtain guidance about how to develop a path for formal qualification as outcome measurements to be used in the real world for assessing future therapeutic intervention.

The following activities will be within the scope of proposals to achieve the topic goals:

- Analysis of existing longitudinal AD datasets and disease model(s) to identify functional domains or markers that are specific and sensitive to early stages of Alzheimer's progression and most predictive of deleterious long-term outcomes such as loss of independence and nursing home entry. Such functional domains should include real world activities such as the ability to perform financial calculations, utilise the phone, navigate around the house/neighbourhood, adhere to a medication schedule, interact socially with appropriate behaviour and perform other everyday tasks that require episodic memory and executive function. The applicants should identify and gain access to the appropriate longitudinal datasets that allow retrospective analysis of cognition, function and caregiver / payer relevant long-term outcomes.
- Obtain and incorporate feedback from regulators (i.e. scientific advice) regarding the potential use of technology-enabled functional end-points to be possibly considered in future for registration studies of drugs.
- Obtain and incorporate feedback from patients, caregivers and payers to ensure that the functional domains being measured are relevant and meaningful.
- Implement a platform technology-enabled system of sensors and devices to continuously analyse data from identified functional domains, including smartphones, wearable and/or fixed home-based sensors. This can concern measures that are passive (e.g. ability to use phone or computer keyboard, gait speed etc.), or active (a challenge task requiring financial calculations etc.) with respect to patient interaction.
- Validate the platform technology-enabled function assessment system in a real world clinical setting. This cross-sectional validation study will require a short-term (approximatively 3 months) baseline assessment of function to establish a reliable cross-sectional measure of function using the built sensor-based system in cognitively normal, MCI and mild AD cohorts. In addition, moderate AD and some severe AD patients will be also included.

The functional measures will be optimised for the following.

- Ability to best differentiate different stages of Alzheimer's disease (i.e. cognitively normal vs. MCI vs. mild AD vs. moderate AD). The main focus will be to identify functional measures that best separate cognitively normal from early MCI patients.
- Ability to show sensitivity to changes using appropriate modelling-based approaches.
- Correlation with cognitive domains known to be effected in AD (e.g. episodic memory).
- Correlation with established paper and pencil (self-reported) scales to measure function and cognition in AD.
- Correlations with known risk factors for AD (body mass index (BMI), physical exercise, sleep, etc.) for the possible identification of a putative pre-symptomatic cohort.
- Correlation with known biomarkers of pathology, such as positron emission tomography (PET) and cerebro-spinal fluid (CSF) markers, or clinical scales (ADAS-Cog) if available.
- Correlation with caregiver burden and healthcare utilisation costs.
- Ease of use and adherence by technology users in real world clinical settings.

Collaboration agreements

The key objective of the RADAR programme is to develop the foundational components of a digital platform to improve patient outcomes through remote assessment. To ensure the interactions between the projects under the RADAR programme, which are paramount for its overall success, and the necessary data sharing and interoperability, the funded actions are expected to share data and collaborate in domain practices and expertise developed with respect to, among other things, data management procedures, usability, regulatory and policy pathways. Therefore all grants awarded under the RADAR programme will be complementary Grant Agreements. The respective options under Article 2, Article 31.5 and Article 41.4 of the IMI2 Model Grant Agreement will be applied to the relevant Grant Agreements.

Expected key deliverables

- Prioritised list of functional domains relevant to early Alzheimer's disease progression (based on analysis of existing datasets and input from experts, payers, patient and caregiver advocacy groups).
- Prioritisation of pre-existing wearable/home-based sensors & devices and computerised functional tasks that would best measure the target functional domains in early AD populations.
- Development of continuous data-sensing solutions as shown to be needed for the monitoring of the identified relevant parameters in the AD functional domains. The members of the industry consortium of the RADAR-AD topic will make available facilitating tooling and horizontal platform assets to support such development, assuming the integration of pre-existing and newly added components to the evolving platform infrastructure. In this way, the interoperability of all solutions developed on the platform inside and outside the action will be ensured. The solutions developed, irrespective of whether they leverage the planned facilitating common platform infrastructure or are built independently from it, should in any case allow for cross-analysis, data stream sharing and aggregated visualisation both across all solutions developed by the action generated by this topic, and in combination with pre-existing solutions such as those being elaborated under the RADAR CNS action (see what is specified in the introduction to the RADAR programme). It is indeed paramount to the value of the project deliverables that they do not result in vertical, ad-hoc solutions as often seen in today's practice.
- Cross-sectional validation of the developed system/digital platform and ad hoc sensors and devices in clinical cohorts (normal, at risk, MCI, AD) in order to gather cross-sectional validation data from normal, at risk, MCI, mild AD and moderate AD cohorts, and further refinement of the system through optimisation studies: baseline cross-sectional assessment is proposed to last 2-3 months.
- Finalised version of the system ready for deployment in exploratory clinical trials and for real world evidence gathering studies at home settings or in elder/dementia care facilities.

Expected impact

The development of objective and sensitive functional measures will enable potential dementia therapies to demonstrate functional impact and clinical meaningfulness of early intervention without requiring long follow-on studies, thus reducing the time and cost required to bring Alzheimer's disease modifying drugs to market.

An objective, scalable, platform technology-enabled functional assessment system will also allow the measurement of the real world impact of disease trajectory on individual patients in home and caregiver settings and help direct scalable and customised interventions that target specific functional deficits that promote independent living, thus reducing the cost and care-giving burden. Another valuable impact would be given by integrating organisations, e.g. small and medium-sized enterprises (SMEs) with expertise in developing sensors and also in the area of processing and analysing the data from sensors/ devices related to the scope of measuring the functional decline due to Alzheimer disease, as well as addressing the specific problem of the digital platform/user interface for these populations. This approach will allow the SME community to build up their skills and increase competitiveness within this area.

Furthermore, adding AD to the RADAR programme will make the entire system more attractive to professionals involved in dementia care, thus helping with the dissemination and adoption of the entire RADAR platform, ensuring interoperability and technology evolution without disrupting the continuous build-up and extension of the knowledge collection and research practices across the whole RADAR scope (i.e. without having to resort to ad-hoc, un-reusable solutions for specific research topics, with their own visualisation etc.).

To maximise impact, it is expected that the system built within the action generated from the RADAR-AD topic will adhere to well-accepted data standards, where applicable, to ensure compatibility with other systems both within the RADAR programme and more widely. For example, many patients with Alzheimer's disease also have depression as a co-morbidity. The facility to deal with many diseases will make the entire system more attractive to professionals involved in elder care, thus helping with the dissemination and adoption of the entire RADAR platform.

The system created via the RADAR–AD topic has the potential to become a widely used tool to measure and help improve quality of life in elder care homes and assisted-living facilities that focus on dementia and other age-related causes of functional decline. The platform developed to measure function in AD patients by the action will be made available for further refinement and validation in longitudinal clinical studies to each of the industry members of the consortium. Consequent incorporation in any controlled clinical trials will help gain regulatory acceptance of the platform as a valid efficacy endpoint. The platform will also be made available to a broader set of clinical studies that may be ongoing in various IMI-funded projects. Opportunities to deploy

the platform will also be explored in more real world settings such as elder care and dementia care facilities. In the long term it is expected that the platform created by the action will be used both in AD clinical trials, as a valid and sensitive efficacy measure, as well as in real world settings, such as homes and senior care facilities, to track functional decline in patients with AD in a way which will lead to better interventions that improve the quality of life.

Potential synergies with existing consortia

Applicants should take into consideration, while preparing their short proposal, relevant national, European (both research projects and research infrastructure initiatives), and non-European initiatives. Synergies and complementarities should be considered in order to incorporate past achievements, available data and lessons learnt where possible, thus avoiding unnecessary overlap and duplication of efforts.

As indicated in the introduction to the RADAR programme, the action generated from this topic is expected to actively synergise with the already generated RADAR-CNS action (http://www.radar-cns.org/), as well as with future actions that will be generated under the programme. Thus applicants must plan for resources to facilitate these cross-projects activities and consider this key aspect when developing their solutions to ensure interoperability through the horizontal platform.

In addition, synergies should be considered with existing IMI projects in the AD field.

- **EMIF** (http://www.emif.eu/): The applicants should explore collaborations with EMIF to access the datasets required to evaluate functional domains in AD patients. The applicant consortium should seek to utilise the output of IMI EMIF to acquire longitudinal datasets for the evaluation of functional changes in AD subjects.
- **BD4BO ROADMAP (**http://www.roadmap-alzheimer.org/index.html) the action generated from this topic should strive to form a collaboration with the ROADMAP consortium to obtain input from regulators and payers which will be important in developing valid and meaningful functional measures and can be obtained via mechanisms developed in ROADMAP.

Other initiatives to be considered for synergy activities are mentioned below.

- Several initiatives on assessing ageing are taking place in various European countries, as summarised in the SHARE project (www.share-project.org) addressing topics relevant for the Call, .i.e. computerised functional tasks, functional domains of the ageing brain, biomarker/data analysis especially in healthy, ageing or early affected patients. See as example of a national initiative in Germany: http://www.gesundheitsforschung-bmbf.de/de/5765.php.
- There are substantial activities on Ambient Assisted Living (AAL) in various European countries under the umbrella of the AALIANCE2 consortium (see www.aal-europe.eu). For more information on single initiatives, see CORAL (www.coral-europe.eu) and ECHAlliance (www.echalliance.com).

Synergies with other relevant initiatives/projects should also be explored in order to consider learnings as well as the potential for future combination, once the digital platform generated via the RADAR-AD topic has been successfully implemented and validated. These can be initiatives focussed on early risk detection and intervention in the area of active and healthy ageing in relevant EU funded projects, such as those supported by Horizon 2020 Societal Challenge 1: Health, Demographic Change and Well-being, as well as European platforms and infrastructures as relevant. Examples here include:

- NC3: http://www.bioshare.eu/content/nc3
- BBMRI-ERIC Work Programme 2017: http://www.bbmri-eric.eu/wp-content/uploads/2016/07/BBMRI-ERIC_Work_Programme_2017_online.pdf
- ELIXIR: https://www.elixir-europe.org/about-us
- Human Brain Project (HBP) 'Medical Informatics Platform: searching real patient data to understand similarities and differences among brain diseases', released in March 2016, see: https://www.humanbrainproject.eu/sp8;jsessionid=16hxaa8ljljrm1arbzlf32dbt5
- AgedBrainSYSBio: http://www.agedbrainsysbio.eu/
- SENSECog: http://www.sense-cog.eu/.

Applicants should also consider how the results of the action could contribute and align with the policy of the European Commission's Directorate-General for Health and Food Safety (DG SANTE) on Alzheimer's and other dementias (http://ec.europa.eu/health/major_chronic_diseases/diseases/dementia_en#fragment2).

Finally, interesting activities on the validation of digital biomarkers in patients with neurodegenerative disorders are sponsored in the US by the Critical Path Institute's Coalition Against Major Diseases (CAMD) (https://c-path.org/).

Industry consortium

The industry consortium is composed of the following EFPIA companies:

- Janssen (lead)
- Takeda
- Eli Lilly
- Novartis
- Nokia.

In addition, the industry consortium includes the following IMI2 JU Associated Partner:

- Software AG

The industry consortium will contribute the following expertise and assets:

- programme leadership, project management, financial management;
- expertise in longitudinal analysis of AD cognition, function, biomarker and clinical data;
- expertise in payer and regulatory perspectives;
- expertise in data analysis, biosensor evaluations;
- clinical study design, biostatistics, expertise in clinical assessment of AD patients, including cognitive and functional endpoints;
- expertise in patient association and ethical aspects;
- biosensor evaluations;
- clinical study design, biostatistics, data management expertise and monitoring/data review tools, especially with data on demand approaches for visualisation and monitoring of studies utilising smartphone apps;
- expertise in functional assessments, such as activities of daily living (ADL) gained through clinical studies in AD and eventually clinical datasets that may be made available;
- AD therapeutic area expertise and data analysis along with years of digital and clinical endpoint strategy knowledge;
- Nokia will bring IMPACT SW platform licence and support;
- Software AG will bring Apama, Universal Messaging, MashZone, Terracotta, Apama Predictive Analytics add-on, and Device Integration Platform software licences.

Indicative duration of the action

The indicative duration of the action is 36 months.

Future Project Expansion

Potential applicants must be aware that the Innovative Medicines Initiative 2 (IMI2) Joint Undertaking may, if exceptionally needed, publish at a later stage another Call for proposals restricted to the consortium already selected under this topic, in order to enhance the results and achievements by extending the duration and funding. The consortium will be entitled to open to other beneficiaries as it sees fit.

A restricted Call may be launched as part of a future IMI2 JU Annual Work Plan to enable the validation of the biomarkers that have been found promising, following positive regulatory scientific advice, and / or to perform the necessary longitudinal clinical studies to determine the utility of the digital platform, as to being able to detect AD specific change in function, and the feasibility for its integration in clinical trials.

Indicative budget

The indicative in-kind contribution is EUR 3 555 000. This contribution comprises an indicative EFPIA in-kind contribution of EUR 2 830 000 and an indicative IMI2 Associated Partners in-kind contribution of EUR 725 000.

Due to the global nature of the participating industry partners it is anticipated that some elements of the contributions will be non-EU in-kind contribution[59].

The financial contribution from IMI2 is a maximum of EUR 5 000 000.

Applicant consortium

The applicant consortium will be selected on the basis of the submitted short proposals.
The applicant consortium is expected to address all the research objectives and make key contributions to the defined deliverables in synergy with the industry consortium which will join the selected applicant consortium in preparation of the full proposal for stage 2. Therefore, the applicant consortium should be able to demonstrate the full scope of experience and expertise needed in order to address effectively and meet all goals outlined in this topic.

This may require mobilising, as appropriate, the following expertise:

- AD clinical research and trials and disease area expertise, regulatory science, patients and patient organisations, data and knowledge management;
- project management and professional communication expertise, design and conduct of clinical studies (end-points, inclusion criteria etc.);
- expertise in clinical data management and clinical statistics;
- expertise in device and sensor development (including SMEs); IT / analytics expertise (including SMEs);
- expertise in data privacy and security;
- regulatory expertise and experience in development and qualification of novel end-points using digital technologies; clinical and general project management.

It may also require mobilising, as appropriate, the following resources:

- access to patient cohorts in all stages of Alzheimer's disease (preclinical, MCI, mild to moderate AD), possibly with a biomarker characterisation, and non-affected control subjects sharing a similar environment;
- data management architecture, hardware / software platform, state-of-the-art algorithms to process and analyse data from sensors / devices; device, data and connectivity management:

[59] Note: This does not however constitute the justification referred to in Article 4(2) of the IMI 2 JU regulation.

- architecture, hosted semantic web (SW) platform, allowing the on-boarding and life cycle management of medical equipment in a communication secure environment (including SMEs) that could be further developed or modified for use in assessing functional decline due to AD.

Suggested architecture of the full proposal

The applicants should include in their short proposal their suggestions for creating the full proposal architecture, taking into consideration the industry contributions and expertise as indicated.

The final architecture of the full proposal will be defined together with the industry consortium and should enable activities designed to achieve all objectives and deliverables as indicated in the previous relevant sections and in collaboration with EFPIA and the Associated Partner.

In the spirit of the partnership, and to reflect how IMI 2 JU call topics are built on identified scientific priorities agreed together with EFPIA beneficiaries/large industrial beneficiaries, these beneficiaries intend to significantly contribute to the programme leadership and project and financial management.

The final architecture of the full proposal will be defined by the participants in compliance with the IMI 2 JU rules and with a view to the achievement of the project objectives. The allocation of a leading role within the consortium will be discussed in the course of the drafting of the full proposal to be submitted at stage 2. To facilitate the formation of the final consortium, until the roles are formally appointed through the consortium agreement, the proposed project leader from among EFPIA beneficiaries/large industrial beneficiaries shall facilitate an efficient negotiation of project content and required agreements.

All beneficiaries are encouraged to discuss the project architecture and governance and the weighting of responsibilities and priorities therein.

In their short proposal, the applicant consortium is also expected to have a strategy on the translation of the relevant project outputs into regulatory, clinical and healthcare practice. A plan for interactions with regulatory agencies / health technology assessment bodies with relevant milestones should be put forward, and appropriate resources should be allocated to ensure this, e.g. qualification advice on the proposed methods for novel methodologies for drug development, qualification opinion.

A plan for aspects related to sustainability, facilitating continuation beyond the duration of the action should also be proposed.

Work package 1: Management, coordination, dissemination and sustainability

1.1. Set-up of project management boards: governing, steering, communication, intellectual properties.

1.2. Development and implementation of a dissemination programme.

1.3. Development and implementation of internal and external communication tools.

1.4. Financial management, monitoring and project management support and implementation.

1.5. Development of a sustainability plan facilitating continuation beyond the duration of the action.

Industry contribution: shared programme leadership with the action coordinator, project management, financial management; development and implementation of a data management plan and correlated activities; contribution to communication and information diffusion.

Expected applicant consortium contribution: it is expected that the applicant consortium has the necessary skillsets to contribute effectively to all the tasks foreseen in the WP description and in a manner compatible with contributions of the industry consortium.

Work package 2: Assessment of functional domains relevant to early Alzheimer's disease progression

2.1. Assessment of existing clinical, functional, cognitive, digital data regarding AD patients at different stages; collect input from patients & caregivers so as to identify functional domains that are amenable to digital data collection and that are specific and sensitive to the early stages of AD progression and most predictive of deleterious long-term outcomes.

2.2. Identification and use of appropriate longitudinal datasets that will allow a modelling-driven interpretation of the cross-sectional data collected in the clinical study described in WP5; progression and most predictive of deleterious long-term outcomes.

2.3. Prioritisation of functional domains relevant to early Alzheimer's disease progression.

Industry contribution:

- expertise in clinical, functional, behavioural and biomarker measurement mostly gained through clinical studies in AD patients;
- expertise in biomedical statistical analysis;
- expertise in disease modelling , identifying and accessing appropriate datasets, interpreting analyses of longitudinal datasets and prioritisation of functional domains relevant to early Alzheimer's disease progression;
- opportunity to connect with other IMI programmes regarding tools and knowhow that could be transferred into the current project so as to maximise the probability of success.

Expected applicant consortium contribution: the applicant consortium should have the necessary skillsets and the capacity to engage with institutions where they can access patients in all stages of Alzheimer's disease (preclinical, MCI, mild to moderate AD) and their caregivers. They should have a clear understanding of their need and the opportunity to engage with patients for technology pilot testing and eventually for a proper clinical trial. They should have analytical & statistical competence for contributing to the existing data analysis and inclusion in a model-based assessment of the data that will be collected in the project.

Work package 3: Communication with regulatory authorities, patient associations, payers and Ethical Boards

3.1 Connect with patient associations, caregivers and payers of some European countries to understand the ethics and relevance of the functional domains chosen to be measured, the acceptability of technology and the overall feasibility of the project, so as to adaptively define the progression of the project. Furthermore, activities should be considered to ensure, where relevant, alignment with DG SANTE's policy on Alzheimer's and other dementias.

3.2 Align with the regulatory requirements for approaching a possible future qualification of the use for digital technology to monitor AD patients.

3.3 Progress the preparation of the documents required for a European Medicines Agency (EMA) Scientific Advice to lay down a plan regarding the future potential use of technology and related functional end-points and biomarkers, when appropriate, in order to streamline the project progression into a clear deliverable.

Industry contribution: Expertise in payer and regulatory perspectives and processes for obtaining Scientific Advice; expertise in policy, regulatory affairs, patient associations and payers.

Expected Applicant consortium contribution: engaging patient associations or advocacy groups; competences on data privacy and data security. Applicants should also be able to support the industry partners in the process for obtaining a scientific advice from the regulatory agency to lay the foundations for future qualification of the medical device.

Work package 4: Development of a technology-enabled system to measure identified functional domains via smartphone, wearable and fixed home-based sensors

4.1 Prioritisation of pre-existing wearable/home-based sensors and computerised functional tasks that would best measure the target functional domains in early AD populations.

4.2 Development of plug-in solutions for monitoring the parameters relevant to AD in order to be fully interoperable with a pre-existing platform.

4.3 Extension of the assets of the already-existing continuous monitoring and remote assessment platform in order to permit the connection of the plug-in solutions developed.

Industry contribution:

- expertise in data analysis, biosensor evaluations; software licences (Apama, Universal Messaging, MashZone, Terracotta, Apama Predictive Analytics add-on, and Device Integration Platform software licences);
- software licenses (IMPACT CDP device and subscription management, IMPACT secure data gateway, IMPACT connectivity management), related application hosting services;
- experience with digital biomarkers collected through smartphone apps and other wearables for continuous monitoring and data analysis;
- expertise in both the Activities of Daily Living (ADL) and digital biomarkers collected through smartphone apps for continuous monitoring from previous studies;
- prioritisation of pre-existing digital tools that would best measure the target functional domain in early AD;
- scientific search of technologies used in studies to measure functional domains of AD;
- market research of technologies commercially available, and proposed prioritisation along pre-defined criteria;
- identification of gaps / functional domains that cannot be covered by adequate technology (or are not satisfactorily understood).

Expected Applicant consortium contribution: it is expected that the applicant consortium will be able to utilise relevant hardware / software and extend any relevant pre-existing platform for digital data collected in patients with neurologic or psychiatric disorders in order to meet the needs of the action selected under this topic. The applicant consortium is expected to on-board devices (hardware) as seen needed for the specific AD studies at hand and specify data management and analytics procedures (software) with the same aim, on top of the industry-provided and pre-existing platform infrastructure, as such realising the technical environment for validation in WP5. The solution should be modifiable and extendable and able to benefit from technology assets brought forward by the industry (Nokia will bring IMPACT SW platform licence and support; Software AG will bring Apama, Universal Messaging). They should also be able to engage in bench tests, simulations and empirical pilot experiments with patients and caregivers in order to effectively select the sensors / devices that will be used for the actual proof-of-concept study.

Work package 5: Validation of the technology-enabled function assessment system in a real world clinical setting

5.1 Deployment of the digital platform developed by the action in a cross-sectional clinical study to establish correlation to disease stages (normal, MCI, AD), to cognition, to traditional ‘paper-pencil self-reported measures’ of function and other biomarkers.

5.2 Optimisation work of the developed system of sensors and devices in order to establish a reliable cross-sectional measure of function in cognitively normal, MCI, mild AD and moderate AD cohorts.

5.3. Implementation of the results obtained into a model based on longitudinal data, in order to propose a possible progress of the dataset produced into a future longitudinal cohort study, and thus providing a starting point for a process of regulatory validation of this approach.

Industry contribution: To provide qualified support to the definition of the clinical study design and the preparation of the study protocol and the statistical analysis package by implementing expertise and know-how in clinical science, clinical operation, regulatory, biostatistics and data management, report preparation to support a scientific publication

Expected applicant consortium contribution: it is expected that the applicant consortium will contribute to the clinical trial design, to identify and engage the recruitment centres, to manage the implementation aspects of clinical operation required for the actualisation of the study, to manage appropriately the relationship with patients and caregivers that will volunteer in the study, to coordinate the implementation of the digital technology selected for the trial, to ascertain that data are collected and safely stored in the platform in line with the pilot study results, and to contribute to the definition of the statistical analysis plan and to data analysis, data representation and support for a scientific publication.

Topic 2: FAIRification of IMI and EFPIA data

Topic details

Topic code	IMI2-2017-12-02
Action type	Research and Innovation Action (RIA)
Submission & evaluation process	2 Stages

Specific challenges to be addressed

Since 2008, numerous IMI consortia have been generating results in a diverse set of biomedical domains (www.imi.europa.eu/content/ongoing-projects). In many projects these results have been stored in a custom database, sufficient for the project itself but difficult to access by scientists outside the project. In addition, relatively little attention has been paid to making the data from different projects interoperable, i.e. making the databases 'talk to each other'. The same is true for many internal industry research and development databases, including databases that store chemical compounds, proteins, pharmacological activities, Absorption, Distribution, Metabolism, Excretion, Toxicity (ADMET) data, gene and protein expression data, high content image data, phenotypic assay data, video, etc. In addition, clinical data are often stored in separate databases, complicating their analysis in the context of preclinical data. Making a significant portion of the data from IMI projects accessible and interoperable with other datasets and databases will greatly improve the use and impact of the data for translational biomedical research.

The concept of FAIR data principles (Findable, Accessible, Interoperable, Reusable)[60] [61] is perfectly suited for this task. There is a strong and growing acceptance of the necessity of these data principles in ongoing database organisations such as ELIXIR[62], but also in global organisations such as the G20 countries[63]. Very similar principles for data stewardship are described in the H2020 Guideline for data management[64] as part of the H2020 Open Research Data Pilot (ORDP, Art. 29.3 of the MGA) and the IMI2 Data Management Plan template[65].

ICT, legal and contextual interoperability of databases opens up exciting opportunities for data mining and hypothesis generation by using information from multiple domains simultaneously. The linked data can be explored with advanced analytical methods such as computer reasoning and inferencing, making the value of the collection of linked databases much greater than its constituent parts. For clinical data this will open opportunities in bench-to-bedside translational research, by connecting preclinical with clinical information. Corporate databases usually contain proprietary data that is not publicly shared, but significant value will be obtained if their scientists can perform data exploration and mining across all the datasets available to them, including public, licensed/commercial, along with their own companies' private databases. For academia and SMEs this project will facilitate working with pharmaceutical companies, as they will have a much better understanding of the content and format of the industry's internal data and the industry's specific needs and future directions.

Need and opportunity for public-private collaborative research

The expertise in this field is highly complementary between academia, SMEs, and industry, and a collaborative approach on this topic is necessary for the following reasons:

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[60] https://www.force11.org/group/fairgroup/fairprinciples
[61] Wilkinson et al. The FAIR Guiding Principles for scientific data management and stewardship Scientific Data 3. 2016. Available at http://dx.doi.org/10.1038/sdata.2016.18
[62] https://www.elixir-europe.org
[63] http://europa.eu/rapid/press-release_STATEMENT-16-2967_en.htm
[64] http://ec.europa.eu/research/participants/data/ref/h2020/grants_manual/hi/oa_pilot/h2020-hi-oa-data-mgt_en.pdf
[65] http://www.imi.europa.eu/sites/default/files/uploads/documents/New_Folder/DataManagementPlanTemplate.docx

- SME and academic expertise on implementation of FAIR principles in databases has evolved significantly, and this expertise is highly needed for executing the FAIRification of public and private databases. Good examples of this are the FAIR data creation and conversion projects that are organised by ELIXIR[66] and its member national nodes, in which SMEs and academic groups are essential participants.
- The pharmaceutical industry is well placed to define what data sources are most relevant to drug discovery research, and which ones will give most added value when they can be queried in an interoperable way.
- Joint public-private development of FAIR databases will create a broad acceptance and usability of the data produced in IMI projects, and will allow all scientists in public and private organisations to analyse their internal data in the context of all databases that they have access to.

Scope

The project will focus on IMI projects that have data that is scientifically valuable and amenable to being made FAIR. It is expected that the databases of more than 20 IMI projects will be made FAIR in this project. All IMI projects will be assessed for the presence of data that requires FAIRification, though it should be noted that IMI2 projects are already required to manage their data according to similar protocols.[67]

Three main issues need to be addressed to allow the scientists in academia and industry to maximally use all databases that they can access:

- Use of standard vocabularies, taxonomies, and ontologies to describe the entries in all databases. The objective is not to generate or modify elaborate vocabularies and ontologies, but to define a consensus for minimum metadata information standards in EFPIA-relevant scientific domains.
- Placing the data in a database that is accessible through a user interface and a computer interface (a documented API - application programming interface), while taking into account personal data protection and confidentiality aspects as well as the intellectual property (IP) conditions for access rights to results that are specific to each IMI project, as laid out in the respective project or consortium agreement.
- The project will identify sustainable solutions for hosting the data to help ensure the long term sustainability of the data by developing a strategy for hosting, curation, maintenance, and integration of the databases. Sustainable storage options for the EFPIA databases will also be evaluated but implementation is the responsibility of EFPIA companies themselves. The actual EFPIA databases will not be shared with or made accessible to the consortium, but the process of their FAIRification, including the minimum information standards and the metadata, will be made publicly available. Thus, by making the EFPIA databases FAIR, specific scientific questions can be more easily addressed, and this in turn will speed up the process of drug discovery and development for the benefit of patients and other stakeholders.

It should be noted that FAIR data is not identical to open access data. The ‘Accessible’ part of FAIR implies computer and human accessible data, and applies to parties who are authorised to access specific data under the conditions of established IMI project or consortium agreements, falling under the guidelines and rules of IMI and respecting also general data protection legislation as well as confidentiality issues, if applicable. In the same way that many IMI data have restricted access, the same is true for most internal pharmaceutical industry data. As this project will not own the data being made FAIR, full open access to the data cannot be mandated. However this project will strongly encourage making the IMI data as broadly accessible as possible to maximise the public value of the data through prioritising datasets with open public access. Selected projects for FAIRification that need to keep data access restricted for IP or confidentiality reasons will also be strongly encouraged to make metadata available so the broader public can at least identify if data of interest is present. Access to the data itself can then be requested to the data owners.

[66] https://www.elixir-europe.org
[67] See the IMI2 data management plan template:
http://www.imi.europa.eu/sites/default/files/uploads/documents/New_Folder/DataManagementPlanTemplate.docx

Expected key deliverables

- Development of transparent criteria for the selection of data sources within completed and ongoing IMI projects for FAIRification. The results of this analysis and the rankings based on expected scientific value will be shared.
- Development of transparent criteria for the selection of data sources within pharmaceutical industry participants that will enable relevant questions in pharmaceutical research to be addressed when the data is made interoperable with existing public and other internal databases.
- Development of minimum metadata information standards for data from industry and IMI relevant scientific domains.
- FAIR transformation of databases from at least 20 IMI projects to make them compliant with FAIR principles. Access to the databases for permitted scientists and computers will be provided via an API (application programming interface).
- Multiple FAIR databases per EFPIA company available internally within the company.
- Identification and publication of barriers to making IMI project data fully open, and publication of proposed solutions to reduce those barriers.
- Publication and dissemination of guidelines, advice, and detailed processes (workflows and specific technical details) that can be used by other projects, pharmaceutical companies and their partners to make databases compliant with FAIR principles and able to be integrated with their internal data systems and public databases.[68]
- Dissemination of a data catalogue that lists all FAIRified databases handled by the consortium. Metadata on individual databases will provide information on content, access, and use. Metadata detail level depends on the accessibility of the databases themselves. In some cases, access to the actual FAIRified data may require contacting the data owners. This deliverable is optional for selected internal EFPIA databases.[69]

Expected impact

- Making existing scientific data from completed and ongoing IMI programmes broadly usable and sustainable will allow the scientific community to maximally leverage data from legacy and current IMI projects. Increasing the usability of corporate databases by integration with fast-growing public databases and with other licensed or internal databases will enable future research.
- Strong increase of expertise in the creation, curation, and stewardship of FAIR databases within IT communities.
- Building skills and increasing competitiveness for SMEs in Europe.
- Better understanding of the complexity, structure, and breadth of pharmaceutical data; minimum metadata standards will allow the SME community to make their data, analysis tools and services better connected and aligned to pharma data and facilitate future collaboration. Better understanding on the storage and usage of emerging data types, such as images.
- Interoperability of the databases will allow sophisticated data analysis in all phases of drug discovery, including advanced analytical methods such as computer reasoning and inferencing.
- The project will have a significant impact on the scientific community regarding the broad adaptation of FAIR data stewardship. This in itself will have a long-lasting value-adding impact on effective scientific data usage.

[68] Grant Agreement option 28.2a will apply
[69] Grant Agreement options 29.1a and 29.1b will apply

Potential synergies with existing consortia

Applicants should take into consideration, while preparing their short proposal, relevant national, European (both research projects as well as research infrastructure initiatives), and non-European initiatives. Synergies and complementarities should be considered in order to incorporate past achievements, available data and lessons learnt where possible, thus avoiding unnecessary overlap and duplication of efforts and funding.

Applicants should consider any relevant related projects from IMI, FP7, H2020 and other relevant initiatives outside the EU.

This FAIRification project will build on the achievements of the Open PHACTS (www.openphacts.org) project, which has shown that making a large number of public databases interoperable creates unique opportunities for answering scientific questions that were very hard or impossible to tackle previously. Moreover, the eTRIKS project (www.etriks.org) has focused on making data from multiple IMI cohort study projects available on a common platform.

Since this project focuses on data generated in other IMI projects, there is a very high level of synergy with a broad list of existing consortia, see www.imi.europa.eu/content/ongoing-projects for details.

Industry consortium

The industry consortium is composed of the following EFPIA companies

- Janssen (lead)
- Bayer
- GlaxoSmithKline
- Eli Lilly
- AstraZeneca
- Novartis
- Boehringer Ingelheim

Due to the nature of the participation of industry partners, it is anticipated that some elements of the contributions will be non-EU/H2020 Associated Countries in-kind contributions[70]

The industry consortium will provide expertise in scientific domains, ontologies and vocabularies, database management as well as contributing to all work packages as indicated below.

Indicative duration of the action

The indicative duration of the action is 36 months.

Indicative budget

The indicative EFPIA in-kind contribution is EUR 3 730 000

The financial contribution from IMI2 is a maximum of EUR 4 000 000

Applicant consortium

[70] Note: This does not however constitute the justification referred to in Article 4(2) of the IMI 2 JU regulation.

The applicant consortium will be selected on the basis of the submitted short proposals.

The applicant consortium is expected to address all the objectives and make key contributions to the defined deliverables in synergy with the industry consortium which will join the selected applicant consortium in preparation of the full proposal for stage 2. This may require mobilising appropriate expertise, in particular from SMEs, as follows: pharmaceutical research scientific subject matter, scientific data vocabularies and ontologies, the existing database landscape, legal expertise in database access, FAIR data principles, data stewardship, database management, computer programming, data hosting organisations and solutions.

Suggested architecture of the full proposal

The applicant consortium should submit a short proposal which includes their suggestions for creating a full proposal architecture, taking into consideration the industry participation including their contributions and expertise.

The final architecture of the full proposal will be defined by the participants in compliance with the IMI2 rules and with a view to the achievement of the project objectives.

In the spirit of the partnership, and to reflect how IMI 2 JU call topics are built on identified scientific priorities agreed together with EFPIA beneficiaries/large industrial beneficiaries, these beneficiaries intend to significantly contribute to the programme leadership and project and financial management.

The final architecture of the full proposal will be defined by the participants in compliance with the IMI 2 JU rules and with a view to the achievement of the project objectives. The allocation of a leading role within the consortium will be discussed in the course of the drafting of the full proposal to be submitted at stage 2. To facilitate the formation of the final consortium, until the roles are formally appointed through the consortium agreement, the proposed project leader from among EFPIA beneficiaries/large industrial beneficiaries shall facilitate an efficient negotiation of project content and required agreements.

All beneficiaries are encouraged to discuss the project architecture and governance and the weighting of responsibilities and priorities therein

.The architecture outlined below for the full proposal is a suggestion. Different innovative project designs are welcome, if properly justified.

Work package 1: Identification of project data sources for FAIRification and sustainable data hosting platforms.

Work package 1.1 - Identification of closed and ongoing IMI projects with data most suitable for FAIRification.

This WP will prioritise datasets within IMI projects for FAIRification. Criteria that should be taken into account include relevance of the data today and in the future, access to the data (higher priority will be given to open access data), the value of using this data in an integrated way with other databases, and the technical feasibility of FAIRifying the data. For databases that need to maintain restricted access, priority will be given to projects that allow sharing of metadata, allowing a broad audience to identify what data is available. In these cases access to the data itself would still require contacting the data owners. The exact, transparent criteria will need to be defined and communicated. It is recommended that selected partners from the IMI projects and other scientific domain experts be consulted (data owners, domain experts, legal experts, and data interoperability experts).

Work package 1.2 - Identification of industry data sources at industry partners most suitable for FAIRification

As above, but for industry databases. Internal EFPIA experts and public scientific domain experts will need to be consulted (data owners, domain experts, legal experts, and data interoperability experts).

- Industry contribution

Pharmaceutical research scientific domain experts, legal experts, database content experts, data interoperability experts.

- Expected applicant consortium contribution:

Scientific domain experts, legal experts, database content experts, data interoperability experts, FAIRification process experts.

Work package 2: Development of FAIRification process for selected data sources and implementation

Work package 2.1

For the selected data sources, a detailed analysis of the data and how the data will be used is needed. Decisions on what ontology and vocabulary to use need to be made. Minimum metadata information standards will have to be defined, as much as possible by consensus (see for instance the Minimum Information About a Microarray Experiment (MIAME) standards[71]). The development of a level of standardisation for databases from related domains would be highly desired.

Work package 2.2:

Organisation of BYOD (bring your own data) sessions where all relevant experts and data owners come together to develop the details of FAIRification of selected data sources[72]. Deliverables are detailed FAIRification processes that will allow data in the selected data sources to be transformed into the required format.

- Industry contribution:

Pharmaceutical research scientific domain experts, vocabulary and ontology experts, database content experts, data interoperability experts.

- Expected applicant consortium contribution:

Ontology/vocabulary experts, data interoperability experts, IT experts, and scientific domain experts, FAIRification process experts.

Work package 3: Identification of and implementation of data on sustainable data hosting platforms

Work package 3.1:

A sustainable database hosting platform/organisation should be identified for every IMI FAIR database. Selection criteria will include domain expertise, connectivity with the scientific community, cost, and long-term stability of the host.

Work package 3.2:

Transfer of the IMI FAIR databases to the identified sustainable hosting platform.

Work package 3.3:

Identification of sustainable solution options for the industry FAIR databases will be identified. Solutions can be internal EFPIA hosting, external (private cloud) based solutions, and combinations of the two.

- Industry contribution:

Database technology experts, IT experts, legal experts.

- Expected applicant consortium contribution:

Database technology experts, IT experts, database hosting experts.

[71] Brazma, A Minimum Information About a Microarray Experiment (MIAME) – Successes, Failures, Challenges, The Scientific World Journal 2009, 9, 420. Available at http://dx.doi.org/10.1100/tsw.2009.57
[72] http://www.dtls.nl/fair-data/byod/

Work package 4: Communication and outreach to FAIR data user community

To maximise the use and impact of the publically available FAIR databases, academia and SMEs need to be made fully aware of the availability of this data and encouraged to develop analysis tools, incorporate the data into interoperable data systems, and use the data in biomedical data analysis.

- Industry contribution:

Pharmaceutical research scientific domain experts, database content experts.

- Expected applicant consortium contribution:

Scientific domain experts, communication experts.

Work package 5: Project management, coordination, dissemination and sustainability

This work package will establish effective governance and internal communication procedures to allow for the flow of information within the project. It will also fulfil the administrative tasks associated with management of this project:

Work package 5.1: Setting-up of project management boards: governing, steering, communication, IP

Work package 5.2: Development and implementation of data management plan and correlated activities

Work package 5.3: Development and implementation of dissemination programme

Work package 5.4: Development and implementation of internal and external communication tools

Work package 5.5: Financial management, monitoring and project management support and implementation

Work package 5.6: Development of a sustainability plan facilitating continuation beyond the duration of the action

- Industry contribution:

Project management expertise.

- Expected applicant consortium contribution:

Project management expertise.

Topic 3: Development of sensitive and validated clinical endpoints in primary Sjögren's Syndrome (pSS)

Topic details

Topic code	IMI2-2017-12-03
Action type	Research and Innovation Actions (RIA)
Submission & evaluation process	2 Stages

Specific challenges to be addressed

Unmet medical need: Primary Sjögren's syndrome (pSS) is a common systemic autoimmune disease affecting as a hallmark exocrine glands leading to sicca symptoms of the eyes and the mouth[73]. Systemic and extra-glandular manifestations can often develop as well. A negative impact on quality of life (QOL) is prominent, mainly due to the disabling fatigue as the most important factor in loss of work productivity[74]. Moreover, pSS patients have 9-fold higher risk of developing B cell lymphomas[75]. Only symptomatic treatments are available for commercial use. Given the significant heterogeneity in the clinical presentation and course of patients with pSS, success in therapeutic trials will depend on a better understanding of disease phenotypes to drive patient selection and stratification[76]. There are no treatments for systemic correlates of the disease and there have been no industry sponsored studies that have been able to show a disease modifying effect.

Challenges for medicines development: Currently, published data from placebo-controlled and adequately powered clinical trials in pSS are scarce[77]. Although specific novel, validated treatment outcome measures have been developed recently, e.g. European League against Rheumatism (EULAR) Sjögren's syndrome disease activity index (ESSDAI) and EULAR Sjögren's syndrome patient reported index (ESSPRI)[78] [79], their recent use in clinical trials has yielded mixed results[80] [81]. Important features of pSS such as swallowing difficulties, dietary problems, mental health challenges, sexual dysfunction, dental problems (including tooth loss and decay) are not (adequately) captured. Overall, the utility of the currently available measures (including sensitivity to change in Patient Reported Outcomes (PROs) and in various ESSDAI domains) in assessing the efficacy and disease-modifying potential of an investigational drug is still to be determined. Moreover, no objective validated measure or functional marker of disease activity for assessing therapeutic benefits of improvement is currently available. Sensitive and validated endpoints including objective measures/biomarkers of improvement are needed to increase the likelihood of success of drug development in pSS[82].

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[73] Rischmueller M, Tieu J, Lester S. Primary Sjögren's syndrome. Best Pract Res Clin Rheumatol. 2016;30:189-220.
[74] Meijer JM, Meiners PM, Huddleston Slater JJ, Spijkervet FK, Kallenberg CG, Vissink A, Bootsma H: Health-related quality of life, employment and disability in patients with Sjogren's syndrome. Rheumatology. 2009;48:1077-82. See as well footnote 71
[75] See footnote above
[76] Devauchelle-Pensec V, Gottenberg JE, Jousse-Joulin S, Berthelot JM, Perdriger A, Hachulla E et al. Which and How Many Patients Should Be Included in Randomised Controlled Trials to Demonstrate the Efficacy of Biologics in Primary Sjögren's Syndrome? PloS One. 2015;10:e0133907
[77] See footnote above
[78] Seror R, Bootsma H, Saraux A, Bowman SJ, Theander E, Brun JG, et al. EULAR Sjögren's Task Force: Defining disease activity states and clinically meaningful improvement in primary Sjögren's syndrome with EULAR primary Sjögren's syndrome disease activity (ESSDAI) and patient-reported indexes (ESSPRI). Ann Rheum Dis. 2016;75:382-9.
[79] Seror R, Theander E, Brun JG, Ramos-Casals M, Valim V, Dörner T et al. Validation of EULAR primary Sjögren's syndrome disease activity (ESSDAI) and patient indexes (ESSPRI). Ann Rheum Dis. 2015;74:859-66
[80] Devauchelle-Pensec V, Mariette X, Jousse-Joulin S, Berthelot JM, Perdriger A, Puéchal X, et al. Treatment of primary Sjögren syndrome with rituximab: a randomized trial. Ann Intern Med, 2014;160:233–42.
[81] Cornec D, Devauchelle-Pensec V, Mariette X, Jousse-Joulin S, Berthelot JM, Perdriger A et al. Development of the Sjögren's Syndrome Responder Index, a data-driven composite endpoint for assessing treatment efficacy. Rheumatology (Oxford). 2015 Sep;54(9):1699-708.

[82] Seror R, Theander E, Bootsma H, Bowman SJ, Tzioufas A, Gottenberg JE, et al. Outcome Measures for Primary Sjögren's Syndrome: A Comprehensive Review. J Autoimmunity, 2014;51:51-56

Scientific opportunities to address the challenge: With the growing number of clinical trials testing different treatment modalities, there is an emerging opportunity for comprehensive, integrated analysis of the data generated in the past combined with data analysis of future results from pSS clinical trials. Such a two-tiered approach offers an unprecedented opportunity to identify additional or improved outcome measures that are sensitive, reflect the disease biology, and are most suitable as endpoints for clinical trials of new drug development or may confirm the utility of the currently-available pSS endpoints.

Need and opportunity for public-private collaborative research

The ability to measure and monitor clinically relevant endpoints in pSS populations is an early need in the field of drug development in pSS prior to the existence of proven disease-modifying therapies. Furthermore, enhancing clinical development and generating payer-relevant evidence of real world impact of therapeutic interventions will be important. This effort is well suited for a public-private consortium.

The identification, development and validation of clinical endpoints in pSS will benefit most from public-private collaboration between pSS clinical sites / centres, academic and industry experts and regulatory authorities. In addition, the value and impact of the proposed project will be further enhanced by a collaborative partnership with patient advocacy groups, the caregiver community, and privacy and bioethics experts to ensure that the solutions developed can be adopted in the real world.

While outcome measures have been recently proposed and introduced into clinical trials by efforts of the academic community, large, randomised placebo-controlled clinical trials applying and validating these endpoints are lacking. There are regulatory uncertainties with respect to the best registration endpoints for pSS. Involvement of health authorities, patient groups and the pharmaceutical industry can help cover further aspects of and needs for these outcome measures, and generate larger datasets –those can be a challenge if handled by the academia alone. This is why this project may relevantly complement the HarmonicSS H2020 project which shares similar objectives. Therefore it is envisioned that the project funded under this topic will be conducted in close collaboration with this ongoing H2020 project to enhance both efforts in delineating such key scientific questions.

Clinical parameters as well as novel biomarkers (including laboratory and imaging tools) would help better characterise this heterogeneous population, making it possible to link the mechanisms of the disease with clinical manifestations, disease severity and progression. A better patient phenotyping will also be beneficial in the understanding of the clinical endpoints' behaviour and response to therapy.

Scope

The overarching objective of this proposal is to develop sensitive and validated clinical endpoints for use in future clinical trials of pSS. The goal is to identify and eventually propose a single composite endpoint that could provide evidence of disease-modifying and symptomatic efficacy.

The major scope of this effort will be the identification, development and validation of pSS-related outcome measures including clinical, PRO, laboratory, bio-behavioural activity and imaging parameters (biomarkers), applying the following step-wise approach:

- Data generation and review: Existing data including published epidemiology data, results from interventional and non-interventional studies, and from pSS registries will be reviewed and analysed. As a key contribution to this step, data from prospective, randomised, controlled clinical trials comprising baseline data and longitudinal data from the anonymised control (placebo) groups in Phase 2 (or Phase3 if available) trials from the participating industry partners will be made available.
- Development of new outcome measures based on the review and analysis activities.
- Application and validation by prospectively testing these proposed new pSS outcome measures, as well as existing ones, in (at least one) dedicated, prospective clinical trial. It is anticipated that this future clinical study will be an interventional clinical trial adequately designed to determine if the endpoint model is sensitive to detect treatment differences for use in registration trials.
- Analysis of the outcome of the validation trial and validation of the new endpoint(s). The performance of the new outcome measures or scoring systems will be compared to that of the existing ones, with the purpose to select the most promising outcome measures for future validation.

It is anticipated that the scoring system(s) will require a combination of objective and subjective outcome measures to improve upon existing scoring systems (e.g. selected, core set of ESSDAI domains combined with ESSPRI fatigue or other key PRO items).

If industry sponsored, large e.g. Phase 3 trial(s) are conducted for novel therapies in parallel with (but independently of) the validation trial during the project, the proposed new endpoint(s) may be included as exploratory endpoints in the Phase 3 trials to increase the power and robustness of the validation. The analysis of these trials may, however, occur after this IMI project.

Health technology Assessment (HTA) and payer views and expectations will be integrated in determining the endpoints for regulatory approval and market access requirements. Input from patient groups will also be sought and considered in the analyses to capture relevant and currently underestimated or ignored disease aspects.

While the development of the new sensitive and validated clinical endpoints are primarily intended for use in future clinical trials of adult pSS, feasibility in paediatric SS will also be cautiously evaluated for which further validation would be required as part of the project sustainability plan.

Expected key deliverables

Expected deliverables will be a set of sensitive and validated pSS outcome measures with potential regulatory and market access consensus.

The project is also expected to provide evidence for the characterization and usefulness of the currently-available outcome measures (e.g. ESSDAI or ESSPRI).

The following deliverables are anticipated from the project:

- (i) Identification and characterisation, (ii) prospective qualification, and (iii) regulatory acceptance of disease scoring tools to assess key features of pSS including disease activity, organ specific improvement and reduced damage under therapy.
- Identification and validation of a biomarker or sets of prognostic markers that could be used as a surrogate endpoint(s) in Phase II trials, and which would be early predictors of long-term organ specific changes or adverse systemic outcomes, for example lymphoma development.
- Development of an endpoint model to determine what the patient- (and payer-) relevant endpoint measures are, independent of where treatments have an effect. The endpoint model will be used to develop a relevant patient reported outcome measure that can be deployed in future clinical trials.
- Development of a suitable methodology to capture semi-continuous bio-behavioural activity data in pSS patients by exploring activity patterns and features which are specific to pSS fatigue symptomatology.
- Patient phenotyping to characterise different subgroups of pSS (being a heterogeneous disease). For this, clinical data as well as established and novel biomarker data will be used that could identify commonalities and differences across subgroups as well as response to therapies.

Expected impact

This project is expected to enhance the development of new systemic treatments in pSS and to generate evidence for a potential new alternative for consideration by the health authorities.. It is expected to result in more efficient clinical trial designs that will minimise the number of subjects required to be able to detect statistically significant and clinically meaningful differences between treatments. The optimal duration of clinical studies required to demonstrate these differences will also be characterised. Furthermore, new relevant outcomes will have potential to optimise pSS patients' management, and large data sets about the natural history of the disease will provide information about the clinical utility of new and innovative diagnostic and treatment interventions in pSS. Engagement of important stakeholders including regulators, payers and patient advocacy groups will help capture all aspects of pSS.

Consequently, improved and innovative therapies are expected to emerge and be available to pSS patients whose health-related quality of life and productivity will eventually improve. Selection of the optimal treatment for the right patient in a clinically and molecularly heterogeneous disease will be made possible in pSS.

Overall, the project goals and expected impact are in line with the predefined IMI2 JU objectives[83]) in the following aspects:

- the success rate in clinical trials for pSS is expected to increase;
- time to reach clinical proof of concept in medicine development is expected to be reduced for pSS;
- new therapies for pSS for which there is a high unmet need would be developed;
- diagnostic and treatment biomarkers would be developed for pSS.

Potential synergies with existing consortia

Applicants should take into consideration, while preparing their short proposal, relevant national, European (both research projects as well as research infrastructure initiatives), and non-European initiatives. Synergies and complementarities should be considered in order to incorporate past achievements, available data and lessons learnt where possible, thus avoiding unnecessary overlap and duplication of efforts .

Projects and initiatives that may be considered for collaboration by the applicants are:

HarmonicSS (http://cordis.europa.eu/project/rcn/207205_en.html), an ongoing Horizon 2020 project. One of the goals of HarmonicSS is the 'data generation and review', that is very similar to the scope of this topic. Thus, collaboration with this project would allow a more rapid progression and a more thorough and extensive data analysis. The synergy of the two initiatives would therefore be of mutual benefit. The prospective validation trial may also be done in collaboration.

PRECISESADS (www.precisesads.eu), an ongoing IMI project that aims to molecularly reclassify systemic autoimmune diseases. The expected outcomes of this project that will end in Q1 2019 are the generation of clusters of patients defined according to their molecular taxonomy. Such data could provide relevant insights to define patient subpopulations and biomarkers. Therefore collaboration with this project will enhance the scientific impact of this new project as well as of the PRECISESADS project.

EULAR (www.eular.org) task force responsible for classification guidelines and EULAR sponsored EU pSS registries, e.g. Big Data Sjögren Project (EULAR-SS Task Force International Network) and Systemic Involvement at Diagnosis Evaluated by the ESSDAI in 3314 Patients with Primary Sjögren Syndrome[84].

In addition, collaborations with transatlantic projects and initiatives such as ones by the American College of Rheumatology (www.rheumatology.org) and/or by the Sjögren's Syndrome Foundation (https://www.sjogrens.org) may also be considered.

Industry consortium

The industry consortium is composed of the following EFPIA companies:

- Novartis (lead)
- GlaxoSmithKline
- Bristol-Myers Squibb
- Servier

[83] Article 2 (from (i) through (iv)) of the Council Regulation (EU) No 557/2014 of 6 May 2014 establishing the Innovative Medicines Initiative 2 Joint Undertaking (O.J. L169 of 7.6.2014): http://eur-lex.europa.eu/legal-content/EN/TXT/?uri=uriserv:OJ.L_.2014.169.01.0054.01.ENG

[84] Brito Zeron P, Kostov BA, Seror R, Baldini C, Quartuccio L, Kvarnstrom M et al. Big Data Sjogren Project (EELAR-SS Task Force International Network): Systemic Involvement at Diagnosis Evaluated by the ESSDAI in 3314 Patients with Primary Sjögren Syndrome Ann Rheum Dis 2015;74:578.

- Eli Lilly

The industry consortium will contribute the following expertise and assets:

- programme management to oversee budgets, timelines, and administration of all uniform processes and procedures including confidentiality agreements, master contracts, budget templates, and institutional review board/ethics committee processes;
- clinical trial design including adaptive design and the use of modelling/simulation and predictive analytics for determination of dose selection, sample size, and other parameters;
- a clinician, clinical pharmacologist, statistician or clinical scientist from each company to act as a company network champion and facilitate company communication and participation with the network;
- clinicians for communication, on-site visits, and other interactions with academic medical centres, investigators, and advisory boards;
- biostatistical / data management expertise to co-lead the central network data coordinating centre, co-maintain the central organisation website, and co-lead the installation of performance monitoring tools and procedures needed at all participating sites;
- regulatory expertise in interacting with the European Medicines Agency (EMA), and other regulatory health authorities;
- clinical operations including feasibility assessment, informed consent forms and assents, recruitment and retention of subjects, clinical trial monitoring, and assessment of trial performance metrics;
- business planning and development; contractual agreements;
- financial planning and implementation;
- legal counselling;
- industry-sponsored clinical trials and the data generated from such clinical trials to test the viability of the network.

Indicative duration of the action

The indicative duration of the action is 72 months.

Indicative budget

The indicative EFPIA in-kind contribution is EUR 8 200 000.

Due to the global nature of the participating industry partners it is anticipated that some elements of the contributions will be non-EU/H2020 Associated Countries in-kind contributions[85].

The financial contribution from IMI2 is a maximum of EUR 8 200 000.

Applicant consortium

The applicant consortium will be selected on the basis of the submitted short proposals. The applicant consortium is expected to address all the research objectives and make key contributions to the defined deliverables in synergy with the industry consortium which will join the selected applicant consortium in preparation of the full proposal for stage 2. This may require mobilising, as appropriate, the following expertise and resources:

- experience and know-how in conducting clinical trials in Sjögren's;
- expertise in the science of drug development including all aspects of clinical pharmacology and study design and conduct;

[85] Note: This does not however constitute the justification referred to in Article 4(2) of the IMI 2 JU regulation.

- access to a large representative pSS population(s);
- expertise in patient reported outcomes, development and validation;
- physicians and other health care providers covering the spectrum of clinical manifestations of pSS (rheumatologists, dental care etc.);
- patient advocacy organisations able to actively contribute to development and standardisation of study procedures and processes, to assess feasibility, clinically meaningful endpoints, and risk-benefit;
- regulatory expertise, including in interacting with EMA or national regulatory authorities;
- expertise in interacting with national payers (e.g. the National Institute for Health and Care Excellence) will be also important to success;
- information technology / data management;
- expertise in legal and clinical compliance aspects (International Conference of Harmonization) and Good Clinical Practice;
- strong project management and communication expertise;
- office administration and website management.

Efforts should be made to include organisations in as many European countries as possible from the outset as part of the applicant consortium. Small to medium-sized enterprises (SMEs) are also welcome to join this consortium to bring value from a complementary perspective to the academic organisations. Such SMEs may include (but are not limited to) biostatistics and pharmacometrics specialty groups, healthcare research and analysis groups or clinical research organisations (CROs).

Suggested architecture of the full proposal

The applicant consortium should submit a short proposal which includes their suggestions for creating a full proposal architecture, taking into consideration the industry participation including their contributions and expertise.

The final architecture of the full proposal will be defined by the participants in compliance with the IMI2 rules and with a view to the achievement of the project objectives.

In the spirit of the partnership, and to reflect how IMI 2 JU call topics are built on identified scientific priorities agreed together with EFPIA beneficiaries/large industrial beneficiaries, these beneficiaries intend to significantly contribute to the programme leadership and project and financial management.

The final architecture of the full proposal will be defined by the participants in compliance with the IMI 2 JU rules and with a view to the achievement of the project objectives. The allocation of a leading role within the consortium will be discussed in the course of the drafting of the full proposal to be submitted at stage 2. To facilitate the formation of the final consortium, until the roles are formally appointed through the consortium agreement, the proposed project leader from among EFPIA beneficiaries/large industrial beneficiaries shall facilitate an efficient negotiation of project content and required agreements.

All beneficiaries are encouraged to discuss the project architecture and governance and the weighting of responsibilities and priorities therein.

The architecture outlined below for the full proposal is a suggestion. Different innovative project designs are welcome, if properly justified.

The current topic has regulatory and HTA relevance, therefore, in its short proposal, the applicant consortium is also expected to have a strategy on the translation of the relevant project outputs into regulatory, clinical and healthcare practice. A plan for interactions with regulatory agencies / health technology assessment bodies with relevant milestones, resources allocated should be proposed to ensure this, e.g. qualification advice on the proposed methods for novel methodologies for drug development, qualification opinion.

Sustainability

A plan for aspects related to sustainability, facilitating continuation beyond the duration of the project, will be proposed.

Work package 1: Project management and oversight of IMI project

Objectives:

- to establish a framework for collaboration and ensure minimisation of duplicative work and maximisation of sharing across the various work packages as well as to ensure strategic alignment of efforts;
- to define the goals that would benefit from synergistic collaboration with other identified consortia in view and to establish working procedures and a Global Steering Committee to oversee the work progression;
- to coordinate contacts with health authorities between all projects.

Specific activities include:

- project design and charters with clear accountabilities;
- set-up of joint governance structure;
- provide coordination and support to work package teams;
- define work expectations of different work streams, deliverables, dates, activities and review progress regarding adherence to budget, timelines and quality;
- ensure key cross-functional partners are engaged;
- define project interdependencies, stakeholders and risks;
- ensure meetings and interactions between work packages, sub-groups, and consortium governance bodies to coordinate and follow-up on work effort.

Industry contribution:

- project management support with project design and day-to-day operation;
- legal expertise, clinical operations, data management, and clinical expertise to support regular review of deliverables regarding quality and operational ability;
- ensuring the implementation and maintenance of ethical requirements, e.g. patient informed consent forms, data anonymisation etc.

Expected applicant consortium contribution:

- ensuring the implementation of the coordinating tasks and running the day-to-day operation, such as project tracking and reporting, meetings, internal communication, budget management, etc.;
- ensuring the implementation and maintenance of ethical requirements, e.g. patient informed consent forms, data anonymisation etc.

Co-leads from industry partners and applicants will jointly decide on the consortium governance structure and meetings.

Work package 2: Understanding of pSS disease mechanisms and outcomes

Objective: to evaluate currently available evidence as well as prospective clinical trial including clinical as well as biomarker data to set up the scientific consensus necessary to support designing for outcome measures.

Industry contribution:

- clinical trial data (prospective clinical trials considered from the start of the project as well as existing data from clinical industry sponsored clinical trials);
- clinical, medical and drug safety expertise;
- expertise in health economics and outcomes research (HEOR), statistical modelling, epidemiology, and translational science;
- medical writing and medical communication expertise;
- biomarkers operational deployment and analysis;
- specific expertise, investigational/diagnostic products, related centralised bioanalytical facilities, operations to deliver results and reports;
- work package co-chairs.

Expected applicant consortium contribution:

- expertise in conducting literature reviews and on determining relevant outcomes in collaboration with multiple stakeholders including academic environment, regulatory agencies, HTAs, payers, clinical research organisations, patient organisations and advocacy, and cooperative international groups;
- expertise in developing and validating new patient reported outcome measures;
- data management and statistical modelling expertise;
- expertise in medical research;
- scientific clinical expertise in biomarkers including collection, banking and analysis;
- biomarker assay implementation per protocol;
- elaboration of a strategy to liaise l with HarmonicSS or other existing relevant initiatives.

Work package 3: Generation of novel endpoints, design and execution of clinical trial to validate pSS endpoints

Objective: to plan and conduct dedicated clinical trial(s) including novel as well as conventional endpoints based on data generated in WP2.

Industry contribution:

- providing expertise in randomised clinical trial initiation and conduct;
- oversight over the study management, and the accomplishment of overall objectives;
- technical and logistic assistance for the meetings of the study committees, etc.

Expected applicant consortium contribution:

- experience and expertise in conducting clinical trials including clinical and care facilities and adequate trained physicians and specialised personnel to implement the clinical trial protocol;
- state-of-the-art expertise in the field of primary Sjögren's syndrome; own patient cohort data including long-term clinical and biomarker follow-up data;
- efficient patient recruitment capacity by using territorial network.

Work package 4: Evaluation of validation trial results

Objective: To evaluate clinical trial data, with special attention to the outcome measures in order to draw the necessary clinical and regulatory conclusions regarding their future use in trials (with potential regulatory and market access consensus).

Industry contribution:

- data analysis;
- planning, hosting and organising workshop(s) with regulators;
- contributing to results discussion via its experts (including biostatisticians);
- technical support (translations, etc.); (co-)authoring of reviews and white paper(s).

Expected applicant consortium contribution:

- data analysis;
- active contribution to constructive discussion with regulators and payers to achieve scientific and regulatory agreement over the interpretation of study results;
- consolidation of the scientific consensus to support sound operational definitions in terms of use of clinical trial;
- (co-)authoring of reviews and white paper(s);
- Elaboration of a strategy to liaise with HarmonicSS orother existing relevant initiatives .

Work package 5: Biomarkers

Objective: to manage in synergy with other projects the identification of relevant biomarkers able to relevantly separate patient subtypes in relation e.g. to prediction of disease evolution or disease severity.

Industry contribution:

- clinical and scientific expertise;
- expertise in biomarker analyses and development of biomarker identification tools;
- ensuring the preparation of communication with health authorities including scientific advice preparation;
- work package co-chairs.

Expected applicant consortium contribution:

- knowledge of the available or expected outcomes from the other consortia;
- biomarker datasets and analyses from academic groups or consortia;
- expertise in biomarker assays.

Work package 6: Engagement with health authorities, payers and patients' groups

Objective: consensus with health authorities, payers and patients' groups as key stakeholders regarding the use of new endpoints for regulatory approvals and reimbursement, respectively, in the management of primary Sjögren's syndrome.

Industry contribution:

- expertise in developing proposals and recommendations to gain regulatory acceptance, including writing of briefing books as well as presentations of positions and supporting arguments;
- regulatory and reimbursement expertise;
- editorial support.

Expected applicant consortium contribution:

- medical / scientific community: establish link between clinical outcomes and value creation (for individuals and society); insights on future developments in diagnostics and therapeutics;.
- the applicants can help define, interpret and evaluate the value of a new outcome measure; it would be welcome if the applicant consortium can support establishing the link across different perspectives for the new endpoint;
- regulatory, reimbursement, HTA bodies and patient organisations: healthcare delivery needs, gaps and opportunities; insight into policy evolution and potential changes;
- patient advocacy and representative groups: provide point of view of patients in terms of relevant outcomes and current challenges within healthcare delivery.

Work package 7: Legal and ethical compliance

Objective: Develop and maintain ethical and legal framework to provide guidance on patient confidentiality and data sharing and ownership throughout the project,

Industry contribution:

- expertise in legal, ethical, compliance, communication.

Expected applicant consortium contribution:

- expertise in legal, ethical, compliance; patient advocacy, and technical writing support.

Work Package 8: Communication

Objective: to define and execute the overall communication strategy for the project including internal as well as external publications, dissemination of results, web postings, repository of key documents, and quality assessment of documents.

Industry contribution:

- medical communication;

- media interactions;
- medical writing;
- contact with healthcare provider professional organisations and their communication groups;
- contact with patient organisations.

Expected applicant consortium contribution:

- communication and/or media expertise;
- healthcare professional organisations;
- clinical expertise in the key diseases areas;
- guideline commissions;
- expertise on payers / healthcare provider financing;
- market research organisation.

Topic 4: European Health Data Network (EHDN)

Part of the Big Data for Better Outcomes Programme (BD4BO)

Introduction to the BD4BO programme and problem statement

The IMI2 Big Data for Better Outcomes (BD4BO) programme aims to catalyse and support the evolution towards value-based, more outcomes-focused, sustainable and therefore better quality healthcare systems in Europe. Exploiting the opportunities offered by the wealth of emerging data from many evolving data sources via the generation of methodologies with real world data will inform European decision-making in healthcare and policy debates. The programme's objectives are to maximise the potential of large-scale, harmonised data from variable, quickly-developing digital and non-digital sources which will be referred to as 'big data' in the context of this initiative.

This programme will provide a platform and resources for defining and developing enablers of the outcomes transparency evolution, together with patients, payers, physicians, regulators, academic researchers, healthcare decision makers, etc. The key enablers are:

- definition of outcome metrics;
- protocols, processes and tools to access high quality data;
- methodologies and analytics to drive improvements, digital and other solutions that increase patient engagement.

The following topic (the European Health Data Network) sits within the BD4BO programme.

BD4BO Programme structure

The BD4BO programme is composed of several projects which will be key enablers for the transition of healthcare systems towards more outcomes transparency. These include an over-arching coordination structure (through a Coordination and Support Action (CSA)) implemented by the DO-> IT consortium (http://www.bd4bo.eu/), several disease/therapeutic area (TA) topics focusing on a specific disease, population, therapeutic area or technology: HARMONY (http://www.imi.europa.eu/content/harmony), ROADMAP (http://roadmap-alzheimer.org/), and BigData@Heart and this European Health Data Network (EHDN) topic. Future topics may be added to the programme as indicated below.

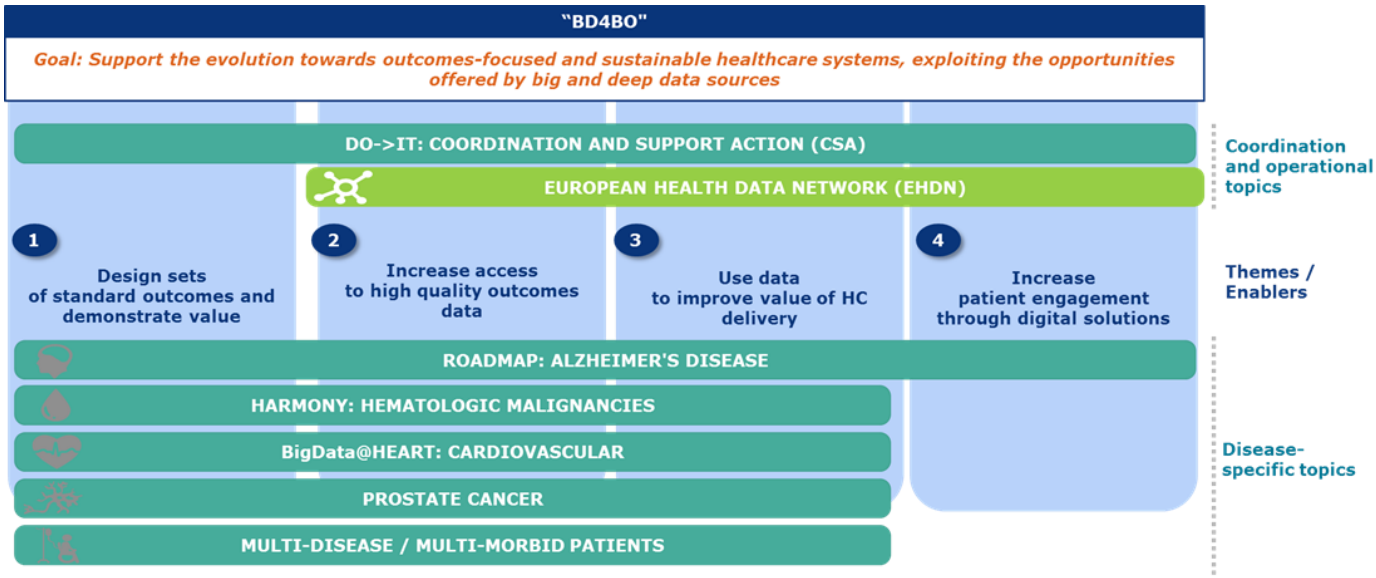


Figure 1: Programme structure, themes / enablers and CSA

The success of the overall BD4BO programme will rely on a coordinated approach across projects to ensure strategic alignment and consistency and to define new business and health funding models (including

incentive models) that will allow for healthcare systems transformation. In addition, integration of areas of expertise which are common to most projects (such as legal, ethics, data privacy, sustainability or collaboration with payers/HTAs) will yield higher quality results, consistency and increased efficiency by avoiding duplication of work.

Expected impact of the BD4BO programme

The expected result of the overall BD4BO programme will be a network of different health data sources to support the growing requirement for evidence to support expanding value-based and outcomes-focused healthcare delivery in Europe. Technological development will accompany the network based on prior programmes to support the relationship between data users and data providers, but a key driver for success will be active collaboration within the network (see below). The programme will also enable the evolution and management of R&D portfolios and the prioritisation of research methodologies in line with outcomes focused healthcare services in Europe. It must be recognised that the growing use of multi-centre observational studies, with their increasing complexity, requires organisation and a broader Europe-wide strategy.

Collaboration agreements

It is the absolute objective of EHDN project to fully collaborate with (and support) other projects in the IMI2 BD4BO programme, therefore, the grant awarded for the EHDN will be complementary to the Grant Agreements already awarded under the BD4BO programme[86] and also to future BD4BO Grant Agreements. The respective options of Article 2, Article 31.6 and Article 41.4 of the IMI2 Model Grant Agreement will be applied.

[86] The ROADMAP, HARMONY, DO->IT, BigData@Heart projects

European Health Data Network (EHDN)

Topic details

Topic code	IMI2-2017-12-04
Action type	Research and Innovation Actions (RIA)
Submission & evaluation process	2 Stages

Specific challenges to be addressed

The central theme for the BD4BO programme is the prospect of outcomes-driven, sustainable healthcare systems. At the same time, it is recognised that reuse and analysis of healthcare data holds the key to the transition to these systems, under the maxim that, 'you cannot change, what you do not measure'.

The EHDN initiative seeks to address this critical challenge by converting a large number of relevant datasets across Europe to a common format and standard so that they can be more efficiently used to their full potential within a federated network to achieve the objectives as mentioned above, while respecting patient privacy, local data provenance, governance and applicable regulations. Achieving this is pivotal and implies addressing the following challenges:

1. ***Technical*:** Healthcare data are very fragmented. Even data within one healthcare centre are typically spread across different repositories. Across entities, different standards are used to code diagnosis, lab results, drugs or procedures. In most healthcare systems, a majority of the core clinical data is buried in unstructured (text) notes, making data analysis even more challenging. The EHDN will provide a harmonised model to address the structural heterogeneity and the use of different coding standards, expediting efficiencies in the research process
2. ***Socio-ethical*:** Besides the technical heterogeneity amongst data sources, a similar diversity in governance processes to perform studies using data collected by healthcare providers, can be seen. The project will specifically seek to provide a pragmatic governance framework that can be used to accommodate cross-centre studies, within the confines of societal parameters that manage data use in the EU.

It must be stressed that the EHDN aims at a federated network approach. There is no intention of creating a centralised repository of patient level data. The data will remain local, on the premises of the data owner / custodian, and under their clear control and governance. However, by implementing a harmonised, standardised version of their data set, research and reuse of data can be executed much more efficiently. In essence, the "analysis is brought to the data" and only aggregated results are returned, therefore, no patient data leaves the premises. Reuse of data in a full study can also only happen after approval of local governance bodies. This federated network approach has been used successfully in other initiatives such as the EMIF project (http://www.emif.eu) or in the OHDSI community (www.ohdsi.org/).

To obtain concrete results, it is important to note that the EHDN project's ambition will need to be sharply focused on providing pragmatic solutions thereby reusing results and solutions from prior IMI & other projects as much as possible. To achieve this focus EHDN will focus on facilitating three "Application Domains".

Application domain 1: Research: This initiative will shape and lead a community of interested data sources and data scientist and engage with broader (global) community (e.g the OHDSI community). Topics can range from e.g. discovery, pharmacovigilance, ongoing monitoring of effectiveness / safety of compounds, outcomes research, identification of variability in care delivery, disease background related info or epidemiology of disease.

Application domain 2: Health services efficiency: This application domain will focus on how best to deliver real world data that is relevant to evaluating real world outcomes for therapeutic interventions. Activities could cover e.g. outcomes based contracting, optimizing patient pathways, quality improvement of health services (dashboard driven / financial incentives / driving changes to health care systems). Regulatory applications will also be covered within this domain. Recent experience in projects such as GetReal (https://www.imi-

getreal.eu/) and EMIF (http://www.emif.eu/) point to the growing interest and support for real world data (RWD) by the European Medicines Agency (EMA) and the Health Technology Assessment (HTA) bodies.

Application domain 3: Individual patient care: This domain is focused on the application of the federated data network to support patient level decision-making in clinical care. Aspects to cover could be e.g. providing an interoperable data standard to facilitate and stimulate a market in digital health solutions, expert systems, predictive algorithms, etc., integration with mobile health.

Need and opportunity for public-private collaborative research

To achieve the objectives mentioned, health care systems are challenged with

1) lack of definition and alignment on outcomes that are relevant to all stakeholders and patients;
2) policy makers having limited benchmark data to evaluate the risk/benefit ratio and value;
3) personalised medicine allowing for more focused treatment options thus increasing the difficulty of demonstrating the risk/benefit in the real world, driven by rapid technological and biological innovation;
4) clinicians having to make treatment choices based on short-term, surrogate and often not comparable data;
5) patients not having access to the right treatment at the right time;
6) payers having to make reimbursement decisions on life prolonging options with limited data and finite budgets.

Collaboration among healthcare systems and relevant stakeholders is necessary to capture and aggregate data, analyse it and extract relevant insights. Engagement of payers, providers and regulators will ensure these outcomes and clinical endpoints are measured and used in healthcare systems (e.g. for reimbursement or assessments). A critical element in achieving a more outcomes based healthcare system is the adoption of well-suited standards. EHDN will apply two important standards, the Observational Medical Outcomes Partnership Common Data Model (OMOP CDM) and the International Consortium for Health Outcomes Measurement (ICHOM) standards[87].

The OMOP CDM is the result of a public-private collaboration, currently under the umbrella of the Observational Health Data Sciences and Informatics project (OHDSI, pronounced 'Odyssey', https://ohdsi.org/) project[88]. OHDSI is an international collaboration of more than 120 researchers (public and private) from 12 countries that contributes expertise at all levels, from infrastructure to clinical research, ensuring that the developed infrastructure meets clinical research needs. OHDSI's Common Data Model[89], originally developed as part of the Observational Medical Outcomes Partnership (OMOP)[90], is a deep information model that specifies how to encode and store clinical data at a fine-grained level, ensuring that the same query can be applied consistently to databases around the world. OHDSI has chosen data standards that dovetail with those of the United States government and the international community, and it also supplies tools and mapping tables for converting data from other standards. At the last count, 52 databases, with a total of 682 million patient records, had been created using the Common Data Model[91]; this number may include duplicate records for databases with overlapping populations. As such the OHDSI suite of standards and tools is rapidly becoming a de facto international standard for working with real world data.

The ICHOM standards[87] identify specific outcomes metrics for a number of diseases. Where possible, the BD4BO programme is reusing the metrics. For some disease areas, no such metrics have been proposed and

[87] http://www.ichom.org/
[88] Hripcsak G, et al. (2015) Observational Health Data Sciences and Informatics (OHDSI): Opportunities for observational researchers. Stud Health Technol Inform 216:574–578
[89] Observational Health Data Sciences and Informatics (OHDSI) OMOP Common Data Model V5.0. Available at www.ohdsi.org/web/wiki/doku.php?id=documentation:cdm:single-page . Accessed June 1, 2015.
[90] Overhage JM, Ryan PB, Reich CG, Hartzema AG, Stang PE (2012) Validation of a common data model for active safety surveillance research. J Am Med Inform Assoc 19(1):54–60.
[91] Hripcsak G, et al. (2015) Observational Health Data Sciences and Informatics (OHDSI): Opportunities for observational researchers. Stud Health Technol Inform 216:574–578

hence, the first step for a number of the BD4BO projects is to define relevant disease specific outcomes metrics. Whereas the OMOP CDM provides a common model (and controlled vocabulary) for data, ICHOM standards provide metrics. Both are complementary and many of the ICHOM metrics (or other outcomes metrics) can be informed by the OMOP CDM. In cases where data elements are lacking (e.g. patient reported outcomes) novel approaches can be developed to capture data.

Besides standardisation and technical aspects, there is also a paramount need for further shaping a trusted environment for data sharing in Europe. To move the data sharing agenda forward, creating benefits for all stakeholders in the eco-system, several non-technical dimensions are of critical importance. These are, for example legislative aspects, data security and privacy or data quality improvement.

Scope

The EHDN project is a critical enabling component of the IMI BD4BO programme and is responsible for supporting the research aspects of the other BD4BO projects in delivering the vision of large scale medical outcomes research. Therefore, the *EHDN should focus on being an enabling project* with the aim of developing a data network to allow other researchers to 'find' and safely 'reuse' data.

The European landscape for the secondary use of medical data is fragmented across different nations and providers. The resulting paucity of common standards makes outcomes based research difficult to perform in Europe. Several initiatives such as the FP7 projects EU-ADR (www.euadr-project.org/) and TRANSFORM (cordis.europa.eu/project/rcn/93775_en.html), the IMI projects EH4CR (http://www.ehr4cr.eu/) and EMIF (http://www.emif.eu/) and the US-based OHDSI project (https://ohdsi.org/) have demonstrated methodologies that can be used to perform such research.

The first goal of the EHDN is to 'reduce to practice' the approaches pioneered in these earlier research projects and develop a standard methodology.

The European 'market' for health outcomes research is limited to commercial providers and a limited number of academic health science centres with funds available to develop secondary use platforms for research. This both biases the research that can be undertaken as only data collected by these providers can be used and in some cases, creates a monopolistic environment that prevents health outcomes research from gaining more traction. It would likely be true to say that not one data source provides the whole truth in the real world, and as such collaboration is critical to supporting quality evidence.

The second goal of EHDN is to help mature both the supply side and the demand side of this 'health data eco-system' in compliance with robust privacy and ethics governance.

The adoption of common enabling technology across all nodes in the EHDN will stimulate a new generation of (digital) providers to develop and deliver services in data transformation, data semantics and analytical capabilities. This will be achieved through the implementation of a certification process for SMEs and other providers. This has the halo effect of creating a second generation of practitioners and services who can further reap the benefits of health outcomes research, ensuring a common stewardship to the use of health data.

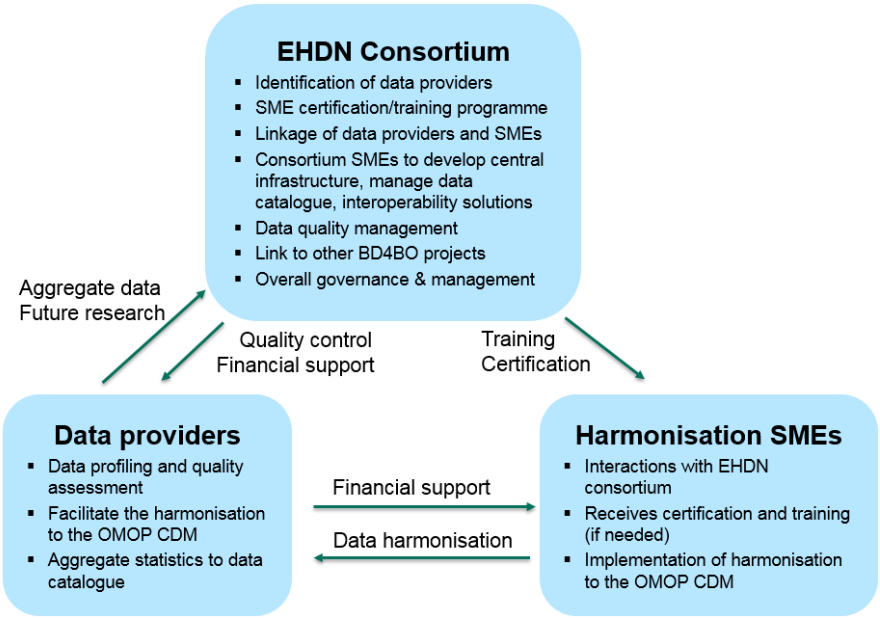
The third goal of EHDN is to stimulate development of new and augmented health services through available and expanded technologies, in the interest of health outcomes.

The EHDN will implement a federated data network, the implementation of which is based on the OMOP Common Data Model and will utilise existing solutions and methodology approaches as such, no further development or research is needed: the use of the OHDSI toolsets and EMIF contributions have already validated this approach and method. By doing this, EHDN will fully adhere to the FAIR principles of data networks. Via technical and governance solutions, data will be made Findable, Accessible, Interoperable and Reusable. For more information on the FAIR principles, see http://ec.europa.eu/research/participants/data/ref/h2020/grants_manual/hi/oa_pilot/h2020-hi-oa-data-mgt_en.pdf

Through the EHDN, a business ecosystem will be stimulated by matching data consumers with data providers (via a data set catalogue) under a standardised governance process, with an upfront agreed and transparent business model. This ecosystem will facilitate the provision of additional services through a platform being

built on open source components with public standards. Small and Medium-sized Enterprises (SMEs), both within and outside the consortium, can develop and offer commercial services to data providers or consumers (see section on Applicant Consortium for the distinction of SMEs in- and outside of the consortium).

The process is summarised as follows:



Collaboration agreements

The grant awarded for the EHDN will be complementary to the Grant Agreements already awarded under the BD4BO programme as described in the introduction, above. Therefore, the respective options of Article 2, Article 31.6 and Article 41.4 of the IMI2 Model Grant Agreement will be applied.

Expected key deliverables

The EHDN project executive will administer am open, transparent call process where third party data providers (e.g. hospitals, regional data sets, disease registries) that can provide data for the selected priorities (disease areas, type of data, data quality requirements etc) will be identified. These third party data providers can apply for financial support to have the OMOP common data model constructed and deployed within their firewall, and also ensure their staff receive the necessary training.

It is envisaged that the technical IT services to perform the data harmonisation will be provided by a number of EU based SMEs. These SMEs will normally not be part of the applicant consortium but will be identified once the project is underway in through an open, transparent, objective process.

By linking the third party data providers to suitable data harmonisation SMEs, the ultimate outcome of the project will be a set of harmonised data sets that will remain within the firewalls of the respective data owners' organisations. The data sets will be compliant with the EHDN suite of tools for reusing data. This will enable the data providers to carry out outcomes focused research projects through the BD4BO programme and elsewhere.

Overall the EHDN project will support:

The implementation of the OMOP common data model within data provider firewalls to deliver an operational network of data sets covering up to 20% of the EU population or approximately 100 million people (estimated to be around 200 data sets) in support of existing and new BD4BO or other health outcome related initiatives. Key performance indicators will be developed to monitor the progress in terms of the absolute number of data sources covered, diversity across different disease areas, geographical coverage and breadth of coverage across different types of data sets.

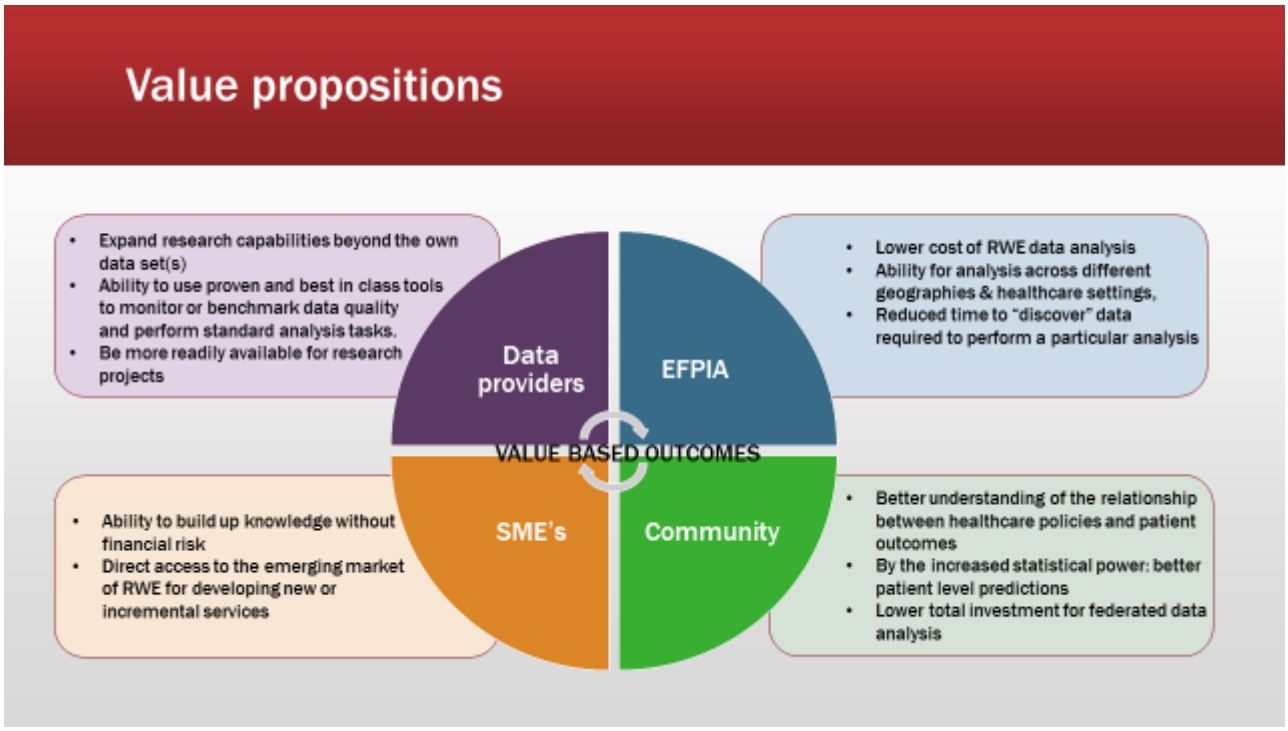
The validation of harmonised data sets as compliant with the EHDN suite of tools for accessing data thereby providing the opportunity for the data owners to participate in BD4BO and other research projects. This will imply the existence of an operational data quality management framework for real world data. This data quality management framework (definition of criteria, applicable procedures, technical implementation) will be operational by the end of year 1.

European SMEs experienced in building innovative services for data providers and/or consumers. This will be further facilitated by organising hackathons and targeted competitions.

Certification of the IT technical services of EU SMEs where the technical services relate to the preparation, execution, testing, deployment and documentation of the transformation from source to harmonised data sets.

EHDN project governance with a focused approach to manage the recruitment and approval of third party datasets, to oversee the data harmonisation and to interact with other BD4BO projects

Expected impact



The EHDN project aims to improve Europe's (technical) capabilities to undertake systematic health outcomes research at an unprecedented scale across the entire region. It will achieve this by taking advantage of, and implementing the validated and robust OHDSI collaboration tools and common data model; supporting data providers with the transition to the common data model for easier reuse of data, and consistency across data platforms; ensuring full compliance and governance is in place to protect integrity of the data; and offering the BD4BO projects a platform for successful and compliant data reuse and analysis.

The aim of the EHDN is to not just create a network of data providers that are making data available, but also to facilitate further research that will allow these data providers to gain additional value while working towards a value based outcome mandate. This additional research will be carried out through collaboration with other initiatives such as the existing and future IMI2 BD4BO projects.

By implementing a common data model, the data providers should find it easier to also participate in other future research studies.

For the community at large, the research enabled through this platform will contribute to the BD4BO objective of an outcomes-driven and sustainable healthcare. This project should therefore also result in an increased use of outcomes based models in actual healthcare delivery and regulatory/HTA decision making.

Potential synergies with existing consortia

Applicants should consider incorporating technologies, experience and insights from previous/ongoing projects including:

- EMIF (http://www.emif.eu/)
- EHR4CR (http://www.ehr4cr.eu/)
- GetReal (https://www.imi-getreal.eu/)
- ENABLE (http://nd4bb-enable.eu/)
- eTRIKS (https://www.etriks.org/)
- OHDSI (https://ohdsi.org/)

Industry consortium

The industry consortium is composed of the following EFPIA companies:

Janssen Pharmaceutica (lead)

- Pfizer
- AbbVie
- Servier
- Sanofi
- Bayer
- Eli Lilly
- Ipsen
- AstraZeneca
- Novartis
- UCB

The industry in-kind contributions will be dedicated to project governance, communication, and general and project management.

Indicative duration of the action

The indicative duration of the action is 60 months.

Following an initial two-year period, a project review will be held to ensure the project is on track to deliver the expected impacts within the five year period.

Potential applicants must be aware that the Innovative Medicines Initiative 2 (IMI2) Joint Undertaking may, if exceptionally needed, publish at a later stage another Call for proposals restricted to the consortium already selected under this topic, in order to enhance their results and achievements by extending their duration and funding. The consortium will be entitled to open to other beneficiaries as they see fit.

Such further work could include, but is not limited to, additional extension of the data network and further development and refinement of tools. The decision for this will be based on progress of the project and decision envisioned to be made in the sustainability work stream of the project.

Indicative budget

The indicative EFPIA contribution is EUR 14 127 000[92].

The financial contribution from IMI2 JU is a maximum of EUR 14 127 000.

[92] This figure includes both in-kind and financial contributions.

The overall objective of the EHDN project is to significantly extend the volume of 'readily available' data sets for outcomes research through the harmonisation of data on approximately 100 million people. These data harmonisation activities are estimated to cost approximately EUR 17 million and are expected to be carried out by third parties receiving financial support (see below).[93] This financial support will include a EUR 10 million financial contribution from the above indicative EFPIA contribution and the remainder from IMI2 JU funding. Therefore, at stage 1, applicant consortia should allocate half of the IMI2 JU contribution to the data harmonisation effort, to be primarily implemented as direct costs of providing financial support to third parties.

Applicant consortium

The applicant consortium will be selected on basis of the submitted short proposals.

The applicant consortium is expected to address all the objectives and make key contributions to the defined deliverables in synergy with the industry consortium which will join the selected applicant consortium in preparation of the full proposal for stage 2.

As described above, the prime focus of the EHDN project is on implementation of established data standards to facilitate outcomes research in Europe. The ideal consortium therefore will contain a limited number of partners with proven expertise in the domain of real world data management and analysis, focusing on very specific goals. Data sources will not be part of the consortium, but will be financially supported as third parties, mainly due to their diversity and significant expected number. This model has been successfully used in e.g. EMIF-AD and in EPAD.

In their short proposal, the applicant consortium is expected to have a strategy on the translation of the relevant project outputs into regulatory, clinical and healthcare practice. A plan for interactions with regulatory agencies / health technology assessment bodies with relevant milestones should be included, and appropriate resources should be allocated to ensure this, e.g. qualification advice on the proposed methods for novel methodologies for drug development, qualification opinion. An outline plan for aspects related to sustainability, facilitating continuation beyond the duration of the action should also be proposed.

While the focus is on implementation, the EHDN project also wants to illustrate the value of the approach via a limited number of research 'use cases' that will demonstrate the societal value of the network. The applicant consortium is therefore also expected to have experience in the practical use of a federated network of data sets. The applicant consortium should also bring innovative approaches, for example in work package 3.

The applicant consortium should mobilise the following expertise:

- A limited number (ideally up to three) leading public partners in this domain:
  - They will serve as evangelists and key stakeholders. Ideally, these centres represent the various European regions. The ideal consortium will have a broad geographic representation throughout Europe. These centres will have practical expertise in working with real world data and the mentioned data standards e.g. OMOP CDM, ICHOM. As the EHDN project will also provide support for the OHDSI community in Europe, it is expected that the leading public partners will have active on-going or previous collaborations within this community. This will serve as an important additional "validation" of the approach of working with a network of harmonised data sets.
  - The centres are expected to contribute specific domain knowledge on applicable standards in medical coding and terminologies in the relevant disease areas. Decisions need to be made on how to implement the OMOP CDM in the identified disease areas and possible extensions to the applicable standards will need to be agreed upon.
  - An important element in the selection of relevant data sets is the data quality evaluation (considering the research question envisioned). Expertise in the deployment of data quality evaluation is necessary. Ideally, the EHDN project will develop a 'data quality benchmark' approach, allowing for a standardised and routine way of measuring data quality. We will leverage where possible, e.g.

[93] Implemented through article 15.1 of the IMI2 model grant agreement. A small portion may also be awarded as prizes according to article 15.2 of the IMI2 model grant agreement. The open, transparent, objective process for awarding these prizes must be elaborated in the full proposal.

some work going on in the Institute for Innovation through Health Data (iHD) and other EU initiatives such as SPOR and IDMP[94]. As described above, EHDN will adhere to the FAIR principles.

  - Having led similar initiatives on a local, regional or disease level across a significant set of data sources where a substantial harmonisation effort was required, is recommended.

- A limited number (ideally up to three) technical SMEs with the following capabilities:
  - Technical skills necessary to maintain and further develop the key infrastructural components, including the data catalogue solution, the central platform components and quality assessment solutions. Having developed or supported one or more of these applications in a public private partnership is required.
  - The technical knowledge to support extensions of the vocabulary mappings. Experience in different healthcare coding systems, master data management systems and/or terminology services is expected. This would include either existing commercial product offerings or services in this area by the respective SME or previous delivery of such solutions in other public private partnerships.
  - Technical capability to develop and improve interoperability solutions. EHDN may consider the development of 'inflow or outflows' from several common data formats instead of doing this for every data source independently. As an example, one could consider an outflow to i2b2 / TranSMART or to the backend of the hospitals data warehouse (e.g. i2b2) of institutions participating in the Champion Programme (follow-up from IMI-EHR4CR). Requests for interoperability with CDISC (SDTM, BRIDG) could also be expected. Experience in developing interoperability solutions and in one or more of the mentioned standards is required.

    Please note that SMEs charged solely with the actual data harmonisation tasks are NOT expected to be part of the applicant consortium. Such activities are expected to be covered by the financial support to third parties described below.

- Given the challenges and potential risks with reuse of healthcare data, it is crucial to have deep experience in data governance aspects, as well as the privacy and ethical aspects of secondary data use. Legal expertise in data protection law is essential.
- The involvement of regulatory and HTA organisations is recommended:
  - Given the important regulatory and/or HTA context of the BD4BO projects, a strong link to EMA and/or an HTA body is a requirement. Ideally as part of the consortium, otherwise, these partners should be engaged in an advisory role. Experience from IMI projects like GetReal should be leveraged.
- At least one partner should be a pan-European patient advocacy group, in order to build trust and engage patients proactively in the definition of health outcomes driven use case selection. Participation of patient representatives would be very useful in e.g. WP 2 and 3.

It would be advantageous to include:

- Expertise in development of distributed statistical analysis or machine learning methods. A limitation of the current federated network is that a particular data analysis is performed at a single data set. A 'focused engagement' could be considered that explores the feasibility for executing data analysis methods across an entire set of data sources while preserving the applicable constraints of the federated network.
- Ability to render structured content harmonised to the applicable data standards from unstructured text (text mining).

Financial support to third parties[95] for the provision & harmonisation of data sets

The EHDN project requires the recruitment, mapping and OMOP data model implementation of a EU-wide operational network of data sets. The providers of this data will mostly be third parties external to consortium that would be recruited during the project lifetime through open call(s) and would agree that their data is

[94] See http://www.ema.europa.eu/ema/index.jsp?curl=pages/regulation/general/general_content_000645.jsp

[95] In accordance with Annex K of the Horizon 2020 Work Programme and the article 15 of the IMI2 Model Grant Agreement.

harmonised to the common data model. This will be normally done by qualified SME(s) hired by the same data-providers. Becoming a third party would allow the respective organisation to participate in the network of data sources and as such engage in different research initiatives but also requires the data source to:

- provide aggregate statistics on their data for inclusion in a data catalogue (e.g. number of patients per year of birth, gender distribution, distribution of person years covered, outcomes measured etc);
- agree to the publication of this metadata in a data set catalogue;
- have a documented governance process for engaging and / or reviewing research questions from participants in the consortium (including other data providers).

In order to cover the related costs for the above mentioned activities (i.e. hiring SMEs with the technical capability to implement the OMOP CDM), the EHDN consortium will provide financial support to the third parties of up to EUR 100 000 per third party[96], selected under an open call launched by the selected consortium in the form of reimbursement of actual costs.

Therefore, in their full proposal, at stage 2, the consortium must clearly detail the objectives and the results to be obtained and include at least the following elements:

- a fixed and exhaustive list of the different types of activities for which a third party may receive financial support;
- the definition of the categories of legal entities which may receive financial support;
- the criteria for awarding financial support;
- the criteria for calculating the exact amount of the financial support;
- the maximum amount to be granted to each third party and the criteria for determining it.

Suggested architecture of the full proposal

The applicants should include in their short proposal their suggestions for creating the full proposal architecture, taking into consideration the industry contributions and expertise as indicated.

The final architecture of the full proposal will be defined together with the industry consortium and should enable activities designed to achieve all objectives and deliverables as indicated in the previous relevant sections and in collaboration with the members of the industry consortium.

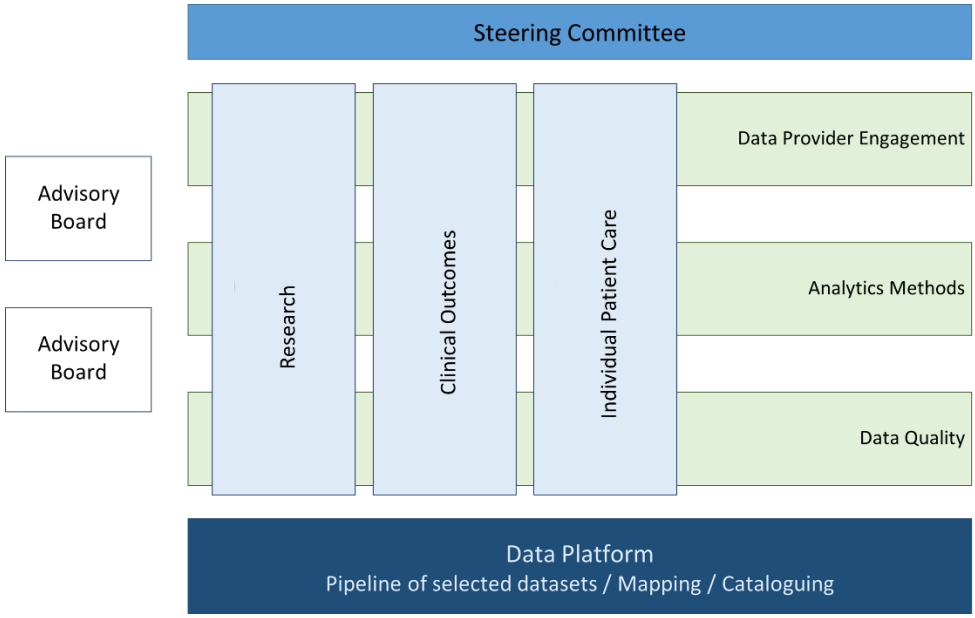
In the spirit of the partnership, and to reflect how IMI 2 JU call topics are built on identified scientific priorities agreed together with EFPIA beneficiaries/large industrial beneficiaries, these beneficiaries intend to significantly contribute to the programme leadership and project and financial management.

The final architecture of the full proposal will be defined by the participants in compliance with the IMI 2 JU rules and with a view to the achievement of the project objectives. The allocation of a leading role within the consortium will be discussed in the course of the drafting of the full proposal to be submitted at stage 2. To facilitate the formation of the final consortium, until the roles are formally appointed through the consortium agreement, the proposed project leader from among EFPIA beneficiaries/large industrial beneficiaries shall facilitate an efficient negotiation of project content and required agreements.

All beneficiaries are encouraged to discuss the project architecture and governance and the weighting of responsibilities and priorities therein.To ensure the project stays focused on the end users, the driving force of the project should come from the identified ‘application domains’. These application domains (WP1 through 3) share a set of cross cutting concerns (e.g. data provider engagement, quality management, analysis methods) while the actual implementation of these concerns might be different. It is expected that the consortium will set up the necessary mechanisms to provide the coordination across these shared ‘concerns’. A separate work package will deal with the implementation of the technical platform and with the management of the ‘data harmonisation’ pipeline. Overall governance in the project will be done by a Steering Committee. Advisory

[96] The costs of data harmonisation can vary greatly between different data sources. The harmonisation of existing, highly structured and integrated research databases may be relatively cheap, while harmonising unstructured or semi-structured data will be a resource-intensive effort. Therefore, the cost to perform such a conversion are estimated to vary between EUR 30 000 and EUR 100 000 per data source.

boards could be anticipated for, e.g. data governance, analytics methods or data quality. The exact composition of the project will be subject of further discussion once the full consortium has been established.



The applicant consortium should submit a short proposal which includes their suggestions for creating a full proposal architecture.

Work packages 1 to 3 – application domains

Each application domain focuses on a specific domain but shares common 'process' elements. These common elements include:

- Data provider engagement: Attracting relevant data sets through an open call for recipients of financial support based on needs of the other BD4BO projects and other criteria to be developed in the full proposal[97]. Contact and coordination with IMI-2 (BD4BO) and other projects to understand their data needs and /or to engage data sets in the respective BD4BO projects
- Data quality evaluation
- Requirements for the analytical methods: while it is not the objective of EHDN to perform the analysis (this should rather be performed in the BD4BO projects that are being supported) the EHDN will define the requirements that the analytical methods should adhere to and will provide input in how analytical methods can be shared / distributed across the network
- Identification and engagement with the relevant internal and external stakeholders (Regulators, HTA agencies, …)

The specifics for WP1 to 3 are as follows:

Work package 1: Application domain 'research'.

Work package 1 focuses on setting up a network of organisations who, on the basis of a shared data model can execute research questions and facilitate research studies at an unprecedented scale, WP 1 will lead and shape that community, engage with the relevant data sources and the broader (global) community (the above mentioned OHDSI community). The analysis methods and the method to share or deploy them across the

[97] In compliance with article 15.1 of the IMI2 Grant Agreement.

community is one of the key deliverables from this work package. A specific issue this WP will address deals with the question of potential 'information loss' between source data and harmonised data. To develop reliable, acceptable 'evidence', it is necessary to show consistency from source data to harmonised data and to illustrate analytical rigour in the generation of evidence. This work package will seek input and definition from regulatory and HTA agencies as to what constitutes valid 'real world evidence' as it relates to applicable data input as well as the required analytical methods and tools which could be deployed against the common data model (pharmacovigilance, comparative effectiveness etc). Essentially this work package will develop the technological framework to enable connectivity with real world data from hospital and other sources, enabling health research (within e.g. IMI BD4BO), whilst working with key stakeholders, such as regulators to evaluate the methodological, analytical and data outputs for relevant quality requirements. While the main focus is on development of analytical methods, it may be efficient to work on a few 'exemplar' cases to develop and proof the method.

Work package 2: Application domain 'health care system efficiency – outcomes based models'

The central theme to work package 2 will be the concrete implementation of transitioning to an outcomes driven healthcare system. This includes a specific collaboration with disease specific projects on applicable outcome measures, data source engagement to provide the appropriate outcome measures, translating the outcomes metrics to the common data model, defining quality criteria for applicable data sets and input from payers and providers on the barriers and tools required to implement outcomes based models. WP2 will also consider what other requirements might apply to outcomes based contracts and analytical tools which could facilitate benchmarking and contracting activities within health systems aimed at driving quality and efficiency. In summary, this work package will focus on how best to deliver real world data that is relevant to evaluating real world outcomes for therapeutic interventions, incorporating the required data connectivity, methodology, analytics and outputs that meet the needs of, and in conjunction with, healthcare payers.

Work package 3: Application domain 'individual patient care'

WP3 is focused on the application of the federated data network to support patient level decision-making in clinical care. As such, it will integrate patient-generated data (e.g. clinical sensors, wearables, patient reported outcomes and others), as well as developing federated analytics to support clinical decision-making (e.g. , patient risk identification, patient disease prediction, advanced bioinformatic diagnostics, etc.) in designated use cases for evaluation. This work will necessitate further developing technical aspects (e.g. integration of digital health input, federated analytics, machine learning), as well as critical governance requirements with guidelines, policy and law. Given this is an area of fast and exciting technical developments, we are looking forward to public partners which have access to novel patient engagement technologies and/or novel ways of running (federated) analytics. As for work package 1, while most of the attention will be on the development of methods, it may be efficient to work on a few exemplar cases.

Work package 4 – Technical implementation

This work package will focus on:

- set-up, maintenance and gradual improvements to the data catalogue;
- data harmonisation and standardisation of selected data sets;
- coordination of work with the use cases.

The EHDN will maximally leverage from ongoing or prior projects in this area such as EMIF, EPAD (ep-ad.org), EHR4CR. Part of the solution should be an integration of the full process, going from 'finding relevant data sets' to 'reusing data sets' under specific conditions. Important elements in the architecture are therefore also implementation of IT security, authentication and authorisation.

Work package 5 –Governance and adoption

This work package will focus on:

- shaping of governance;
- ensuring optimal adoption among each of the stakeholders, given legal/data privacy context.

Clearly governance is a crucial element in safe reuse of patient level data. Where possible, we will leverage from other projects (IMI and other). The BD4BO coordinating project, DO->IT will be a prime source of input, but there are other projects from which solutions, tools and policy documents / approaches can be leveraged. In the context of EMIF, an extensive document was developed describing the overall process of data cataloguing, data assessment (via predefined dashboards) and data reuse. This document (the EMIF code of practice, eCOP[98]) will be very helpful in establishing all required governance aspects for EHDN.

Work package 6 – Overall project governance, project management, dissemination and sustainability

This work package will focus on:

- governance ensuring close alignment and collaboration across work packages;
- project Management Office;
- internal and external communication (dissemination to the greater research community);
- development of a sustainability model.

[98] http://www.emif.eu/assets/e/m/emif_d10_4_first_draft_ethical_code_of_practice_exec_summary_website.pdf

Topic 5 : Analysing the infectious disease burden and the use of vaccines to improve healthy years in aging populations

Topic details

Topic code	IMI2-2017-12-05
Action type	Research and Innovation Actions (RIA)
Submission & evaluation process	2 Stages

Specific challenges to be addressed

We observe that today the shape of the demographic pyramid in Europe evolves into a mushroom-like design[99] [100]. Multiple dynamic age-processes are tailoring this age-structure leading to the situation that the older population augments in size every year also because they live longer[101]. But older people are more vulnerable to infectious diseases because their immune system becomes weaker with age[102]. The consequences are that one may observe an increasing burden of infections in the elderly with a high transmission rate. They are often treated with antibiotics causing resistance. In addition, infectious diseases are often the trigger for an underlying manifestation of chronic disease conditions those elderly are suffering[103]. We therefore have to tackle two health problems with infectious diseases in the elderly: a volume problem and an inhomogeneous demand for health care. Older people need more costly treatment because of their increased frailty condition.

If those infections could be avoided, we should be able to delay, reduce, or avoid the exposure to institutionalised health care with lengthy and costly stays related to slow recovery. Avoiding infections, therefore, impacts the ambition of supporting healthy aging, a condition that helps optimise the opportunities of good health so that aged individuals maintain their activities of social life and enjoy an independent high quality of life[104]. A solution to avoid those infections is to develop a well-conceived vaccination programme for the elderly as we did for children years ago. If we apply the same strategy for the elderly we should help reduce the infection problem and its consequences of being exposed to anti-microbial resistance (AMR). But this whole situation has not been so well studied with enough detail in an integrated way. Rather bits and parts have been assessed but without having a clear overall picture on how this whole process of aging, infection exposure[105], immune response to vaccination[106], is developing and potentially evolving. Therefore, before getting to the programme of vaccinating the elderly, we need to study the infection problem in greater detail. We are therefore facing the following challenges in getting the full picture well presented:

1. getting access and demonstrating how to evaluate and report epidemiologic data for obtaining a clear picture on the infectious disease burden in the aged people (50 years +) (trend analysis, frequency, Quality of Life (QoL), and cost) split by specific age and gender groups, vaccine-preventable or upcoming vaccine preventable diseases, and exposure to the health care system (at home care, day care, medical care, institutional care (hospital, recovery));
2. better understanding the immune response in elderly (65 years +) by deciphering the changes taking place due to age and to other factors, the role of different facets of the immune responses, the role of new immune-modulation techniques, and to explore the potential for developing better vaccines for the elderly;
3. having disease and economic models available that predict how the current situation may further evolve without any specific intervention, and how we may project a change in disease frequency, cost and QoL of

[99] EUROSTAT (2017). "Population structure and aging".
[100] Flinch, C (2010). Evolution of the human lifespan and diseases of aging: roles of infectoion, inflammation, and nutrition. PNAS, 107 (1).
[101] Gloersen, E (2016). The impact of demographic change on European regions: 147
[102] Lambert, N. D., et al. (2012). "Understanding the immune response to seasonal influenza vaccination in older adults: a systems biology approach." Expert Rev Vaccines 11(8): 985-994.
103 Westendorp R, (2006). What is healthy aging in the 21st century? AM J Clin Nutr 83(2):404S-409S.
[104] Lagiewka, K. (2012). "European innovation partnership on active and healthy ageing: triggers of setting the headline target of 2 additional healthy life years at birth at EU average by 2020." Arch Public Health 70(1): 23
[105] Ozawa, S., et al. (2016). "Modeling The Economic Burden Of Adult Vaccine-Preventable Diseases In The United States." Health Aff (Millwood) 35(11): 2124-2132.
[106] Gruver, A. L., et al. (2007). "Immunosenescence of ageing." J Pathol 211(2): 144-156.

the elderly, if we implement an extended vaccination programme to reduce the burden of infections with the overall societal consequences;

4. being able to communicate an integrated view of the problem (epidemiology, cost, and QoL burden, vaccine and immunology working, economic consequences of implementing a vaccination programme among elderly) through training and education of health care professionals (HCP).

Need and opportunity for public-private collaborative research

Public and private sectors are today involved at varying degrees in a variety of assessments on aging such as research on immune-senescence[107] [108] [109] [110], identifying external factors that could influence the process, epidemiology and the cost of vaccine preventable infectious diseases in elderly[111]. Industry has a long-lasting experience with approaches of vaccinating the elderly adults as demonstrated with the development of specific vaccines for that target group. For example, progress has been reported in the past few years by various industries in the development of vaccines for influenza, pneumococcal infections, and herpes zoster for elderly[112] [113] [114] [115]. However, success in these approaches is often based on empirical knowledge and observations rather than on understanding well the underlying mechanics of the vaccine working. On the other side, various public groups such as academic teams, governmental and public health bodies, small and medium-sized enterprises (SMEs) have an established track record of expertise and achievements in specific aspects of ageing (epidemiology, immunology, health economics, training). This suggests that a more integrated approach between public and private sectors may pave the way for a deeper understanding of the problem and a definition of novel solutions.

Only through joined efforts of public and private sponsors can a holistic approach be successful in adding value as compared with the many projects in the area of aging which mostly have focussed on a single aspect (most of the time on immune-senescence).

For example:

Vaccine industries and academic groups may currently perform their own epidemiologic studies with the collection of cost information and QoL data that are conducted independently from each other, using different types of analysis, QoL instruments, and reporting with different definitions because different age-groups have been selected or different time horizon perspectives have been considered. There is a need for more cooperation between the different groups, for sharing of information, pooled analyses of larger anonymised datasets, uniformed analysis and reporting. This should lead to more robust findings that will increase the credibility of the research.

Developing new programmes to study the immune response amongst aged persons is often a very costly undertaking, which makes it challenging for individual organisations or stakeholder sectors to conduct such studies. Collaboration between sectors will result in optimal use of financial resources and avoid duplication of efforts.

Vaccine industries and academic groups can develop their own disease and economic models to explore the cost-benefit of new interventions. While those models are today often developed in different environments with little incentive to share the full details of their construction, for third party evaluators they remain black boxes with a low possibility of achieving a high level of transparency. There is a need for working together on model development between industry and academia, and

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[107] Gruver, A. L., et al. (2007). "Immunosenescence of ageing." J Pathol 211(2): 144-156.
[108] Lambert, N. D., et al. (2012). "Understanding the immune response to seasonal influenza vaccination in older adults: a systems biology approach." Expert Rev Vaccines 11(8): 985-994
109 Ovsyannikova I, (2012). Impact of cytokine and cytokine receptor gene polymorphisms on cellular immunity after smallpox vaccination. Gene, 510(1): 59-65.
110 Boraschi, D., et al. (2013). "The gracefully aging immune system." Sci Transl Med 5(185): 185ps188.
111 Ozawa, S., et al. (2016). "Modeling The Economic Burden Of Adult Vaccine-Preventable Diseases In The United States." Health Aff (Millwood) 35(11): 2124-2132.
112 DiazGranados C, et al (2014). Efficacy of high-dose versus standard-dose influenza vaccine il older adults. N Engl J Med, 371(1): 635-45.
113 Bonten M, et al. (2015), Vaccine against penumococcal pneumonia in adults. N Engl J Med, 373(1): 93.
114 Lal H, et al (2015). Efficacy of an adjuvanted herpes zoster subunit vaccine in older adults. N Engl J Med, 372 (22): 2087-96.
115
Cunningham A, et al (2016). Efficacy of the Herpes Zoster subunit Vaccine in Adults 70 Years of Age and Older. N ENgl J Med, 375 (11): 1019-32.

possibly governmental institutions, so that maximum transparency and agreement is reached on how the models are constructed, tested and validated. This should create a deeper trusted relationship, including with decision makers, about the model output and sensitivity analyses.

Once the problem is understood and once potential solutions are found, it will be key that the results become an integral part of communication and teaching programmes involving all stakeholders working with the elderly. Such communication and reporting about the project requires intense collaboration between public and private organisations, to develop joined messages for healthcare professionals and decision-makers.

Scope

The scope of the project is to:

- obtain a clear picture on the infectious disease burden in an aging population (50 years +);
- quantify the problem such as number and type of hospitalisations and medical visits when the 50 years + group is exposed to the health care system;
- understand this evolution over the coming years;
- obtain a better insight in the immune response in the age-group of 65 years +;
- develop cost-benefit predictions based on an extended vaccination programme;
- better control the burden in that age-group through simulations with advanced disease models, and finally;
- develop strategies to educate all stakeholders working with the elderly.

The strength and attractiveness of the project is to achieve an integrated, multi-disciplinary approach of the problem making necessary links of collaboration between the different activities proposed in the different pillars presented hereunder.

Four pillars represent the objectives under the overall scope of the project. They are identified as burden of disease (pillar 1), immune response investigation (pillar 2), economic value (pillar 3), and communication (pillar 4). To reflect project priorities, pillar 1 and 2 would have main allocation of resources, but to reflect their significance, pillars 3 and 4 would still receive a significant allocation of the total indicative budget.

Pillar 1: Burden of infectious diseases in aging adults (50+)

It is expected that the activities of this project will lead to the development of an appropriate protocol design for collecting epidemiologic and economic data about infectious diseases in an aged population (50 years +) across the health care systems in place. A starting point will be a pilot project in a specific region that has the facilities to develop and test in depth the designed approach for collecting and analysing the data. Based on that experience and depending on budget and time allocation, the programme could then progressively expand to different regions in Europe with the goal of obtaining a consolidated data-base system. It is not the ambition to be able to cover the whole of Europe within the budget and time frame but to demonstrate the applicability of the programme in different environments across Europe that best illustrate the heterogeneity of the problem from west to east and from north to south.

The protocol in the pilot region could begin with the collection and analysis of retrospective data, moving to a more advanced and well-established prospective epidemiologic study programme.

The primary objectives under this pillar are to:

1. obtain more accurate ‘real world’ knowledge on the epidemiology and the economics of infectious diseases in aging adults split into 2 categories: existing vaccine-preventable (VP) diseases and upcoming potential vaccine-preventable (PVP) diseases. VP includes vaccines against influenza, pneumococcal, zoster, pertussis, meningococcal, and rotavirus. PVP included vaccines against for example RSV, Clostridium difficile, staphylococcus, E. coli, enterococcus, urinary tract infections, and specific anti-microbial resistant germs;
2. be able to report precisely on specific mortality, morbidity, hospitalisation, medical visits, access to health care, cost and productivity loss, overall QoL, and specific QoL;
3. investigate and explore potential links to diseases/co-morbidities and risks in which infectious diseases could be the trigger for developing more complex disease conditions (cardio-vascular, respiratory, stroke, metabolic problems, etc.).

4. In addition, the project should explore the generation of a consolidated database on infectious disease burden in aging adults (epidemiology & cost) across Europe that can be consulted by decision makers when selecting new vaccines to be implemented.
5. The activities under this pillar might also support the development of an estimate of the increase of the infectious disease volume in the aged population and the level of heterogeneity of the problem (different demand of health support by age and gender), however this is not considered a primary objective of this action. Likewise, the activities under this pillar might be useful building blocks for creating a natural infectious disease pattern of the elderly, but this is not considered a primary objective of this action.

Pillar 2: Changes in immune response with age (65+ years compared to adults 18-50 years of age) and internal factors influencing the process

The primary objectives under this pillar are to:

1. select novel approaches that enlarge our knowledge about what leads to the decline of immune response causing higher susceptibility to infectious diseases and poor vaccine response;
2. expand the field of investigating immune decline with age (termed immune-senescence) and identify the several compartments of the immune system that senesce with age;
3. develop and perform a prospectively designed clinical research study to assess the immune response of the elderly (65+ years) compared with adults (18-50 years) following vaccination. An appropriate informed consent would allow the collection of serum and whole blood to assess systems biology profiles and biomarker signatures. A frailty assessment at enrolment could be established. A state-of-the-art dissection of the immune response could be conducted focussed on immune compartments not well studied or not studied to date – for example, T-cell follicular help (TfH), individual cell profiling (e.g. RNA sequencing), mucosal markers and B-cell immune compartments. Particular attention should also be given to innate immunity in the peripheral blood and, whenever possible, at the site of priming of the immune system (e.g. skin, muscle, mucosal level). The role of dendritic cells, macrophages, NK cells is becoming more important in the events triggered by novel adjuvants, novel delivery systems, etc. Their role in the elderly is still poorly understood.
4. In addition, the project should also propose how the vaccination field of analysis could be expanded beyond influenza to create an optimal vaccination programme with durable protection for non-influenza vaccines in elderly, namely Tdap/Td, Herpes Zoster and Pneumococcal. This is particularly important for those vaccines for which the elderly are immunologically naïve and which should provide a strong priming, which is expected to be difficult to achieve in subjects with a paucity of naïve T and B cells. Therefore equal emphasis should be put in place on the assessment of immune-senescence in response to influenza and non-influenza vaccines.
5. The activities under this action might inform the following, however these points are not considered primary objectives of the action:
6. Application of the technique of machine learning to unravel the complex inter-relations between immunological biomarkers and vaccination in the elderly, to better understand complex patterns associated with aging and vaccination. New profiles of immune aging should direct areas of research for the application of immunomodulation and/or new vaccine technologies, able to overcome or mitigate immune devolution.
7. Hypothesis testing on extrinsic factors that could influence the immune response: nutrition, physical exercise, medical treatments, other technologies applied in medical care. It is well known that nutrition significantly influences immune responsiveness in the old subjects. Caloric restriction has a positive effect, while obesity has a negative effect on immune responses. In addition, some drugs have been recently unexpectedly shown to have either positive or negative effect on vaccination in old people. Prospective studies are needed to investigate the relationship and its strength.
8. The creation of the right vaccine development programme against certain infectious healthcare problems in elderly.
9. Application of new data analysis methods to derive immune profiles associated with aging.

Pillar 3: Vaccine impact assessment and economic value of vaccination in aging adults

The primary objectives under this pillar are to:

1. be able to evaluate the effectiveness and impact of vaccination through modelling exercises with simulations and scenario-analysis (best, worst case) using well-developed epidemiologic and economic models including optimization and a vaccine portfolio management approach;
2. develop a natural disease model with data obtained from the epidemiologic studies that should also help in answering the questions: when do we need to vaccinate to obtain optimal results of prevention;
3. be able to elaborate on what could be the consequences expressed financially (private, public), in health gain (life years and quality life years), and in health care development (more beds, more home care, improvement in quality of care).

It is expected that the activities under this pillar will inform whether vaccination may help in reducing the anti-microbiological drug resistance over time.

The activities under this pillar might also support the development of an estimate of what the new threat of living longer under healthier conditions for our social security system with increased spending in pensions will be (do we need to work longer?), however this is not considered a primary objective of the action.

Pillar 4: How to best communicate to stakeholders through education and training of HCPs

The objective under this pillar is to:

- build a framework of innovative educational and training initiatives on infectious diseases based on adequate prevention strategies including vaccination in aging adults for all HCPs.

Expected key deliverables

The expected key deliverables of the project should be:

- **a database on infectious disease burden in aging adults (repository of knowledge);**
- **standard methods and definitions on how to analyse and report the disease burden for that age-group;**
- **an estimation of the full burden of infectious diseases for VP and PVP. The burden should include frequencies, costs, Quality of Life (QoL), with trend results stratified by age-groups, risk level, relative importance of hospitalization/surgery, gender, social classes, access to medicine, underlying chronic diseases or sequelae;**
- **the identification and validation of intrinsic parameters impacting the decline of immune responsiveness with age characterised to advance the prevention of infectious disease in the elderly through vaccination;**
- **computational models to conduct simulations of immune function in elderly (with/without disease);**
- **the characterisation and validation of the role of external environmental factors (nutrition, physical exercise, pharmacological treatments, etc.) on the immune responsiveness in the elderly;**
- **models with scenario-testing that simulate the impact of different vaccination programmes based on their health benefit and economic consequences;**
- **a recommendation for optimal vaccination strategies of the older adults based on model simulations and the data collection;**
- **the development of a vaccine confidence roadmap targeting HCPs: understanding of the levers/barriers to vaccination and drafting of possible actions.**

Expected impact

The project will have an impact at many different levels:

- Societal gain for healthy aging: Based on the data-collection and model simulation, a recommendation will come out on how to create an optimal vaccination strategy for the older adults. If

that strategy will be implemented, an evidence-based vaccination programme for the aging adult will enhance the health condition of the elderly, make important cost offsets in health care, result in benefits in leisure time of the target group and the care-givers, reduction in production loss of care-givers, and improve the quality of care. In addition, an enhanced overall knowledge of what matters among the elderly will be an important societal gain.

- Health science development: Agreed-upon standards of analysis and reporting in the field of epidemiology and economic evaluation in people over 50 years old will have a positive impact on the results of vaccination.

- Basic research in immunology and vaccinology: It is expected that the results of the project will significantly contribute to a deeper understanding of the immune-response in aging adults. This new knowledge would not be a stand-alone acquisition, but it would instead reside within the frame of a more comprehensive body of knowledge encompassing epidemiology, environmental factors, etc. The results should help to develop better vaccines or better vaccination-schedules/programmes for the target group.

- Economic analysis: The elderly are a challenging group to assess in health economic evaluations when it comes to measuring precisely health and health gain. In the elderly the cohort of evaluation is not fixed but reduces over time because of the deaths moving into the absorbing state. Many competing causes of death and interactions between various co-morbidities do not allow a readily available valuation of expected health benefits. This project should allow to more accurately estimate health gains achieved through new interventions like vaccination and cost calculations using more appropriate techniques of modelling.

- Communication strategies: Our society is evolving very rapidly in a modern area of communication that is well established in the young generation with the social media. Having a good communication strategy in place will enhance the promotion of prevention strategies such as new vaccination programmes to reduce the burden of infections in elderly.

- Through the participation of industrial partners, in particular small and medium-sized enterprises (SMEs), an additional impact in relation to strengthening the competitiveness and industrial leadership of Europe can be expected.

- Interaction with regulatory agencies. It is expected that some of the outcome of the project may be interesting for the regulatory bodies at international (e.g. EMA), national or regional level. For this reason, updates of the progress of the project will be provided regularly as appropriate.

Potential synergies with existing consortia

The project is expected to directly contribute to the goals and activities of the European Innovation partnership on Active and on Healthy Ageing.

Applicant consortia will propose a strategy to emphasis/maximize potential synergies with other initiatives in the field of health interventions on aging adults such as epidemiology, economics, immunology, physiology, among other initiatives. For example, links to existing lists of initiatives within Horizon 2020, Millennium goals, Healthy Aging programmes via EuroHealthNet, should be explored, such as the H2020 I-MOVE+ project.

In addition, special consideration should be given to exploring synergies with existing IMI projects and utilising learnings generated there to build upon in this project. The following non-exhaustive list of IMI projects might be of relevance in this respect:

- projects under the New Drugs for Bad Bugs (ND4BB) programme, http://www.imi.europa.eu/content/nd4bb ;

- RESCEU (Respiratory syncytial virus consortium in Europe), www.resc-eu.org;

- the Better Data for Better Outcomes (BD4BO) programme;

- SPRINTT (Sarcopenia and physical frailty in older people: multi-component treatment strategies), www.mysprintt.eu;
- other IMI projects dealing with vaccine data analysis, such as ADVANCE **(Accelerated development of vaccine benefit-risk collaboration in Europe),** www.advance-vaccines.eu, and the project selected for funding under the topic Joint influenza vaccine effectiveness studies (IMI2C9);
- any other project or initiative of relevance, in order to avoid duplication of efforts.

Industry Consortium

The industry consortium is composed of the following EFPIA companies:

- GlaxoSmithKline (lead)
- Sanofi Pasteur
- MSD
- Janssen
- Pfizer
- Vaccines Europe/EFPIA

The EFPIA in-kind contribution will take the form of:

- personnel costs by providing expertise in health economics and outcomes, immunology, epidemiology, statistics, regulatory affairs, patients engagement, project leadership;
- conduct of a large prospective observational epidemiological study;
- giving access to a data-base that has already collected some critical information on the subject;
- disease and economic models already or being developed for elderly;
- roadmaps for good communication practices.

Indicative duration of the action

The indicative duration of the action is 60 months.

Future Project Expansion

Potential applicants must be aware that the Innovative Medicines Initiative 2 (IMI2) Joint Undertaking may, if exceptionally needed, publish at a later stage another Call for proposals restricted to the consortium already selected under this topic, in order to enhance the results and achievements by extending the duration and funding. The consortium will be entitled to open to other beneficiaries as it sees fit.

A restricted Call may be launched as part of a future IMI2 JU Annual Work Plan to build upon the work carried out under this action under the different activities of the different pillars enhancing further development of the results to full deployment as necessary. Examples could be the full development of a database on infectious disease burden in aging adults, the assessment of volume increase of infectious disease over time, or creating a natural infectious disease model.

Indicative budget

The indicative EFPIA in-kind contribution is EUR 5 500 000.

The financial contribution from IMI2 is a maximum of EUR 5 500 000.

Applicant Consortium

The successful applicant consortium will be selected on the basis of the submitted short proposals and their experience in working in a multi-disciplinary environment including epidemiology, modelling, health economics, experience in conducting clinical studies, knowing well the other IMI projects.

The applicant consortium is expected to address all the research objectives and make key contributions to the defined deliverables in synergy with the industry consortium.

The consortium should combine partners with established and well-recognized experience in the field of aging, encompassing aspects related to human vaccination, public health, human immunology, epidemiology, infectious diseases, physiology, medicine, nutrition, economics, advanced disease modelling, training and education capacities and experiences, etc.

The consortium should include partners with experience in assessing vaccination programmes and the decision-making processes leading to the implementation of new vaccination programmes, as well as regulatory experience.

The applicant consortium is expected to include the necessary project management skills suitable for the expected funded project.

It is expected that the applicant consortium will guarantee regular (at least annual) contacts with regulatory agencies (national and/or supranational) as appropriate to inform them on the progress of the project. This could take place via regular teleconferences and/or face-to-face meetings as felt appropriate by the consortium and by the regulatory agency.

Suggested architecture of the full proposal

The applicant consortium should submit a short proposal which includes their suggestions for creating a full proposal architecture, taking into consideration the industry contributions and expertise provided below.

The final architecture of the full proposal will be defined by the participants in compliance with the IMI2 rules and with a view to achieving the project objectives.

In the spirit of the partnership, and to reflect how IMI 2 JU call topics are built on identified scientific priorities agreed together with EFPIA beneficiaries/large industrial beneficiaries, these beneficiaries intend to significantly contribute to the programme leadership and project and financial management.

The final architecture of the full proposal will be defined by the participants in compliance with the IMI 2 JU rules and with a view to the achievement of the project objectives. The allocation of a leading role within the consortium will be discussed in the course of the drafting of the full proposal to be submitted at stage 2. To facilitate the formation of the final consortium, until the roles are formally appointed through the consortium agreement, the proposed project leader from among EFPIA beneficiaries/large industrial beneficiaries shall facilitate an efficient negotiation of project content and required agreements.

All beneficiaries are encouraged to discuss the project architecture and governance and the weighting of responsibilities and priorities therein.

The architecture of the proposal is based on four major pillars. It is expected to support the development of a comprehensive programme about the relationship between vaccine and healthy aging. The architecture outlined below for the full proposal is a suggestion. Different innovative project designs are welcome, if properly justified, as long as the objectives of the project are fully supported.

It is expected that the objectives of the project can be achieved by the following five work packages.

Work Package 1: To determine the burden of infectious diseases in aging adults (50+)

The objectives of this work package will be as follows:

- Through retro- and prospective epidemiologic study design and review of existing databases, starting with a pilot project in a particular region in order to obtain a robust protocol of evaluation that can be expanded progressively over time;
- Acquiring a deeper knowledge on the epidemiology of infectious diseases split into 2 categories (existing vaccine-preventable (VP) diseases (e.g. influenza, pneumococcal, zoster, pertussis, meningococcal, rotavirus), upcoming potential vaccine-preventable (PVP) diseases (e.g. RSV, C diff, staphylococcus, E coli, enterococcus, urinary tract infections, specific anti-microbial resistance germs) in aging adults);
- Acquiring a deeper knowledge on the economics of the infectious diseases (cost of illness) split into the 2 categories (VP, PVP);
- Investigate potential links to diseases/co-morbidities and risks within that age group in which infectious diseases could be the trigger for developing more complex disease conditions (cardiovascular, respiratory, stroke, metabolic problems, etc.);
- The work package 1 should report about the volume increase of the infectious disease in the aged population because of the demographic age-change and about the level of heterogeneity in the target group related to possible immune response rates.

Work Package 2: To better understand the immune response of aging adults (65+) and how it is modulated or affected by internal and external factors after vaccination

The objectives of this work package will be as follows:

- Prospectively designed clinical research studies to assess the immune response of the elderly (65+ years) compared to adults (18-50 years) following vaccination. An appropriate informed consent would allow the collection of serum and whole blood to assess systems biology profiles and biomarker signatures. Establishment of a frailty assessment related to the infection condition at enrolment.
- Learning about mechanisms leading to immune waning or reduced immune responsiveness at the level of both innate and adaptive (both T- and B-cell) immunity, and the ability to respond to vaccination with age.
- State-of-the-art dissection of immune responses at the site of the priming of the immune response (e.g. related to skin condition, muscle condition, mucosal conditions), role of B and T-cell immunity, immune modulators (PD-1) among others, in order to better understand why the immune-response reduces with age. This large field of exploration needs an urgent, well-focussed and designed research programme for obtaining reliable and workable results that can improve next generation of vaccines and vaccination-schedules and programmes for the elderly. The field is starting to know and observe important processes of immune-senescence occurring with age, but we need to focus on immune compartments pertinent to optimal vaccine elicited responses and other immune processes not yet adequately addressed such as T-cell follicular help (TfH), B-cell immunity, innate immunity (e.g. dendritic cells, macrophages, monocytes, NK cells, etc. in the blood and, whenever possible, at other priming and/or effector sites of the immune response), mucosal markers, antibody effector functions, immune profiling at the individual cell level (e.g. single cell RNA sequencing), among others.
- The waning of the immune responsiveness is not merely due to the ‘physiological’ decline by age, but also by extrinsic factor, which can accelerate or retard the decline. Understanding how these factors such as physical activity, nutrition, other medical treatments, existing comorbidities may affect the immune responsiveness in aging adults becomes important to better appreciate the heterogeneity of the phenomenon of immune-senescence.
- Application of new data analysis methods to derive immune profiles associated with aging. Machine learning should be applied to identify complex profiles of inter-related factors.

Work Package 3: To assess with disease models the current management status of infectious diseases in older adults and to simulate the impact of (potentially) vaccine preventable infections

The objectives of this work package will be as follows:

- The models should set new standards of analysing and reporting health economic results for such population (cost-effectiveness analysis, budget impact, optimisation modelling). It is expected to advance the impact options in a transparent way when analysing and reporting health economic results.
- Based on information collected in Work Package 1, developing advanced modelling programmes (agent-based modelling) simulating different conditions in which elderly people may normally operate (home care, day care, hospital care) to demonstrate the impact of vaccination according to various level of immune-senescence and to define best strategies to maximise the overall public health impact of vaccination for aging adults, taking into account potential enablers. The models developed through this programme, should be made available across all the participants of the project.

Work Package 4: To develop a roadmap about training and education of HCPs

The objectives of this work package will be as follows:

- Vaccination of adults and elderly subjects is not fully perceived as a major need with great value assessment for the target population and society, as compared with the vaccination of the paediatric age-group. Appropriate and innovative communication tools for all stakeholders (decision makers, prescribers, payers, target population) on the value of vaccines and on vaccination should represent a key need for achieving the scope of healthy aging.
- Building a framework of innovative educational and training initiatives on infectious diseases for all HCPs based on adequate prevention strategies including vaccination in aging adults.
- Developing a network of specialists/experts in the field across Europe to exchange experience and set-up new collaborative projects would be very helpful.
- Demonstrate how to secure training of the HCPs in charge of implementing adult vaccination: include systematic HCPs vaccination training both in curriculum and in Continuous Medical Education (CME) (use of Massive Open Online Courses (MOOC) to be leveraged), taking into account that HCPs should include GPs, specialists, nurses and pharmacists

Work Package 5: project coordination, management, and dissemination activities

The objectives of this work package will be as follows:

- Skilled project management support will be an essential part to ensure project success.
- Managing all aspects of project governance, management and coordination. Facilitation and streamlining of cooperation between the different partners of the project and between work packages.
- Carrying out all aspects of the dissemination of results, and communication strategy.
- Coordinating and communicating with other European initiatives and projects handling complementary activities.

Topic 6: Discovery and characterisation of blood-brain barrier targets and transport mechanisms for brain delivery of therapeutics to treat neurodegenerative & metabolic diseases

Topic details

Topic code	IMI2-2017-12-06
Action type	Research and Innovation Actions (RIA)
Submission & evaluation process	2 Stages

Specific challenges to be addressed

The **blood–brain barrier** (BBB) acts as a strict control point for what can enter the brain, and is created by drug efflux transporters (transport barrier) expressed on cerebromicrovascular endothelial cells and by tight junctions and adherens junctions between those endothelial cells (biophysical barrier) supported by basement membrane, astrocytic end-feet, pericytes, and neuronal innervation. The barrier functions of the BBB lie in the integrity and physiological regulation of the neurovascular unit (NVU). The BBB facilitates the passage of nutrients and metabolic necessities to the brain but restricts the entry of most blood-borne drugs and neurotoxic agents into the brain. The ability to cross the BBB must be considered for neurotherapeutics administered peripherally. In particular the BBB remains a major obstacle for biopharmaceuticals (e.g., antibodies, peptides) and restricts the choice to passive brain-permeable small molecules[116]. While there are examples of actively transported central nervous system (CNS) drugs (e.g. Lyrica®) the state of transporter substrate specificity understanding makes development of these largely dependent on luck rather than design. This also explains why no centrally acting biopharmaceuticals (e.g. antibodies, peptides, proteins, oligonucleotides) are currently on the market[117]. Transport receptors or carriers, mostly mediating receptor- or carrier-mediated transcytosis (such as transferrin (TfR) and insulin (InsR) receptors, Low density lipoprotein receptor-related protein 1 (LRP 1), Glucose transporter 1 (GLUT1), Amino Acid Transport Associated to Cluster of Differentiation 98 Heavy Chain (CD98hc)) triggered by antibodies or peptides, have been reported to ferry biopharmaceuticals across the BBB[118]. However, these systems have not totally proven their safety and efficacy yet and no development of transferrin receptor antibody-enabled biopharmaceutical has been reported to-date. Insulin receptor antibody has been recently employed to deliver iduronate-2-sulfatase to the brains of MPS-II (Type II mucopolysaccharidose or Hunter syndrome) patients in a phase II clinical trial (NCT02262338). It appears to be safe, tolerable and improve cognitive scores in the patients. In addition to Receptor Mediated Transcytosis (RMT) and Carrier Mediated Transcytosis (CMT) mechanisms, liposomes[119], nanoparticles, and more recently exosomes[120] have been explored to enhance brain delivery of therapeutics. These have targeted both passive and active uptake mechanisms and have shown mixed results to date. Studies have also explored approaches of employing viral vectors/particles/vesicles or protein fragments to deliver genes or biopharmaceuticals into the brain. Other approaches of drug delivery, such as intranasal delivery of therapeutics across the olfactory epithelia into the brain, still remain to be explored further. While all these results seem promising, a major challenge in this field is validation of the various transport mechanisms and drug delivery systems by independent researchers and further understanding challenges to advancing into clinical drug development by biotech/pharma.

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[116] For general reviews, see for instance Banks, W. A. From blood–brain barrier to blood–brain interface: new opportunities for CNS drug delivery. Nat. Rev. Drug Discov 15, 275 (2016); B. Obermeier,R. Danemanand R. M Ransohoff, Development, maintenance and disruption of the blood-brain barrier, Nature Medicine 19, 1584–1596 (2013).
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[118] W.M. Pardridge, Re-engineering therapeutic antibodies for Alzheimer's disease as blood-brain barrier penetrating bi-specific antibodies, Re-engineering therapeutic antibodies for Alzheimer's disease as blood-brain barrier penetrating bi-specific antibodies, Expert Opinion on Biological Therapy 1471-2598, 2016; Zuchero, Y. J. et al. Discovery of novel blood–brain barrier targets to enhance brain uptake of therapeutic antibodies. Neuron 89, 70–82 (2016)
[119] F. Lai, , A. M. Fadda and C. Sinico, Liposomes for brain delivery, Expert Opinion on Drug Delivery, 10:7, 1003-1022, 2013.
[120] L. Alvarez-Erviti, Y. Seow, H. Yin, C. Betts, S. Lakhal and M. J. A. Wood, Delivery of siRNA to the mouse brain by systemic injection of targeted exosomes, Nat. Biotechnol., 2011, 29, 341–345.

A goal of the action to be generated by this topic is to work precompetitively to validate targets and transport mechanisms at the BBB and provide additional insight into any developmental challenges.

One of the central hurdles in driving structure-activity relationship (SAR) for brain uptake and in identifying new mechanisms of brain delivery is the lack of **blood-brain barrier models** truly predictive of *in vivo* exposures of biologics as well as lack of selective BBB targets for brain transport. Even if some reports in the literature present human inducible pluripotent stem cell (hiPSC)-derived BBB models[121], their robustness and predictability remain to be assessed, and no fully reconstituted human model convincingly mimicking the neurovascular unit has been successfully developed to-date[122]. To this end, 3D- or spheroid models and microfluidics could be ideally suited and a few interesting directions are starting to emerge in the literature[123] even though some less reported models – at least in the context of BBB- such as hollow-fiber models could also be of use, provided that they bring value to the project.

A **compromised or altered permeability of BBB** has been reported in brain tumours and for several **neurological and metabolic diseases[124]**. Even though it is still a matter of debate, it seems increasingly evident that this BBB dysfunction might be at the very root and pathogenesis of some of these neurological diseases (such as multiple sclerosis and vascular dementia)[125]. And even though the pharmacological understanding of many of these diseases has identified attractive potential therapeutic targets, most of these are currently not believed to be developable due the hurdle of the BBB and the lack of predicted brain penetration based upon general understanding of BBB characteristics. Availability of *in vitro* and *in vivo* models of the BBB representative of those characteristics present in these diseases would allow much more aggressive testing of hypotheses around therapeutic delivery. This potentially may lead to greater investment in targeting these diseases due to the improved tools and mechanistic understanding to explore novel delivery strategies and to develop therapeutic agents. Both of these outcomes would improve the probability of developing successful therapeutic agents to treat these diseases. Moreover, it would provide a more expansive suite of experimental tools with which to further develop an understanding of the fundamental biology, which underpins the absorptive-/receptor-mediated processes across the BBB. **Thus, the physiology of the BBB and the transport mechanisms in health and diseases play a critical role in the development of brain delivery technologies for the treatment of neurodegenerative diseases.**

Human iPSC-derived cell models hold great promises for human ***in vitro*** **BBB and disease modelling** and could be used to understand the pathogenesis of neurodegenerative disorders, the roles of BBB in the pathogenic process, and to identify new potential improved screening tools for new drugs[126]. Thus iPSC cell-derived BBB models might represent a promising tool to link human neuropathology to BBB dysfunction and a screening tool for permeability, mechanistic and functional studies. However, there is no report on patient-derived human iPSC's BBB models or disease/genetic models generated by Clustered Regularly Interspaced Short Palindromic Repeats (CRISPR)-cas9 technology. In addition there is a general lack of a consensus on the clinical characteristics of such disease models and on what successful validation would be required.

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[121] Ethan S. Lippmann, A. Al-Ahmad, S. M. Azarin, S. P. Palecek and E. V. Shusta A retinoic acid-enhanced, multicellular human blood-brain barrier model derived from stem cell sources Scientific Reports, 1-10, 2014.

[122] A. Wolff, M. Antfolk,B. Brodin,M. Tenje, In Vitro Blood–Brain Barrier Models—An Overview of Established Models and New Microfluidic Approaches,Wolff et al., J.Pharm. Sci. 104:2727–2746, 2015. J.Pharm. Sci. 104:2727–2746, 2015.

[123] Y.I. Wang, H. Erbil Abaci, M. L. Shuler Microfluidic Blood–Brain Barrier Model Provides In Vivo-Like Barrier Properties for Drug Permeability Screening, Biotechnology and Bioengineering, Vol. 9999, 1, 2016; H. Cho, J. Hae Seo, K. H. K. Wong, Y. Terasaki, J. Park, K. Bong, K. Arai, E. H. Lo and D. Irimia Three-Dimensional Blood-Brain Barrier Model for in vitro Studies of Neurovascular Pathology Scientific Reports 5:15222, 2015; M. Raasch, K. Rennert, T. Jahn, C. Gärtner, G. Schönfelder, O. Huber, A. E. M.Seiler and A. S. Mosig, An integrative microfluidically supported in vitro model of an endothelial barrier combined with cortical spheroids simulates effects of neuroinflammation in neocortex development, Biomicrofluidics 10, 064101064101 (2016); K. M. Haston and S. Finkbeiner, Clinical Trials in a Dish: The Potential of Pluripotent Stem Cells to Develop Therapies for Neurodegenerative Diseases, Annual Review of Pharmacology and Toxicology,Vol.56:1-653, 2016.

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[125] B.V.Zlokovic, Neurovascular dysfunction and neurodegeneration in dementia and Alzheimer's disease BBA 1862, 887-900 (2016); Zlokovic, Berislav V. "The blood-brain barrier in health and chronic neurodegenerative disorders." Neuron 57.2 (2008): 178-201.

[126] Some examples applied to ALS: Y. Liu et.al. Reverse engineering human neurodegenerative disease using pluripotent stem cell technology Brain Research 1638(2016)30–41; D.B.Re et.al. Necroptosis Drives Motor Neuron Death in Models of Both Sporadic and Familial ALS Neuron (2014), 81(5), 1001-1008; An Truong, Emily Si, Thomas Duncan, Michael Valenzuela, Modeling neurodegenerative disorders in adult somatic cells: A critical review Front. Biol. (2016) 11: 232

Although results reported in the literature describing efforts to profile brain endothelium via microarray analysis, transcriptomics and proteomics approaches[127] are in principle useful, they do not necessarily resemble the disease situation. In this situation, the composition of the surface proteome of brain endothelial cells, the organization and interaction between cells and cell types and permeability in this barrier may be altered. This could strongly impair the efficacy of a brain delivery system if the employed **transport** protein/receptor is down-regulated **in disease**. As a consequence, the therapeutic efficacy of such a delivery system would be greatly reduced. The identification of transport mechanisms which remain stably expressed or, even better, upregulated in disease, would greatly improve the chances for a successful delivery of therapeutics for treatment of CNS diseases. There is also a lack of computational or *in silico* models for studying the pharmacokinetics (PK) of drugs and biopharmaceuticals as penetration of the BBB (levels and capacity of relevant receptors and carriers at the BBB for receptor/carrier-mediated transcytosis for drug delivery) and the distribution and clearance of drugs/biopharmaceuticals in different compartments of CNS under normal and disease conditions (such as interstitial fluid ISF, neurons, and cerebrospinal fluid (CSF)). *In vitro* and *in vivo* data from published sources or pharma industrial database may be collected to build such an *in silico* model. It is known that neurotropic viruses can selectively penetrate the BBB and CNS or infect nerve and neurons. However, the mechanisms of those viruses in penetrating BBB and CNS have not been fully characterised. Understanding the mechanisms of the viral mediated processes would generate useful knowledge to inform potential approaches for the development of brain selective delivery technologies.

Thus several challenges have yet to be addressed to better understand the role and alterations of the BBB and transport mechanisms in health and diseases. Relevant diseases are neurodegenerative diseases (e.g. Alzheimer and Parkinson's diseases, Amyotrophic Lateral Sclerosis (ALS)), vascular dementia, multiple sclerosis and metabolism-related central diseases (diabetes and obesity). It will be also important to understand the mechanisms of neurotropic virus-mediated BBB and CNS penetration, and to be able to apply this knowledge for the development of innovative drug delivery systems, especially for biopharmaceuticals, and the identification of novel drug targets.

Need and opportunity for public-private collaborative research

In light of the above, the magnitude and complexity of the BBB in health and diseases is beyond the reach of a single company or institution, such that it can better be addressed by a major public-private-partnership involving a variety of stakeholders and expertise. Shared understanding of measurable attributes of disease-specific BBB models combined with successful development of both the methodologies and technologies to identify validated predictive human models is necessary to enable significant advances in strategies to expand the brain-accessible repertoire and to encourage renewed investment to develop treatments for these disorders. Specific areas of immediate focus are identified in the Scope section. Because of the scale and scope of this endeavour, success will require the collaboration of a cross-functional/cross-institutional consortium of academic, SME/biotech and industrial scientists.

The engagement of leading pharmaceutical companies with detailed understanding of pre-clinical and clinical consequences of disease-modified BBB and with the chemical/analytical resources necessary to both validate and implement these models will enable the partnership to capitalise on the knowledge and innovation generated. The role of industry in this endeavour is crucial as they benefit from state-of-the-art equipment not always available to universities or academia (such as Next-generation sequencing (NGS) technologies or high throughput and robotized material for cell culture) and experienced people to run them, along with powerful and connected bioinformatics with a direct link into the clinic.

Biotech small and medium-sized enterprises (SMEs) would be very valuable in contributing with innovative technologies and tools and know-how in iPSC- or progenitor-derived cells and/or defined extracellular matrix hydrogels and/or human BBB models.

Academic groups will be necessary to provide strong know-how on BBB and disease models (neurodegenerative/metabolic) and to contribute on characterising the mechanisms of brain transport or virus-mediated transport. A few iPSC-based BBB models have been reported in recent years with good barrier properties and transport of various known brain-penetrating agents; however, their robustness and

[127] Y. Zhang, K. Chen,S. A. Sloan,M. L. Bennett,A. R. Scholze,S. O'Keeffe,H. P. Phatnani,P. Guarnieri,C. Caneda,N. Ruderisch,S. Deng,S. A. Liddelow,C. Zhang,R. Daneman,T. Maniatis,B. A. Barres,and XJia Qian Wu. An RNA-Sequencing Transcriptome and Splicing Database of Glia, Neurons, and Vascular Cells of the Cerebral Cortex The Journal of Neuroscience, 2014 ,34(36):11929 –11947

predictability needs to be put to the test[128] [129]. In addition, these models are based on 'healthy' iPSC clones and not based on iPSC cells from patients. The expertise of such academic partners in establishing iPSC-based endothelial cultures/models and in characterising brain transport mechanisms will be important for the successful conduction of the program. Even more so, the ideal situation would be to be able to develop a full BBB neurovascular unit with all cell types derived from patients and understand the mechanisms of brain transport under health and disease conditions. Successful collaboration and integration in a public private partnership of all these diverse stakeholders will be key for success in implementing the objectives of this topic.

Scope

The **objectives** of the project to be delivered from this topic are:

1. establishment and characterisation of BBB models relevant for healthy and disease conditions for evaluation of disease-modifying agents (human *in vitro* cell based, in particular iPSC or progenitor-derived cells, and *in vivo*);
2. identification of translational readouts closer to the pathogenesis of neurodegeneration and mimicking altered BBB under disease conditions;
3. in-depth understanding of the biology of the BBB and characterisation of various transport mechanisms across the BBB (including virus-mediated BBB and CNS penetration);
4. discovery and development of innovative and efficacious brain delivery systems.

These objectives could be attained through the milestones shown hereunder. Each of them could represent an independent work package and will be described later in the topic text:

1. select specific genes and pathways expressed in endothelial cells of normal and/or diseased human brains or preclinical models;
2. validate *in vitro* and *in vivo* that these genes or pathways are responsible for normal/deficient/altered transport at the BBB and the impacts of disease development and progression on these genes or pathways;
3. this will enable the generation of improved BBB models for neurodegenerative/metabolic diseases predictive for the disease situation with optimized *in vitro-in vivo* correlation compared to established models; develop *in silico* models for predicting BBB penetration and PK of therapeutics in CNS;
4. identify and validate novel targets for brain delivery;
5. understand the mechanisms of neurotropic virus-mediated BBB and CNS penetration to inform innovative ways of brain-selective delivery.

The **diseases** in the scope of the topic are neurodegenerative diseases (in particular, Alzheimer and Parkinson's diseases), ALS, vascular dementia, multiple sclerosis, and metabolism-related central diseases (diabetes and obesity). **Metabolic disorders** such as type II diabetes (T2D) and **Alzheimer's Disease** (AD) were conceptually considered as two independent disorders. Recent evidence points to a link between impaired insulin signalling and dementia. This has even led researchers to propose the term "type III diabetes" for AD to capture the connection between these diseases. Impaired insulin signalling in the brain will cause neurodegenerative changes in cerebral glucose metabolism and can lead to mitochondrial dysfunction, excitotoxic damage to neurons, reactive oxygen species production, neuroinflammation etc., which can trigger apoptotic cell death and ultimately lead to dementia. This link is not only supported by impaired insulin signalling but also from other mechanistic pathways which are altered in obesity such as adipocyte secreted proteins, hormones as well as inflammatory cytokines which, when crossing the BBB, may be involved in the pathophysiological changes leading to dementia.

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[128] Y.I. Wang, H. Erbil Abaci, M. L. Shuler Microfluidic Blood–Brain Barrier Model Provides In Vivo-Like Barrier Properties for Drug Permeability Screening, Biotechnology and Bioengineering, Vol. 9999, 1, 2016; H. Cho, J. Hae Seo, K. H. K. Wong, Y. Terasaki, J. Park, K. Bong, K. Arai, E. H. Lo and D. Irimia Three-Dimensional Blood-Brain Barrier Model for in vitro Studies of Neurovascular Pathology Scientific Reports 5:15222, 2015; M. Raasch, K. Rennert, T. Jahn, C. Gärtner, G. Schönfelder, O. Huber, A. E. M.Seiler and A. S. Mosig, An integrative microfluidically supported in vitro model of an endothelial barrier combined with cortical spheroids simulates effects of neuroinflammation in neocortex development, Biomicrofluidics 10, 064101064101 (2016); K. M. Haston and S. Finkbeiner, Clinical Trials in a Dish: The Potential of Pluripotent Stem Cells to Develop Therapies for Neurodegenerative Diseases, Annual Review of Pharmacology and Toxicology,Vol.56:1-653, 2016.

[129] Neuwelt, E.A. Bauer, B.; Fahlke, C.; Fricker, G.; Iadecola, C.; Janigro, D.; Leybaert, L.; Molnar, Z.; O'Donnell, M. E.; Povlishock, J. T.; et al Engaging neuroscience to advance translational research in brain barrier biology , Neuwelt et all Nature Rev Neuroscience (2011), 12(3), 169-182

For example, a meta-analysis has shown that people with obesity (BMI >30 kg/m2) have an increased risk factor for AD, while there are several yet unclarified possible mechanisms for the obesity-AD connection ranging from changes in amyloid transport and clearance to alterations in lipid metabolism[130].

Expected key deliverables

The overall aim of the proposed research topic is to further the understanding of the BBB in health and disease states towards the development of innovative brain delivery systems, especially for biopharmaceuticals (e.g., peptides, antibodies, etc.) and the identification of novel disease drug targets (Alzheimer's Disease, PD, etc.). The related key deliverables would be as follows:

Identification and validation of specific genes and/or mechanisms which are altered in brain endothelial cells of the diseases of interest in this topic, namely neurodegeneration (AD/PD), vascular dementia, MS, ALS, central metabolic disorders, and which modify the BBB properties *in vitro* and *in vivo*.

Generation, validation and characterisation of robust and predictive iPSC-derived BBB models: The developed models should be more reflective of the *in vivo* situation than existing models, in the healthy as well as in the disease state. The validation employing existing preclinical disease models should make them more predictable for the human clinical pathology. The use of defined media and hydrogel matrices will add to the robustness (reproducibility) and predictability of the BBB models.

New, efficacious and safe mechanisms and technologies of brain delivery. Capitalising on the findings in particular from the IMI COMPACT consortium, namely several potential new targets for brain delivery identified through an -omics approach, could be a key asset in this endeavour[131], if this data becomes available at the time the consortium gets formed. The output of this topic should also result in an expanded and deepened understanding of the fundamental processes that underpin drug-trafficking across the BBB, which in turn can further support endeavours to elucidate novel and more efficacious brain delivery mechanisms.

Characterised new genetic models for the diseases of interest in this topic which are better amenable to evaluate disease-modifying agents. Findings from the –omics studies on patient- or preclinical model-derived endothelial cells may give novel insights into disease pathways which may also lead to the development of new models that are more disease relevant.

Characterised mechanisms of neurotropic virus-mediated BBB and CNS penetration for development of selective brain delivery systems.

Established *in silico*/mathematical models in predicting BBB penetration of therapeutics (such as receptor-or carrier-mediated transcytosis for delivery across the BBB) and pharmacokinetics of biopharmaceutics in different compartments of CNS.

Identification of relevant translational readouts which are better amenable to elucidate the role of the BBB in the pathogenesis of neurodegeneration and could eventually lead to new targets for the treatment of the neurovascular causes of the diseases. The vascular hypotheses of some neurological diseases involve BBB dysfunction in their pathogenesis. However, to-date no compelling evidence allows to clearly assess whether these neurovascular dysfunctions are cause or consequence of the neurodegenerative disease. Identification of specific readouts common to preclinical models and human pathologies would be a great advance for the field.

Expected impact

The IMI2 action generated from this topic ("the project") is expected to deliver new state of the art *in vivo* and *in vitro* validated models, validated new neurovascular targets to address the BBB and tools required to predict efficacy and safety of new therapeutic approaches.

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[130] Rhea, E. M.; Salameh, T. S.; Logsdon, A. F.; Hanson, A. J.; Erickson, M. A.; Banks, W. A. , Blood-Brain Barriers in Obesity, AAPS J, 2017, in press

[131] I. Mager, A. H. Meyer, J. Li, M. Lenter, T. Hildebrandt, G. Leparc, M. J.A. Wood, Targeting blood-brain-barrier transcytosis-perspectives for drug delivery Neuropharmacology, in press.

The **potential impact of the deliverables** of the project to be created are several: The use of 'healthy' and patient-derived specimens, iPSC clones and other types of progenitors offers compelling approaches due to the direct connection to patients with the underlying disease.
The impacts of these new models could include: (1) yielding novel insights into currently identified BBB transport mechanisms for drugs, especially biopharmaceuticals, (2) allowing to use comparative assessment between 'healthy' and 'diseased' BBB, including *in silico* models, to prioritise some approaches for specific disease(s) because the transport mechanism is modified in the disease state, (3) leading to the identification and characterisation of novel transport mechanisms that are unaffected or upregulated in the disease or neurotropic virus-mediated, making them even more interesting, and (4) facilitating the discovery and characterisation of novel targets addressing the vascular aspect of neurological disorders like AD and thus open up novel routes for therapy.

These achievements will benefit the biomedical research community and will rapidly accelerate the pace of research in the development of new therapies and new delivery technologies for diseases for which there is a high unmet medical need, such as Alzheimer's disease. As the project learnings might eventually enable brain access for large molecules, the project will facilitate academics/SMEs/pharma to open new ways for treatments and delivery systems, encouraging a renewed investment in developing drugs for neurodegenerative & metabolic disorders where the brain is the target. In particular biotech SMEs will be able to stress-test their technologies in a non-competitive open innovation environment which will help them to bridge the "valley of death" for turning these into products ready for market.

Thus, it can be anticipated that the results of the project will benefit patients and society through the accelerated discovery of new drugs targeting the brain and new delivery technologies, which will provide effective therapies for neuro-related diseases.

Altogether, the results generated from the implementation of this topic hold promise in many of the most important aspects of pharmaceutical R&D and therefore have a potential impact on the objectives of IMI2:

- improving the current drug research process by providing better translational tools and models to assess efficacy;
- improving the drug development process by providing biomarkers for diseases clearly linked to clinical relevance; better models (including *in silico* models) in predicting BBB permeability and PK of therapeutics in CNS;
- reducing the time to reach clinical proof of concept in the area of neurological and neurodegenerative diseases;
- increasing the success rate in clinical trials of highly challenging diseases such as those of the CNS;
- developing new delivery systems and/or therapies, based on characterisation and understanding of novel transport mechanisms and/or neurotropic virus-mediated transport, for diseases for which there is a high unmet need, such as Alzheimer's disease and Parkinson's disease;
- reducing the failure rate candidates in phase III clinical trials through new biomarkers for initial efficacy and safety checks.

Potential synergies with existing Consortia

Applicants should take into consideration – while preparing their short proposal – relevant national, European (both research projects as well as research infrastructure initiatives), and non-European initiatives. Synergies and complementarities should be considered in order to capitalise on past achievements, available data and tools/models and lessons learnt where possible, thus avoiding unnecessary overlap and duplication of effort.

The project generated from this topic in particular should, among others, build strongly on reported achievements and knowledge from other relevant IMI projects such as COMPACT (http://www.compact-research.org/ and http://www.compact-research.org/publications/).

As the current proposal focusses heavily on iPSC technology, it could have strong synergies with other iPSC-focused efforts like the IMI projects Stembancc (http://www.stembancc.org/) and EBiSC (https://www.ebisc.org/) which have established, characterised and banked Alzheimer's and Parkinson's disease patient-based iPSC clones. These clones could be a valuable tool for the identification of interesting clones for the establishment of BBB and/or disease models in this consortium and thus provide 'added value'.

The action generated from this topic should also consider relevant findings from the FP7 projects:

- JUSTBRAIN,(http://www.justbrain-fp7.eu/index.php?id=779)

- EURIPIDES http://cordis.europa.eu/project/rcn/88178_en
- NEUROBID (http://www.neurobid.eu/)

Industry Consortium

The industry consortium is composed of the following EFPIA companies:

- Sanofi (Lead)
- Pfizer
- GSK
- Janssen
- Novartis
- NovoNordisk
- Fujifilm

The industrial consortium is expected to provide benchmarks biopharmaceuticals to validate the BBB models, access to iPSC's from patients, high capacities in transcriptomic and proteomic studies, disease models of neurodegeneration and knowledge on translational clinical design.

Indicative duration of the action

The indicative duration of the action is 60 months.

Indicative budget

The indicative EFPIA in-kind contribution is EUR 9 000 000.

Due to the global nature of the participating industry partners, it is anticipated that some elements of the contributions will be non-EU/H2020 Associated Countries in-kind contributions[132].

The financial contribution from IMI2 is a maximum of EUR 9 000 000.

Applicant Consortium

The applicant consortium will be selected on the basis of the submitted short proposals. The applicant consortium (in which it would be of value to also include SMEs having relevant know-how and technologies) is expected to address all the objectives and make key contributions to the defined deliverables in synergy with the industry consortium which will join the selected applicant consortium in preparation of the full proposal for stage 2.

The applicant consortium should be able to demonstrate the full scope of expertise in order to address effectively and meet all goals outlined in this topic. This may require mobilising, as appropriate: expertise ranging from translational medicine, *in vivo* models of neurodegeneration, biomarker development to data and knowledge management, project management and professional communication expertise. In particular the following expertise and resources are highly relevant:

- Know-how on state-of-the-art BBB model (IPSC or progenitor-based would be high priority but any other cell model are acceptable), including 3D models, microfluidics or spheroids. Experience in this field would allow generation of innovative approaches to *in vitro* BBB modelling, from classical Transwell® models to more sophisticated, more *in vivo* like models.
- Expertise in mathematical/*in silico* modelling of BBB/blood-CSF-barrier and PK of therapeutics in CNS.
- Expertise and access in/to iPSC- or progenitors-derived endothelial cell models in mono- and co-cultures.

[132] Note: This does not however constitute the justification referred to in Article 4(2) of the IMI 2 JU regulation.

- Expertise in the biology of molecular transport systems of the BBB (endocytosis, receptor- or absorptive-mediated transcytosis, endosomal trafficking etc.,), in discovery and characterisation of novel targets/mechanisms more specific for brain delivery, and in the design and development of delivery systems, such as antibodies, bispecific antibodies, liposomes/nanoparticles, aptamers, affimers, etc.
- Expertise and access to disease models in particular models of neurodegenerative diseases such as AD, PD, vascular dementia, MS, ALS, neuropathic/chronic pain, metabolic diseases of central mechanisms. In order to be able to assess the translatability of the developed *in vitro* models and to establish an *in vitro-in vivo* correlation, state-of-the-art disease models are needed.
- Expertise and know-how in the study of neurotropic viruses and their brain-penetrating mechanisms.

Suggested architecture of the full proposal

The applicant consortium should submit a short proposal, which includes their suggestions for creating a full proposal with an effective and simple architecture, taking into full consideration the deliverables, and the industry participation taking into account their contributions and expertise.

The final architecture of the full proposal will be defined by the full proposal applicants in compliance with the IMI2 rules and with a view to the achievement of the project objectives.

In the spirit of the partnership, and to reflect how IMI 2 JU call topics are built on identified scientific priorities agreed together with EFPIA beneficiaries/large industrial beneficiaries, these beneficiaries intend to significantly contribute to the programme leadership and project and financial management.

The final architecture of the full proposal will be defined by the participants in compliance with the IMI 2 JU rules and with a view to the achievement of the project objectives. The allocation of a leading role within the consortium will be discussed in the course of the drafting of the full proposal to be submitted at stage 2. To facilitate the formation of the final consortium, until the roles are formally appointed through the consortium agreement, the proposed project leader from among EFPIA beneficiaries/large industrial beneficiaries shall facilitate an efficient negotiation of project content and required agreements.

All beneficiaries are encouraged to discuss the project architecture and governance and the weighting of responsibilities and priorities therein.

The below architecture for the full proposal is a suggestion; different innovative project designs are welcome, if properly justified.

It is suggested to organize the work-plan into six main themes (each corresponding to a specific work package, see chart at the end of the document):

Work-Package 1: Selection of genes or pathways candidates associated with neurodegenerative diseases, expressed in brain endothelial cells and/or the neurovascular unit (NVU)

Targets identified by different approaches like:

- genetic analyses of existing data (GWAS, other published databases);
- transcriptomic and proteomic profiling of patient primary brain endothelial cells, cells from the neurovascular unit or tissues;
- transcriptomic and proteomic profiling of preclinical disease models primary brain endothelial cells, cells from the neurovascular unit or tissues;
- glycomics of BBB cells and/or cerebral vasculature of diseased brains.

Deliverables: disease-associated or differentially expressed genes and/or pathways which play roles in the alteration of BBB integrity and transport mechanisms in endothelial cells/cells of the NVU of potential importance to brain delivery.

EFPIA contribution: patients primary cells, omics, genetic analyses, preclinical disease models.
Applicant consortium contribution: genetic analyses, omics.

Work-Package 2: Phenotypic validation of the identified genes and/or pathways in brain endothelial cells/NVU:

This could be achieved in four steps:

- generation of endothelial cells from iPSC or Progenitors;
- generation of iPSC cells from primary cells from patients;
- induce mutations of genes/pathways involving BBB permeability and transport by genome editing (such as CRISPR cas9 technology);
- produce evidence for phenotypic or transport differences in monocultures or 3D/co-cultures.

Many parameters could be analysed such as glucose and amyloid transport, immune cell migration, permeability to other specific proteins or toxics. The clones displaying phenotypic differences between healthy and disease situation might be prioritised for further work.

Deliverables: validated disease-specific or differentially expressed genes and/or pathways of potential relevance to brain transport.

EFPIA contribution: iPSC cells or progenitors, differentiation into endothelial cells and other cell types (astrocytes, pericytes, neurons…), monocultures, 3D/co-cultures, CRISPR.
Applicant consortium contribution: iPSC or progenitor cells, CRISPR, Benchmark tools and methods for transport analysis and other phenotypic investigations (IgG's, TfR Ab, InsR Ab …).

Work-Package 3: Develop best state-of-the-art (e.g. hiPSC- or progenitor-derived) BBB models (mono- or co-cultures, 3D, etc.) by differentiation into endothelial cells and barrier formation characterisation

This could be done using mono- or co-cultures, 3D-setting, microfluidics or other settings by differentiation into brain endothelial cells and barrier formation characterisation. Full characterisation such as apical/basolateral receptor activity would be essential. The model would be considered as validated if it is able to predict *in vivo* exposures of biopharmaceuticals in the various disease or normal state. A last step would be the employment of validated models to further elucidate mechanistic studies pertaining to BBB absorption biology and transport mechanisms.

Mathematical/*in silico* modelling of receptor-/carrier-mediated transcytosis across the BBB (the capacity of each receptor in mediating transcytosis and brain delivery), and PK of biopharmaceutics in the brain (particularly the PK and clearance of antibodies/proteins in ISF, neurons, and CSF) should be also a part of this characterisation, including disease conditions (such as the expression levels of relevant receptors, carriers and proteins).

Deliverables: characterise apical/basolateral receptor activity, validate model with a set of reference compounds with known *in vivo* BBB transport data, validate candidates *in vitro*; a more in-depth understanding of the fundamentals and principles of absorption-/receptor-mediated processes of transcytosis across brain capillary endothelial cells and validate candidates *in vitro*. At least one *in vitro* BBB-model and an *in silico* model reproducing/predicting disease features and BBB permeability *in vivo* are expected.

EFPIA contribution: BBB models, microfluidics, organ on a chip, spheroid technologies.
Applicant consortium contribution: benchmark tools for transport analysis (IgG's, TfR Ab, InsR Ab, small molecules with available *in vivo* neuro PK data); *in silico* modelling; complex 3D cell systems.

Work-Package 4: Characterisation of neurotropic virus-based BBB and brain penetration mechanisms

A number of neurotropic viruses are capable of entering the CNS to infect neurons and/or glial cells, such as rabies virus, JC (John Cunningham) virus, West Nile virus, adeno-associated virus (AAV) variants. However, the mechanisms by which those viruses either penetrate the BBB or retrograde transport from peripheral nerve to CNS are not fully characterised. Understanding the mechanisms may help in the development of drug delivery technologies selective or specific to CNS.

Different approaches may be employed to characterise the mechanisms and/or to identify the targets/proteins/peptides for brain penetration:

- genetic and proteomics analyses of the viral genes, proteins and protein fragments for their interactions with human cells and proteins;
- cellular, molecular and biochemical characterisation of viral interactions with cellular proteins and/or receptors and virus-mediated penetration of BBB or peripheral nerve/neuronal cells;

- preparation and testing of viral particles (empty viral vesicles) for interactions and penetration across the BBB *in vitro* or *in vivo* animal models;
- viral proteins or protein fragments if identified for BBB penetration may be employed to functionalize liposomes and/or nanoparticles for crossing the BBB *in vitro* and/or *in vivo* animal models.

Deliverables: viral proteins and protein fragments and/or viral mechanisms and human proteins/receptors which play roles in virus-mediated BBB and CNS penetration.

EFPIA contribution: human cells, omics/genetic analyses.

Applicant consortium contribution: genetic analyses, omics, virology, *in vitro* and *in vivo* models.

Work-Package 5: Follow-up on identification and characterisation of new potential targets from WP1/WP2/WP4 for brain delivery.

These targets could be investigated as new mechanisms of brain delivery. Building and providing tools and models for validation of the new mechanisms would be full part of this package (Ab's, ligands, cell lines). Testing tools against these novel targets *in vivo* will be an important aspect of the validation strategy as well. This could be done in disease models as well as in healthy wild-type model systems.

Deliverables: tools for validation and characterisation of the new mechanisms and targets (Ab's, ligands, cell lines). *In vivo* set ups for validation (including e.g. imaging). Validated new brain-delivery targets (by demonstration of increased *in vivo* brain exposure of Ab or ligand of the target). Validated new neurovascular target with potential for brain delivery in a neurodegenerative disease in disease models or validated such virus-based targets.

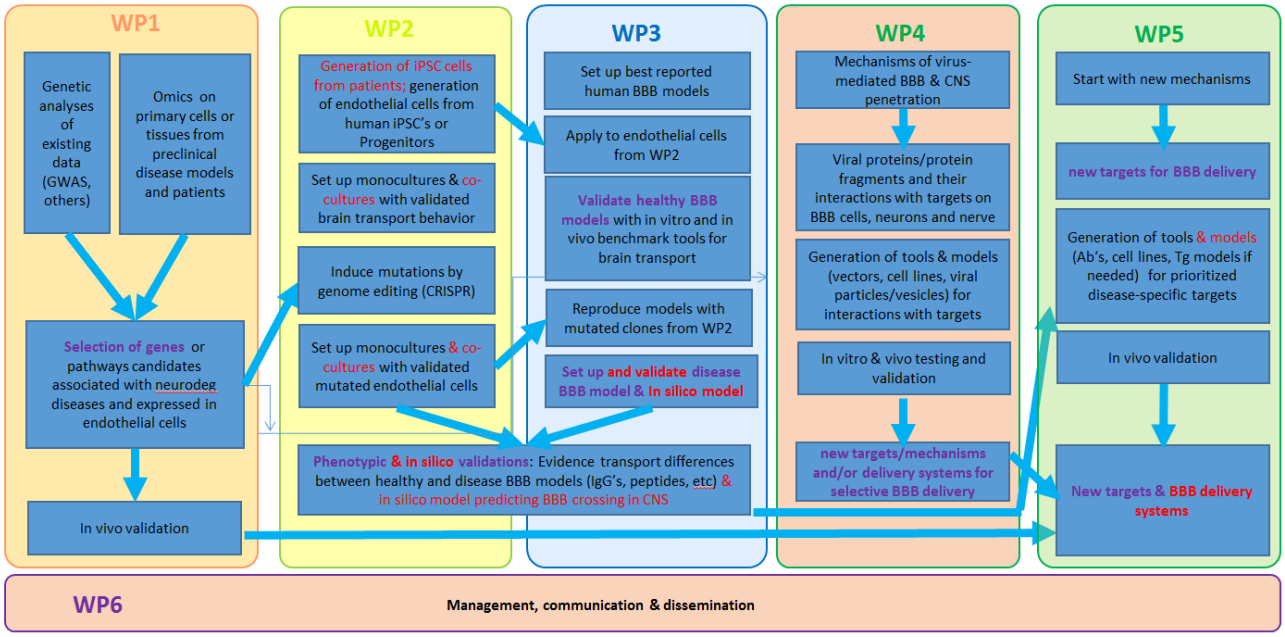
EFPIA contribution: preclinical disease models.
Applicant consortium contribution: tools for validation of the new mechanisms (Ab's, ligands, cell lines); *in vivo* PK; disease models.

The new targets identified in WP1 WP2 and WP4 should be fully characterised.

Work-Package 6: Management, communication & dissemination

This work-package should be designed to be fit for purpose to govern and implement the project as a successful public-private partnership and cover all necessary activities for its governance, management, communication and dissemination. It should also include activities to ensure proper data and knowledge management of the results following the H2020 rules and guidelines.

Flow Chart of Proposed Project



Topic 7 : European Screening Centre: unique library for attractive biology (ESCulab)

Topic details

Topic code	IMI2-2017-12-07
Action type	Research and Innovation Actions (RIA)
Submission & evaluation process	2 Stages

Specific challenges to be addressed

The translation of novel biological concepts into drug discovery projects critically requires chemical matter that has the potential to become a valuable tool in the treatment of a disease[133] The leveraging of basic biological research of SMEs, academia and their spin-offs into drug discovery and clinical applications still suffers from a scarcity of suitable chemical starting points that can be optimised into clinical candidate molecules allowing safe evaluation in patients. One of the key barriers is access to high-quality compound libraries and high throughput screening facilities.

Since January 2013, the European Lead Factory (ELF) project (http://www.europeanleadfactory.eu) [134] [135] a public-private consortium, has offered a unique high quality compound library and state-of-the-art industrial ultra-high throughput screening (uHTS) capabilities to targets submitted by the public (public targets). By having their targets screened on the compound library at this top tier screening facility, public target owners[136], including biotechs/SMEs, obtain a qualified hit list (QHL) that can be used either as probe compounds to pre-clinically validate a disease hypothesis or as starting point for lead finding and optimisation. Participating pharmaceutical companies benefit from the mutual sharing of their respective libraries and early partnering opportunities with public target owners.

The ELF project is scheduled to finish at the end of 2017, but the necessity for public target owners to access high-quality compound libraries and high throughput screening facilities remains.

Need and opportunity for public-private collaborative research

Universities, research organisations and SMEs have a diverse range of potential drug targets but cannot easily access suitable compound libraries and screening facilities. Pharmaceutical companies need access to high quality targets in order to bring innovative therapies to patients. Combining the large high-quality compound libraries held by the pharmaceutical industry with the innovative targets held by academic organisations in a public-private partnership offers an ideal platform to transform biological discoveries into medicines.

Confirmed HTS hits and leads are the chemical starting points for significant further investment to produce clinical candidates, and, eventually, new medicines. As such, a neutral, trusted honest broker is needed to facilitate sharing of confidential assay and compound data. In addition, all parties bringing targets [background] to the project (target owners) must be confident that they retain their rights to that background and are also able, where possible, to further exploit the resulting developments of their contribution.

Facilitating such a platform through a neutral, SME-led compound management and uHTS screening facility will allow all partners to participate in confidence that their targets will be screened in an independent way with

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[133] C.H. Arrowsmith et al. “The promise and peril of chemical probes” Nature Chem. Biol. 2015, 11, 536-541.
[134] H. Laverty, K.M. Orrling, F. Giordanetto, M. Poinot, E. Ottow, T.W. Rijnders, D. Tzalis, S. Jaroch, “The European lead factory—an experiment in collaborative drug discovery” J. Medicines Development Sciences 2015, 1, 20-33.
[135] J. Besnard, P.S. Jones, A.L. Hopkins, A.D. Pannifer, “The Joint European Compound Library: boosting precompetitive research”, Drug Disc. Today 2015, 181-186.
[136] The term ‘public target owners’ used throughout this text refers to academic groups, biotechs, SMEs, charity organizations and patient foundations.

maximal protection of their intellectual property. ESCulab will also provide the opportunity for academics / SMEs to collaborate with EFPIA partners and see their projects moving ahead along the value chain, whereas the pharmaceutical companies have a chance to tap into innovative academic biology. ESCulab will also significantly lower the hurdles for charity organisations or patient foundations that want to initiate drug discovery in their specific field of interest.

Scope

1. **Screening library**
   The core of the ESCulab library will ideally consist of 350 000 compounds from the pharmaceutical companies, and 200 000 compounds provided by the short proposal applicant consortium. Additional compounds may be added if further pharmaceutical companies join. The 200 000 compounds contributed by the applicant consortium must be novel, drug-like, not commercially available, and show a high fraction of sp3 hybridised carbon atoms (sp^3 count > 0.48, MW ~430, clogP ~2.3) without structural overlap with four reference libraries: The Maybridge Screening Collection, Molecular Libraries and Small Molecule Repository (MLSMR), ChEMBL and eMolecules[137] [138] [139].

2. **Compound logistics and uHTS screening facilities**
   Appropriate industry-like infrastructure, including laboratory automation / robotics to support both compound logistics and HTS will be provided, as well as: firewalled IT solutions to support the compound management of the compound library; HTS data management from quality control to chemo-informatic analysis of HTS results; the evaluation and confirmation of hits through medicinal chemistry follow-up activities.

3. **Assay development**
   In order to access a broad range of innovative biology, ESCulab will support the conversion of public target assays into an automation-friendly format, both in target-focused and phenotypic approaches.

4. **Screening**
   ESCulab is expected to run 50 public programmes. The project is also expected to develop a strategy to enable the screening of externally-funded screens on top of the IMI-funded activities. Each industry partner will schedule 20 programmes or 10 programmes, the IMI2 Associated Partner 5 programmes (135 screens in total, including phenotypic screens). The inclusion of phenotypic screening will allow the development of cellular models of increasingly more translational value using, for instance, patient derived material or human induced pluripotent stem (iPS) cell-derived phenotypes.

5. **Hit Confirmation**
   The outcome of the screening campaign should be a qualified hit list (QHLs) with max. 50 compounds.

6. **Long-term sustainability**
   In addition to the IMI2 JU-funded screens, ESCulab should offer screening on targets proposed by charity organisations, patient foundations and other organisations against external funding. Thus, it should establish itself as the centre for translating basic biology into chemical matter. Mechanisms and terms and conditions to secure maintenance and continued access to the compound library after termination of ESCulab will be negotiated with the partners providing compounds.

Expected key deliverables

1. **Screening Centre**
   The screening centre will host the compound library and manage the logistic processes around the library to support compound logistic processes for up to 37 HTS projects per year. The screening centre will also support assay development and perform HTS campaigns & follow-up tests for academic groups, biotechs, SMEs, charity organisations and patient foundations.

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[137] On 3D structures see: F. Lovering, J. Bikker, C. Humblet, “Escape from Flatland: Increasing Saturation as an Approach to Improving Clinical Success”, J. Med. Chem. 2009, 52, 6752–6756; F. Lovering, “Escape from Flatland 2: complexity and promiscuity”, Med. Chem. Commun. 2013,4, 515-519. For a more recent review see: O. Mendez-Lucio, J.L. Medina-Franco, “The many roles of molecular complexity in drug discovery”, Drug Disc. Today 2017, 120-126.
[138] A. Karawajczyk, F. Giordanetto, J. Benningshof, D. Hamza, T. Kalliokoski, K. Pouwer, R. Morgentin, A.Nelson, G. Müller, A. Piechot, D. Tzalis, “Expansion of chemical space for collaborative lead generation and drug discovery: the European Lead Factory Perspective”, Drug Disc Today 2015, 1310-1316.
[139] S. Dandapani, L. A. Marcaurelle, “Grand challenge commentary: Accessing new chemical space for 'undruggable' targets”, Nature Chem. Biol. 2010, 6, 861–863.

2. **Hit Confirmation**
   Responsible for providing a list of confirmed hits constituting the QHL which affords medicinal chemistry expertise.

3. **Sustainability plan**

   A business model based on fee-for-service and milestone-based income to ensure self-sustainability at the end of the ESCulab period; the funding of screens by charity organisations or patient foundations already during the ESCulab term serves to explore the business model.
   Establishing the maintenance of the compound library beyond the lifetime of the ESCulab project.

Expected impact

The project is intended to lower the hurdles for academic groups and SMEs to translate early innovative biology into chemical series that have the potential to be optimised into drug candidates. The delivery of up to 50 public and 135 EFPIA/IMI2 AP QHLs should create value from the libraries and cut timelines to arrive at clinical proof of concept in diseases with unmet medical need, such as cancer, immunological, respiratory, neurological and neurodegenerative diseases[140], anti-infectives, and neglected (tropical) diseases.

By including phenotypic screening that mimics cellular events relevant in disease, hit series that show clear structure-activity relationships might trigger target deconvolution activities that ultimately might lead to the discovery of novel pathways / drug targets.

Including SMEs in the applicant consortium should contribute to strengthening the competitiveness and industrial leadership of Europe.

To ensure the maximum impact of the project and stimulate the significant future investment needed to develop the project results into new medicines, it is necessary for the target owners to secure ownership of the results of their screens. Therefore, in the short proposal, the applicants must briefly demonstrate that they can provide target owners with this security by, for example, developing a strategy for the transfer of ownership upon generation of the screening results to the target owners. This strategy should be further determined between the parties at the full proposal stage and the terms be agreed between the beneficiaries as part of the consortium agreement.

At the end of the IMI funding term, there must be a self-sustainable, well recognised screening centre with access to a high-quality library which adopts a business model relying on externally funded screens.

ESCulab should be the operational partner of choice for scientists to bring modulation of their targets with small molecules from theory into practice.

Potential synergies with existing consortia

Applicants should take into consideration, while preparing their short proposal, relevant national, European (both research projects as well as research infrastructure initiatives), and non-European initiatives. Synergies and complementarities should be considered in order to incorporate past achievements, available data and lessons learnt where possible, thus avoiding unnecessary overlap and duplication of efforts and funding.

Applicants should consider any relevant projects from IMI, FP7, H2020, as well as other relevant European research infrastructures such as EU-OPENSCREEN (www.eu-openscreen.eu) and other initiatives outside the EU. With respect to IMI projects:

- European Lead Factory (www.europeanleadfactory.eu/)

[140] Council Regulation (EU) No 557/2014, art. 2 (ii) and (iii)). http://eur-lex.europa.eu/legal-content/EN/TXT/?uri=CELEX%3A32014R0557

- The ESCulab consortium should liaise with the ELF so that the libraries and target programmes not fully exploited within ELF could be carried through to ESCulab. Also, they should explore whether the ELF database could be used as a resource to support ESCulab hit selection activities.

Projects potentially allowing access to novel screening assays

- **BTCure (www.btcure.eu/), UltraDD (www.ultra-dd.org/), Autism Spectrum Disease (IMI2 Call 10) for potential targets;**
- **ND4BB (New Drugs for Bad Bugs, www.nd4bb.eu/) to discover and develop new, effective antibacterial strategies for the treatment of infections caused by antibiotic-resistant pathogens;**
- **NEWMEDS (www.newmeds-europe.com/) to identify biomarkers to allow more targeted treatments for schizophrenia and depression;**
- **EUROPAIN (www.imieuropain.org/), to better understand chronic pain mechanisms to aid the development of novel analgesics;**
- **IMIDIA (www.imidia.org/) to generate novel tools and fundamental knowledge on β-cell organisation to accelerate the path to improved diabetes management;**
- **PREDECT (www.predect.eu/) to develop new models for novel treatment for cancers of the breast, prostate, and lung;**
- **PHAGO (www.phago.eu/) to discover novel drug targets along TREM2/CD33 pathway in Alzheimer's disease.**

Industry consortium

The industry consortium is composed of the following EFPIA companies

- **Bayer (lead)**
- **AstraZeneca**
- **Grünenthal**
- **Janssen**
- **Merck**
- **Sanofi**
- **Servier**
- **UCB**

In addition, the industry consortium includes the following IMI2 JU Associated Partner:

- **Malaria Medicine Ventures**

The companies in the industry consortium will bring at least 350 000 screening compounds at the beginning of the project and run 130 screens in their own facilities. The IMI2 JU associated partner will run 5 screens at the ESCulab facility.

After the establishment of an agreement on appropriate access rights terms, and until the submitted compounds have been consumed, EFPIA companies will allow their compound set to be offered to charity organisations and patient foundations for externally funded screening, on terms and conditions to be decided.

Indicative duration of the action

The indicative duration of the action is 60 months.

Indicative budget

The indicative in-kind contribution is EUR 18 250 000. This contribution comprises an indicative EFPIA in-kind contribution of EUR 17 500 000 and an indicative IMI2 Associated Partners in-kind contribution of EUR 750 000.

The financial contribution from IMI2 JU is a maximum of EUR 18 250 000.

Applicant consortium

The applicant consortium will be selected on the basis of the submitted short proposals.

The applicant consortium is expected to address all the research objectives and make key contributions to the defined deliverables in synergy with the industry consortium which will join the selected applicant consortium in preparation of the full proposal for stage 2. This may require mobilising, as appropriate, the following expertise:

- **Strong European-wide network for public target recruitment with outreach to ongoing and future IMI projects and other European and national initiatives.**
- **Professional, industry-like management of compound logistics process centred around a single entity for the collection, storage, distribution and management of the ESCulab compound library.**
- **The consortium must include a specialised party ('honest data broker') who can manage and broker (blinded and un-blinded) confidential information on compounds and screening results data according to the honest data broker concept, i.e. one single, centralised unit with dedicated staff bound by confidentiality and non-use obligations.**
- **Strong experience in assay development, miniaturisation, validation for HTS both employing platform techniques and introducing novel experimental approaches. Capabilities to develop HTS/HCS ready target-focused and phenotypic cellular assays.**
- **Extensive experience in the execution of HTS to industry standards, providing solutions also for complex experimental protocols, e.g. with multiple liquid handling and signal detection steps, kinetic readouts, etc. Necessary expertise in molecular and cellular pharmacology and medicinal chemistry to drive a rigorous hit characterisation process.**
- **Industrial-like experience and proven track record for successful hit confirmation including expertise in medicinal chemistry and pharmacology.**
- **Extensive experience in applying IT solutions to the management of compound collections, HTS data management from quality control to chemo-informatic analysis of HTS results.**
- **Project management capabilities supporting overall governance and steering and experience developing business plans to ensure the long-term sustainability of the project.**

It may also require mobilising, as appropriate, the following resources:

- **A library of approximately 200 000 screening compounds. Applicants should demonstrate that their compounds are suitable for HTS, i.e. novel, drug-like, not commercially available, with high sp^3 count (sp^3 count > 0.48, MW ~430, clogP ~2.3), clearly differentiated from vendor libraries.**
- **A centralised facility for carrying out the HTS screening operations on the targets originating from public target owners. Preferably, the HTS screening operations are performed in a country with a research exemption limiting IP complexity.**
- **Software to support the blinding and un-blinding of information**
- **A firewalled IT infrastructure to handle data related to the compound library.**

In their short proposal, applicants should provide an initial plan for the sustainability of the platform beyond the IMI2 JU funding term. This outline plan should also benchmark the proposed ESCulab project against existing screening infrastructures.

Suggested architecture of the full proposal

The applicant consortium should submit a short proposal which includes their suggestions for creating a full proposal architecture, taking into consideration the industry participation including their contributions and expertise.

The final architecture of the full proposal will be defined by the participants in compliance with the IMI2 rules and with a view to the achievement of the project objectives.

In the spirit of the partnership, and to reflect how IMI 2 JU call topics are built on identified scientific priorities agreed together with EFPIA beneficiaries/large industrial beneficiaries, these beneficiaries intend to significantly contribute to the programme leadership and project and financial management. The final architecture of the full proposal will be defined by the participants in compliance with the IMI 2 JU rules and with a view to the achievement of the project objectives. The allocation of a leading role within the consortium will be discussed in the course of the drafting of the full proposal to be submitted at stage 2. To facilitate the formation of the final consortium, until the roles are formally appointed through the consortium agreement, the proposed project leader from among EFPIA beneficiaries/large industrial beneficiaries shall facilitate an efficient negotiation of project content and required agreements. All beneficiaries are encouraged to discuss the project architecture and governance and the weighting of responsibilities and priorities therein.

The architecture outlined below for the full proposal is a suggestion. Different innovative project designs are welcome, if properly justified.

A plan for aspects related to sustainability, facilitating continuation beyond the duration of the project should also be proposed.

Industry contribution

All EFPIA participants contribute screening compounds as indicated above and will run screens of the compound library in the course of the ESCulab project. Assay development and screening efforts are EFPIA participants' in-kind contributions. With these in-kind contributions, EFPIA participants enhance the database for developing public QHLs and increase the value of hits from the public compound collection. For the sustainability of the platform beyond the ESCulab lifetime, the EFPIA partners will negotiate terms to maintain the compound library after the project ends.

Work package 1 – Programme recruitment

With a strong emphasis on innovative biology, recruitment of targets and biology amenable to phenotypic screens need to be gathered across Europe intensively with the entrance barriers considerably lowered for ESCulab.

Over a 4 year period of target sourcing, the goal should be to recruit more than 100 proposals.

Programmes from other IMI projects will be proactively sought and will include:

- **proposals that still require assay development activities;**
- **phenotypic, target-agnostic programmes;**
- **targets from foundations and charities worldwide to reserve screening slots in exchange for a monetary contribution.**

Targets can be screened several times, but qualified hits will be removed from the compound library.

Expected applicant consortium contribution

Professional target / programme recruitment acquiring 100+ public proposals from academics / SMEs over four years for selection. Therefore, a strong European-wide network for public target recruitment with focused outreach to ongoing and future IMI projects is essential.

Work package 2 – Review and selection

The review and selection of target proposals offers an opportunity to connect target owners to pharma partners early on. Therefore, the review body must be staffed with external experts and EFPIA delegates. Targets proposed by charities and foundations who fund the screen are exempt from the review process.

Work package 3 – Compound logistics

Hosting the physical compound collection, plating and distributing screening decks and samples for retests is the remit of this work package. Costs incurred should be in alignment with benchmarking references.

Once fully operational, the centre will need to accommodate resources sufficient to support compound logistic processes for up to 37 HTS projects per year (10 from public projects, 27 from EFPIA projects) providing plated copies of the compound library for public and pharma screening programmes.

- **The pharma companies will receive a copy of the library and perform the screening at their disposal in a blinded fashion.**

Expected applicant consortium contribution:

- **Professional, industry-like management of the compound logistics process centred around a single entity for the collection, storage, distribution and management of the ESCulab compound library.**

Work package 4 – Assay development

Allowing for target proposals which are not yet assay-ready and phenotypic programmes requires an effort in assay development and screening. The adaption of academic test systems to suitable HTS formats needs professional expertise and needs to be properly staffed. For pharma screens the assay development will be done at the pharma partners' facilities, as follows:

- **Development and/or adaptation of target or pathway-specific bioassays for HTS;**
- **Development and/or adaptation of phenotypic assays.**

Expected applicant consortium contribution:

A proven track-record in assay development. A track-record in automated image capturing and multi-parametric automated image analysis will be crucial to master phenotypic assay development. The applicant consortium is expected to progress the 5 projects of the associated EFPIA partner from assay development through QHL.

Work package 5a – Target-based ultra high throughput screening

Industry contribution

EFPIA screens will be run at pharma screening sites or their selected subcontractors.

Expected applicant consortium contribution

Industry-like uHTS infrastructure and expertise (e.g. proven experience in 1536 MTP format HTS)

Work package 5b – Target-agnostic cellular screening

Industry contribution

EFPIA phenotypic screens will be run at pharma screening sites or their selected subcontractors.

Expected applicant consortium contribution:

Industry-like equipment and know-how (endpoints, counter-screens) to run phenotypic assays in a high throughput format (1536 MTP format, at least 384 low volume MTP format).

Work package 6 – Hit characterisation and confirmation

- **Re-synthesis of hits and confirmation of activities to assemble a qualified hit list (QHL).**
- **Support the assembly of a programme dossier for an option notice for public target owners.**

Expected applicant consortium contribution:

Industrial-like experience and proven track record for successful hit confirmation including respective expertise in medicinal chemistry and pharmacology.

Work package 7 - Information technology

The honest data broker will be the data repository to handle IP sensitive information in a secure manner, and an annotated data source for hit-to-lead activities and library analyses.

Work package 8 - Project management

Overarching project management independent from the day to day consortium activities should steer the administrative aspects referring e.g. to budget and legal aspects including continuous legal support.

Conditions for this Call for proposals

All proposals must conform to the conditions set out in the H2020 Rules for Participation (https://ec.europa.eu/research/participants/portal/doc/call/h2020/common/1595113-h2020-rules-participation_oj_en.pdf), the Commission Delegated Regulation with regard to IMI2 JU (http://eur-lex.europa.eu/legal-content/EN/TXT/PDF/?uri=CELEX:32014R0622&from=EN) and the relevant general conditions of the IMI2 JU AWP2017.

Applicants intending to submit a Short proposal in response to the this first 2017 Call should read this topics text, the IMI2 JU Manual for submission, evaluation and grant award and other relevant documents (e.g. IMI2 JU model Grant Agreement).

Call Identifier	**H2020-JTI-IMI2-2017-12-two-stage**
Type of actions	**Research and Innovation Actions (RIA)**
Publication Date	**19 July 2017**
Stage 1 Submission start date	**19 July 2017**
Stage 1 Submission deadline	**24 October 2017 (17:00:00 Brussels time)**
Stage 2 Submission deadline	**16 May 2018 (17:00:00 Brussels time)**
Indicative Budget From EFPIA companies and IMI2 JU Associated Partners	EUR 62 362 000
From the IMI2 JU	EUR 64 077 000

Call Topics

IMI2-2017-12-01	The indicative contribution from EFPIA companies will be EUR 2 830 000 The indicative IMI2 JU Associated Partners contribution will be 725 000 The financial contribution from IMI2 JU will be a maximum of EUR 5 000 000	Research and Innovation Actions (RIA) Two-stage submission and evaluation process. Only the applicant consortium whose proposal is ranked first at the first stage is invited for the second stage.
IMI2-2017-12-02	The indicative contribution from EFPIA companies will be EUR 3 730 000 The financial contribution from IMI2 JU will be a maximum of EUR 4 000 000	Research and Innovation Actions (RIA) Two-stage submission and evaluation process. Only the applicant consortium whose proposal is ranked first at the first stage is invited for the second stage.

IMI2-2017-12-03	The indicative EFPIA in-kind contribution will be EUR 8 200 000 The financial contribution from IMI2 JU will be a maximum of EUR 8 200 000	Research and Innovation Actions (RIA) Two-stage submission and evaluation process. Only the applicant consortium whose proposal is ranked first at the first stage is invited for the second stage.
IMI2-2017-12-04	The indicative EFPIA in-kind contribution will be EUR 14 127 000 The financial contribution from IMI2 JU will be a maximum of EUR 14 127 000	Research and Innovation Actions (RIA) Two-stage submission and evaluation process. Only the applicant consortium whose proposal is ranked first at the first stage is invited for the second stage.
IMI2-2017-12-05	The indicative EFPIA in-kind contribution will be EUR 5 500 000 The financial contribution from IMI2 JU will be a maximum of EUR 5 500 000	Research and Innovation Actions (RIA) Two-stage submission and evaluation process. Only the applicant consortium whose proposal is ranked first at the first stage is invited for the second stage.
IMI2-2017-12-06	The indicative EFPIA in-kind contribution will be EUR 9 000 000 The financial contribution from IMI2 JU will be a maximum of EUR 9 000 000	Research and Innovation Actions (RIA) Two-stage submission and evaluation process. Only the applicant consortium whose proposal is ranked first at the first stage is invited for the second stage.
IMI2-2017-12-07	The indicative EFPIA in-kind contribution will be EUR 17 500 000 The indicative IMI2 JU Associated Partners contribution will be 750 000 The financial contribution from IMI2 JU will be a maximum of EUR 18 250 000	Research and Innovation Actions (RIA) Two-stage submission and evaluation process. Only the applicant consortium whose proposal is ranked first at the first stage is invited for the second stage.

Annex III – IMI2 Call 13 topics text

Topic 1 : Assessment of the uniqueness of diabetic cardiomyopathy relative to other forms of heart failure using unbiased pheno-mapping approaches

Topic details

Topic code	IMI2-2017-13-01
Action type	Research and Innovation Action (RIA)
Submission and evaluation process	2 stages

Specific challenges to be addressed

Diabetes contributes to the development of heart failure (HF) indirectly by promoting the progression of coronary artery disease and directly through the development of cardiomyopathy. Thus, diabetic patients have a 2.5-fold greater risk for HF as compared to those without diabetes. Epidemiological studies have reported a 4-fold higher prevalence of diabetes mellitus in HF patients (20%) compared to age-matched populations without HF (5%) which rises up to 40% in hospitalised HF patients. Over the last decades it became clear that there is a relationship between diabetes and HF, although not all patients with diabetes develop cardiomyopathy or evolve toward HF.

Traditionally, heart failure is divided into two types based on ejection fraction:

1) heart failure with reduced ejection fraction (HFrEF) or systolic heart failure caused by left ventricular systolic dysfunction, which manifests when the ejection fraction is less than 40%;
2) heart failure with preserved ejection fraction (HFpEF) also known as diastolic heart failure or heart failure with unaltered ventricular contractility and normal ejection fraction. In this type of HF, the ventricle typically fails to adequately relax and, therefore, does not fill completely with blood in the relaxation phase.

Diabetic cardiomyopathy is considered as a distinct form of heart failure that occurs in diabetic patients in absence of coronary artery disease, long standing hypertension, valvular or familial heart disease. It relies on a diagnosis of exclusion based on the presence of symptomatic cardiomyopathy, a long history of diabetes with many exclusion criteria as referred above. The main feature of diabetic cardiomyopathy is left ventricular diastolic dysfunction with impaired relaxation that impedes the efficiency of passive filling during diastole, preserved left ventricular contractility, increased filling pressure with or without cardiac hypertrophy. It is more frequent in obese females with poor glycaemic control. Diabetic cardiomyopathy shares many commonalities with HFpEF and hypertrophic cardiomyopathy (HCM). Although its pathogenesis is yet to be clearly defined, diabetic cardiomyopathy is increasingly recognised as a clinically relevant entity.

Therefore, the overall objective of this topic is to determine whether diabetic cardiomyopathy is unique and distinct from the other forms of heart failure such as HFpEF or HCM by performing unbiased statistical clustering analysis from a dense phenotyping of these patient populations. Similar methodology has recently been used to identify phenotypically distinct and more homogeneous HFpEF segments. This approach would facilitate a molecular taxonomy of diabetic cardiomyopathy which is widely accepted in the scientific community and could be applied in the clinics for differentiation from other forms of heart muscle disorders already at disease onset, thereby enabling an optimised and individualised treatment of patients. Furthermore, a better comprehension of the underlying mechanisms and clinical manifestations of diabetic cardiomyopathy will also allow the development of more translatable and predictable preclinical models to support target and drug discovery.

Need and opportunity for public-private collaborative research

The purpose of this topic is to bring a sufficient level of funding and multi-stakeholder commitment to comprehensively and definitively address the compilation of a set of jointly agreed phenotype criteria enabling the classification and new definition of diabetic cardiomyopathy. The leading edge of this IMI2 JU topic is to make use of extant heart failure cohorts, with or without diabetes, and then prospectively access clinical and imaging data, as well as samples that meet carefully considered criteria. This unprecedented effort will be transformative for the field and is the type of effort needed to gain consensus acceptance by those carrying out basic research into diabetes and heart failure and by clinical investigators.

The magnitude of the issue is such that it can only be addressed by a major public-private-partnership involving a variety of stakeholders, including those primarily involved in understanding the clinical parameters and molecular mechanisms of disease who have a complementary experience and expertise, as well as regulators. This is a topic which cannot be successfully administered by an individual research group or a company but will require a broad consortium to be successful.

- Pharmaceutical companies contribute expertise in diabetes and cardiovascular drug discovery and development, including an understanding of regulatory, economic, and logistical challenges facing drug development for disease prevention and modification. They bring unique expertise in biomarker discovery, data analysis, assay development, and prospective clinical trial design. Furthermore, companies may provide biological samples from control and standard therapy arms of clinical trials.
- Small- and medium-sized enterprises (SMEs) are expected to contribute specific methodologies or technical platforms to foster efficiency and innovation within the project.
- Academic investigators contribute expertise in a range of methods to discover and validate molecular phenotypic biomarkers from human tissues and bio-fluids (e.g. by multi-omics and genetics/epigenetics analyses), to assess clinical and imaging phenotypes, and to analyse the relationship of molecular phenotypic biomarkers with clinical/imaging evaluation of disease development and progression.
- Hospitals, clinical research centres, and practicing physicians with access to patients with diabetes and heart failure will allow prospective assessment of these patients and contribute to the understanding of epidemiology, pathophysiology, clinical, imaging and biochemical phenotypes and provide bio-banked samples that may be used in combination with novel molecular biomarkers to discriminate patients with diabetic cardiomyopathy from other heart failure forms.
- The taxonomy and new classification will need to find acceptance by global regulators and other public bodies, including payers. It will be crucial for the success of the project to interact and integrate these stakeholders as early as possible. This can be achieved by integrating them as participants into the project or, if appropriate, within advisory bodies.

Scope

The overall goal of the proposed topic is to assess the uniqueness of diabetic cardiomyopathy and to unveil the underlying mechanisms of cardiomyopathy in diabetic patients and the impact on cardio-vascular mortality in this population, which may finally allow the clustering of patients into an independent cohort. In consequence, this improved understanding of the clinical manifestations and diagnosis of diabetic cardiomyopathy as well as the linkage between the onset and disease progression with a specific signature will enable patient stratification at an early stage of the disease by clustering of patients into an independent cohort.
The scope of the collaborative research for diabetic cardiomyopathy can be envisioned to ideally encompass objectives, outlined below:

- definition of the inclusion criteria for patients with preserved ejection fraction (EF > 50%) and diastolic dysfunction of four different origins including:
    - non-ischemic diabetic cardiomyopathy,
    - non-diabetic HFpEF,
    - idiopathic HCM,
    - type 2 diabetes mellitus (T2DM) with no HF or cardiomyopathy;
- enrollment of patients according to pre-defined inclusion criteria into the four different patient groups;

A cohort of patients shall be enrolled from registries and prospective clinical trials running at academic centers or EFPIA partners according to the pre-defined and jointly agreed inclusion criteria. Deep pheno-mappingof patients will be done prospectively at baseline. Additionally, blood, plasma and urine samples will be taken for multiple omics and genetics/epigenetics analysis.
It is estimated that approximately 1000 patients per patient group need to be investigated at baseline in order to achieve statistical significance of cluster discrimination. Since the initiation of the sample analyses is dependent on a phenotype overlap of less than 10 % across the different clusters (see below), study recruitment and deep phenotyping shall be completed within three years.

- application of non-invasive imaging technologies (transthoracic echocardiography, speckle tracking echo-cardiography (STE), doppler echocardiography and magnetic resonance imaging (MRI) to detect subclinical myocardial dysfunctions;
- assessment of cardiac, endothelial and metabolic functions in all patient groups;
- unsupervised machine-learning applied to the dense phenotypic data with the goal to identify more homogeneous and differentiated clusters;
- analysis of patients' lipidomic, metabolomic, proteomic and transcriptomic profiles in blood, plasma or urine samples, if pheno-mapping of the different clusters shows discriminative phenotypes;

A phenotype overlap of less than 10 % is being considered as criterion for the initiation of multi-omics and genetics/epigenetics analyses of baseline samples. A go/no go decision will be taken during the course of the project based on the ability to significantly differentiate and cluster newly defined diabetic cardiomyopathy from other patients in the cohort. The expectation of the multi-omics/genetic analysis is to discover a panel of novel biomarkers that (i) predicts cardiac function decline in T2DM patients, (ii) allows for early preventative life style changes, (iii) facilitates tailored therapies to slow disease progression and (iv) enables the discovery of new pathophysiological pathways responsible for diabetic cardiomyopathy or heart failure and complications. Traditional biomarkers associated with cardiomyopathy and heart failure will be monitored to determine whether the novel biomarkers offer greater predictive value for each newly defined cluster.

- system biology data analysis for disease modelling;
- compilation of existing pre-clinical models for diabetic cardiomyopathy which will serve as a "state-of-the-art" reference;
- translation of clinical results back into pre-clinical settings to improve the knowledge on translatable preclinical models for diabetic cardiomyopathy and develop relevant and reliable *in silico*, *in vitro* and *in vivo* models based on disease modelling.

The proposed action's duration allows in-depth systematic evaluation of collected clinical parameters for pheno-mapping and molecular analysis of biological samples from registries and prospective patient cohorts. Further, the obtained insights will be integrated both into novel to-be-established and existing pre-clinical models.

Expected key deliverables

The expected deliverables should be achieved during the five years duration of the funded project.

Through a network of clinical databases and laboratories, efforts to enable the classification of diabetic cardiomyopathy and validation of relevant biomarkers and imaging modalities, in addition to parallel efforts towards pathway/target identification for future therapeutics development shall be initiated. These will include the following aspects:

- definition of jointly agreed inclusion criteria/parameters that will be used for initial patient enrollment;
- successful patient enrollment into the four groups (1000 patients/group) to ensure successful deep phenotyping and prospective assessment of phenotyping markers including clinical, imaging and biological ones;
- applied unsupervised machine learning algorithms to deep phenotyping in order to identify patients with diabetic cardiomyopathy and distinguish them from other heart failure populations;
- identification of causal mechanisms and pathways responsible for diabetic cardiomyopathy resulting from the comparative evaluation of the four clusters;

- better understanding of the disease biology of diabetic cardiomyopathy based on disease modelling that will lead to the development of more translatable and predictive preclinical models;
- pavement of the way for implementing this new classification by communicating value proposition to target audiences (i.e. global regulators, patients, healthcare practitioners and payers).

Expected impact

In terms of research and development (R&D), clinical, regulatory, healthcare practice and patient management:

- proposals are expected to define and assess key phenotypes that characterise diabetic cardiomyopathy and could serve to establish patient diagnosis and ultimately prognosis;
- the stratification of patients into the diabetic cardiomyopathy cluster based on pheno-mapping, supported by biomarkers specific for this group will be transformative for the clinical management of these patients;
- furthermore, novel pre-clinical models with improved knowledge on the translatability to humans will profoundly enable drug development for the treatment of diabetic cardiomyopathy beyond blood glucose control.

Overall, a better comprehension of the mechanisms and clinical manifestations of diabetic cardiomyopathy will allow the development of more translatable and predictable preclinical models supporting target and drug discovery in academia and industry. The molecular taxonomy of diabetic cardiomyopathy to be developed will enable innovative and individualised treatment options for patients.

In terms of strengthening the competitiveness and industrial leadership in Europe the applicants could also include the relevant expertise from the small- and medium-sized enterprises (SMEs).Their involvement might offer a complementary perspective to industry and the academia, and help deliver the long-term impact of the project.

Potential synergies with existing consortia

Applicants should take into consideration, while preparing their short proposal, relevant national, European (both research projects as well as research infrastructure initiatives), and non-European initiatives. Synergies and complementarities should be considered in order to incorporate past achievements, available data and lessons learnt where possible, thus avoiding unnecessary overlap and duplication of efforts and funding.

Currently, there are no synergies with completed or ongoing IMI/IMI2 JU projects.

Consortia like **DIRECT** (http://www.direct-diabetes.org), **RHAPSODY** (https://imi-rhapsody.eu) and **BEAt-DKD** (http://www.imi.europa.eu/projects-results/project-factsheets/beat-dkd) are also investigating T2DM patients. However, their scientific goals are addressing different aspects of research. The focus of DIRECT and RHAPSODY is the identification of novel biomarker panels predictive for glycaemic deterioration / disease progression of pre-diabetes and early onset of T2DM, and treatment response that can be applied for patient stratification, whereas the BEAt-DKD consortium is assessing biomarkers for diabetic kidney disease.

Industry consortium

The industry consortium is composed of the following EFPIA companies:

- Sanofi (lead)
- Bayer
- Lilly

The industry consortium will contribute the following expertise and assets:

The industry consortium will bring expertise in methodologies for the merging, harmonisation and meta-analyses of existing clinical, imaging and biomarker data as well as systems biology and disease modelling. This will include expertise in biomarker evaluation, bioinformatics and statistical expertise and possibly technology for measuring specific biomarkers when appropriate. Additional contributions will include diabetes and heart failure clinical trial and regulatory expertise. Furthermore, it is envisaged that data, results and samples from control arms of ongoing clinical trials may be provided to the consortium.

EFPIA participants have also indicated interest in providing in-kind contributions that will entail efforts at 'back-translation' into preclinical models to help in validating appropriate animal model(s) and biomarkers of diabetes cardiomyopathy.

Indicative duration of the action

The indicative duration of the action is 60 months.

Indicative budget

The indicative EFPIA in-kind contribution is EUR 6 000 000.

Due to the global nature of the participating industry partners it is anticipated that some elements of the contributions will be non- EU/H2020 Associated Countries in-kind contributions.

The financial contribution from IMI2 JU is a maximum of EUR 6 700 000.

Applicant consortium

The applicant consortium will be selected on the basis of submitted short proposals. The applicant consortium is expected to address all the research objectives and make key contributions to the defined deliverables in synergy with the industry consortium which will join the selected applicant consortium in preparation of the full project proposal for stage 2.

To address the ambitious objectives of the topic adequately, the funded project is expected to establish a multidisciplinary network that will include scientists, physicians and imaging specialists, who are recognised experts in heart failure and diabetes and contribute expertise in developing and maintaining the clinical database that is relevant to an in-depth characterisation of the patients enrolled into the four cluster groups. Furthermore, expertise in clinical research recruitment including access to clinical research centres with registries and ongoing prospective trials shall be provided.

Such a network should be capable of mobilising following capabilities to make the following types of contributions:

- access to clinical cohorts of heart failure patients with or without diabetes from registries or prospective clinical trials to ensure the enrolment of 1000 patients per group within the first phase of the project;
- availability of key non-invasive imaging technologies to assess subclinical myocardial dysfunctions;
- development of a structured database that allows the joint analysis of complex datasets;
- strong experience in unsupervised machine learning;
- capability of systems biology analysis by vertical integration of phenotype, clinical, multi-omics and genetics/epigenetics datasets;
- in-depth expertise in pre-clinical models relevant to diabetic cardiomyopathy;
- experience in communication with global regulators, patients, practitioners and payers, who may be members of a to be established advisory board.

The participation of SMEs, in particular, with the following expertise would be highly appreciated:

- machine-learning
- data management
- image analysis
- imaging technologies
- metabolomics analysis
- lipidomics analysis
- project management in the context of IMI2 JU/H2020 projects.

Consequently, partners providing medical record-based information (e.g. data from registries) as project background must be mindful that they, as background contributor, should have sufficient title to said background to authorise its use within the project pursuant to the IMI2 JU IP and legal framework[141] Consideration should also be given to any additional information that may be introduced after the start of the project but is not listed as project background at the start date.

The applicants need also to take into consideration that the sharing of data and samples within the consortium should be allowed and be in conformity with the applicable data privacy laws and laws regarding ethical matters.

Suggested architecture of the full proposal

The applicant consortium should submit a short proposal which includes their suggestions for creating a full proposal architecture, taking into consideration the industry participation including their contributions and expertise.

The consortium is expected to have a strategy on the translation of the relevant project outputs into regulatory practices, regulatory, clinical and healthcare practice. A plan for interactions with regulatory agencies/health technology assessment bodies with relevant milestones and resources allocated should be proposed to ensure e.g. qualification advice on the proposed methods for novel methodologies for drug development.

In the spirit of the partnership, and to reflect how IMI2 JU call topics are built on identified scientific priorities agreed together with EFPIA beneficiaries/large industrial beneficiaries, these beneficiaries intend to significantly contribute to the programme and project leadership as well as project financial management.

The final architecture of the full proposal will be defined by the participants in compliance with the IMI2 JU rules and with a view to the achievement of the project objectives. The allocation of a leading role within the consortium will be discussed in the course of the drafting of the full proposal to be submitted at stage 2. To facilitate the formation of the final consortium, until the roles are formally appointed through the consortium agreement, the proposed project leader from among EFPIA beneficiaries/large industrial beneficiaries shall facilitate an efficient negotiation of project content and required agreements. All beneficiaries are encouraged to discuss the project architecture and governance and the weighting of responsibilities and priorities therein.

A plan for aspects related to sustainability, facilitating continuation beyond the duration of the project should also be proposed.

The architecture outlined below for the full proposal is a suggestion. Different innovative project designs are welcome, if properly justified.

Work package 1 – Consortium management, administration, integration and dissemination

Work package 2 – Clinical study

The goals of this work package will be as follows:

- definition of inclusion criteria for the different patient groups;
- enrollment of patients according to pre-defined inclusion criteria from registries and prospective clinical trials.

Work package 3 – Imaging technologies

The goal of this work package will be as follows:

- application of non-invasive imaging technologies to detect subclinical myocardial dysfunction in diabetic cardiomyopathy patients.

[141] Regulation No. 1290/2013 (11th December 2013) laying down the rules for participation and dissemination in Horizon 2020 (H2020 RfP); Council Delegation Regulation (EU) No. 622/2014 (establishing a derogation from Regulation (EU) 1290/2013 (Delegated Act); Council Regulation (EU) No. 557/2014 (establishing the Innovative Medicines Initiative 2 Joint Undertaking).

Work package 4 – Data management and machine learning

The goals of this work package will be as follows:

- data centralisation in a unique, scalable and secured database for data analysis;
- system biology approach for data analysis using data from multiple sample analysis (work package 5);
- unsupervised machine-learning for clustering on phenotypic differences beyond diabetes.

Work package 5 – Multiple sample analysis

The goals of this work package will be as follows:

- proteomics, lipidomics, metabolomics, transcriptomics and genetics/epigenetics analyses;
- analysis starts after go/no go decision depending on a phenotype overlap of less than 10% across the different clusters.

Work package 6 – Disease modelling

The goal of this work package will be as follows:

- systems biology analysis based on imaging and omics data generated in work packages 3 and 5.

Work package 7 – Preclinical models

The goals of this work package will be as follows:

- identification of existing pre-clinical models for diabetic cardiomyopathy;
- development of relevant and reliable *in silico*, *in vitro* and *in vivo* models based on disease modelling.

Topic 2 : Genome-Environment Interactions in Inflammatory Skin Disease

Topic details

Topic code	IMI2-2017-13-02
Action type	Research and Innovation Action (RIA)
Submission and evaluation process	2 stages

Specific challenges to be addressed

Inflammatory skin diseases affect a significant percentage of our global population. Atopic Dermatitis (AD) affects approximately 10% of children and 3% of adults worldwide. Psoriasis (Pso) affects approximately 2% of our population. These diseases remain poorly understood with limited understanding of their mechanism, endotypes, ontology and co-morbidities, affecting the quality of effective treatments. While there may be aspects of these diseases that overlap, others show little or no similarities e.g. their associated co-morbidities are generally quite distinct with Pso being linked with arthritis, psychiatric disorders, metabolic syndrome and cardiovascular sequelae while AD is associated with rhinitis, asthma, food allergy as well as cardiovascular complications. As a result, there is an immediate need for sophisticated, in-depth investigations of these diseases that address transformative topics. These studies include, but are not limited to, the impact of environmental factors (e.g. via the microbiome) interacting with genomic factors and studies that help elucidate molecular pathways of disease in a comprehensive, patient-driven manner. To this end, the challenge is seeking to define the key heterogeneous and homogeneous aspects of AD and Pso, both within each disease and across their shared biology. Such characterisation can include clinical hallmarks, patient epidemiology and reported outcomes, and assessment of molecular signatures. Expanding our current knowledge to understand unique endotypes of inflammatory skin diseases will help give rise to more precise, targeted treatments that can yield long lasting reductions in disease burden and improved patient quality of life, fulfilling unmet medical needs in patient care.

Need and opportunity for public-private collaborative research

The proposed topic addresses a complex issue related to human diseases. This can only be adequately addressed by a combination of collaboration and specialised expertise, which would be impossible in the setting of a single organisation or institution. Specific contributions to a collaborative effort would likely be:

- Pharmaceutical companies possess access to clinical trial samples related to Pso and AD, and the expertise in specialised technologies that can be applied;
- Academia has the clinical expertise and patient access (both retrospective and prospective) needed, as well as unique, state-of-the-art technologies;
- Patients and caregivers, as well as advocacy groups related to these diseases, provide important inputs into the real-world issues related to inflammatory skin diseases;
- Small- and Medium-sized Enterprises (SMEs), businesses with appropriate interests and Contract Research Organisations may contribute to centralised development of key output information and deliverables.

Scope

The action to be generated from this topic is expected to lead to a step change in our understanding of the molecular mechanism and ontology of the two main inflammatory skin diseases: AD and Pso. Elucidating the molecular pathways of these inflammatory skin conditions over time will give rise to novel and meaningful therapeutic targets for specific patient populations and help address the complex patterns of co-morbidities. In addition, this work will identify biomarkers that will enable robust, efficient and meaningful patient management.

These objectives should be achieved both via a retrospective assessment of Pso and AD patients that can aid in defining key endotypes of disease and the disease commonalities and uniqueness, as well as via access to ongoing prospective studies that will embrace novel approaches and hypotheses relating to defining these. It is expected that reliable access to robustly defined clinical information and specimens will be vital to the overall scope.

Expected key deliverables

1) Identify shared and distinct disease mechanisms of AD and Pso:
    - Establish a BioResource that includes patient samples (blood, skin tissue) reflective of baseline status as well as longitudinal samples of patients under standard of care;
    - Investigate patient-centred outcomes of AD and Pso (e.g. disease progression, quality of life evaluations, patient reported outcomes), particularly taking advantage of patient samples obtained from ongoing longitudinal studies;
    - Investigate the genetic and epigenetic profiles as AD, Pso and healthy controls of these patient samples;
    - Investigate the transcriptome of AD, Pso and healthy controls;
    - Investigate environmental factors (e.g. microbiome) of AD, Pso and healthy controls;
    - Investigate commonalities and differences in samples (e.g. skin biopsies, peripheral blood mononuclear cells PBMCs) from patients with varying levels of disease severity;
    - Apply cutting edge technical approaches to samples obtained from ongoing prospective collections/trials, including single cell profiling, high dimensional immune subset analysis and advanced bioinformatics analysis.
2) Establish a new disease ontology by defining distinct and overlapping inflammatory skin disease endotypes and co-morbidities:
    - Investigate characteristics/pathways associated with disease;
    - Investigate characteristics/pathways associated with disease progression;
    - Investigate how environment (microbiome) interacts with genomic features to drive disease;
    - Develop a molecular understanding of how these factors interact in disease;
    - Investigate the impact on co-morbidities (existing registries):
        - For Pso these would include: arthritis, cardiovascular sequelae (MI, Stroke), metabolic syndrome (insulin resistance) and psychiatric disorders (depression).
        - For AD these would include: rhinitis, food allergy, asthma and other potential comorbidities such as new cardiovascular complications.
3) Identify molecular, immunological and microbial biomarkers that inform prognosis and response to therapy of patients suffering from inflammatory skin disease. Such deliverables should be capable of improving diagnosis and directed care decisions and might include:
    - Identify markers that predict disease severity;
    - Identify markers that predict response to treatment;
    - Identify how endotypes differ in response to therapy;
    - Identify how endotypes differ in prognosis.

Expected impact

Currently, Pso and AD represent diseases difficult to treat and they significantly impact quality of life and medical health care costs for patients. This topic aims to comprehensively address aspects of disease endotypes, underlying pathobiology, and factors contributing to initiation, exacerbation and severity of disease, as well as response to therapy. Consequently, there are broad impacts relevant to the IMI2 goals that include:

- Research and Development (R&D) Process: using a patient-centred approach through comprehensive characterisation of skin disease heterogeneity, it is expected that new understandings into pathobiological processes will be established that should help drive future therapies, as well as stimulate new levels of understandings into skin biology and how it is regulated during homeostasis, disease, and repair.
- Regulatory Pathways and Health Technology Assessment: establishment of comprehensive disease endophenotyping will improve directed care decisions and future clinical trial design, including biomarkers, quality of life considerations, and patient enrolment suitability.
- Clinical and healthcare practices: understanding of early life events and environmental influences over disease progression and severity will support improvement in physician recommendations and management of patients.

The topic expected impact is to establish, and support access to, a world-leading analysis of skin disease, as comprehensively addressed from the perspectives of AD and Pso. This should be achieved through studying unprecedented patient numbers, a robust depth of data available (e.g. clinical, transcriptomic, response to treatment etc.), state-of-the-art approaches to studying the disease biology and central accessibility for users of the BioResource.

- In terms of strengthening the competitiveness and industrial leadership in Europe impact will be significantly enhanced by also including the relevant expertise from the Small- and Medium-sized Enterprises (SMEs).Their involvement might offer a complementary perspective to industry and the academia, and help deliver the long-term impact of the project.

Potential synergies with existing Consortia

Applicants should take into consideration, while preparing their short proposal, relevant national, European (both research projects as well as research infrastructure initiatives), and non-European initiatives. Synergies and complementarities should be considered in order to incorporate past achievements, available data and lessons learnt where possible, thus avoiding unnecessary overlap and duplication of efforts and funding.

While there are no current consortia aimed at the scope of this topic, the proposal has potential synergies with immune-related initiatives such as IMI **U-BIOPRED** (http://www.europeanlung.org/en/projects-and-research/projects/u-biopred/home) examining asthma (potential synergy with AD outcomes), and with a number of other disease specific consortia looking at microbiome regulation over disease (e.g. the Inflammatory Arthritis Microbiome Consortium as well specifically the finalised MAARS consortium: http://www.maars.eu/).

Industry consortium

The industry consortium is composed of the following EFPIA companies:

- Sanofi (lead)
- Boehringer Ingelheim
- Pfizer
- UCB

The industry consortium will contribute the following expertise and assets:

Contributions include prospective clinical study samples and/or data based on samples from atopic dermatitis and/or psoriasis trials; generating, processing and analysing RNA and other –OMICS data, precision immunology based studies incl. and as well as fluorescence-activated cell sorting (FACS), immunohistochemistry (IHC) data and methods. It also includes bioinformatics experts and data management activities as well as translational and clinical expertise. Further details are listed in the section “Suggested architecture of the project”.

Indicative duration of the action

The indicative duration of the action is 60 months.

Future Project Expansion

Potential applicants must be aware that the Innovative Medicines Initiative 2 (IMI2) Joint Undertaking, may publish at a later stage another call for proposals restricted to those projects already selected under this topic in order to enhance and progress the results and achievements by extending their duration and funding to prospectively progress the findings within this consortium.
Consortia will be entitled to include other beneficiaries as they see fit. In the context of this topic, such future expansion refers specifically to progress with translation and validation of key results and findings of this consortium (e.g. disease ontologies, biomarker candidates).

Indicative budget

The indicative industry in-kind contribution is EUR 8 300 000.

Due to the global nature of the participating industry partners it is anticipated that some elements of the contributions will be non-EU/H2020 Associated Countries in-kind contributions.

The financial contribution from IMI2 JU is a maximum of EUR 10 500 000.

Applicant consortium

The applicant consortium will be selected on the basis of the submitted short proposals.

The applicant consortium is expected to address all the objectives and make key contributions to the defined deliverables in synergy with the industry consortium which will join the selected applicant consortium in preparation of the full proposal for stage 2.

The applicant consortium should be comprised of expertise in three key areas: clinical characterisation and patient access (incl. samples and/or data from on-going prospective collections/trials for atopic dermatitis and/or psoriasis), biological specimen-based profiling, and advanced informatics. Consequently, the consortium would likely involve partners who bring expertise in access to and use of medical record-based information; this can be from ongoing clinical care sites and from ongoing clinical trials provided by the industry consortium (see above).
For a successful project, these samples and data will need to be accessible to the whole consortium.

Since access to clinical information and specimens is critical to the overall success of defining endotypes and the consortium goals, applicants should demonstrate their capacity (e.g. patient consent or waiver to consent) and quality to provide access to these. Applicants may involve academic medical centres with existing materials, biobanks, or organisations planning or actively participating in clinical trials and able to obtain consent. Building from previous efforts to define disease endotypes (e.g. as performed with asthma [1]), it is anticipated that access to large numbers of patients will be important to establish the power needed to define endotypes (e.g. 190 asthma patients were used to define a subgroup with high periostin [2]). Value is seen in both cross-sectional and longitudinal approaches but longitudinal data (e.g. patients before and after therapy) is seen as high value.

Consequently, partners providing medical record-based information as project background must be mindful that they, as background contributor, should have sufficient title to said background to authorise its use within the project pursuant to the IMI2 JU IP and legal framework. Consideration should also be given to additional information that may be introduced after the start of the project but is not listed as project background at start date.

Biological profiling will encompass partners with skills in transcriptomics, genetic sequence determination (e.g. SNP variance), microbial characterisation from human samples, proteomics, lipidomics, advanced immune cell phenotyping (e.g. single cell characterization), metabolomics and other specialist technologies. Advanced informatics will coordinate in-depth analysis of the input data to establish endotypes and would require expertise in big-data handling and include machine-based learning, cluster mapping and advanced algorithm

development. Skills in molecular epidemiology, clinical science, and integration of biological profiling with such datasets, will also be considered valuable to the consortium.

The applicant consortium must demonstrate significant experience, possibly through the participation of an experienced SME, in both Advanced Analytical approaches and strong Data Management practices. Advanced Analytical approaches will require the coordination of in-depth analysis of the input data to establish endotypes and would require expertise in big-data analysis and include machine-based learning, cluster mapping and advanced algorithm development. Strong Data Management experience is considered to be a critical strength of the successful applicant and therefore the applicants must be able to demonstrate previous experience of managing/coordinating a multi-centre multi-node clinical-research data-generation activity of comparable scope. Essential experience should also include the legal and ethical challenges associated with integrating multi-centre patient-derived data, as well as physical data-processing/ data-management and data management practices (privacy, security). Crucial will also be a demonstrable ability to deliver analytical platforms to facilitate the above mentioned Advanced Analytical approaches for a range of scientific/medical and analytical communities.

The applicant consortium is expected to include resources for project administration, management and communication.

In addition to industry and academic partners, SMEs can be of great benefit to IMI projects and strengthen the competitiveness and industrial leadership of Europe. Their involvement might offer a complementary perspective to industry and the academia, and help deliver the long-term impact of the project. For these reasons, applicants should consider engaging SMEs throughout the proposal. Under this topic, the contribution of SMEs would be considered especially beneficial in the context of professional data management and orchestrating data collection, analysis and availability to the rest of the consortium in a centralised, scalable and sustainable manner.

Given the nature of the key deliverables it is also expected from the applicant consortium that they provide experience and interaction in communication with Global Regulators, Patients, Practitioners and Payers, who may be members of a to be established Advisory Board.

Suggested architecture of the full proposal

The applicant consortium should submit a short proposal which includes their suggestions for creating a full proposal architecture, taking into consideration the industry participation including their contributions and expertise. Further details are listed below in the outline of the contributions from the different companies as well as the outline of the applicant consortium.

In the spirit of the partnership, and to reflect how IMI2 JU call topics are built on identified scientific priorities agreed together with EFPIA beneficiaries/large industrial beneficiaries, these beneficiaries intend to significantly contribute to the programme and project leadership as well as project financial management.

The final architecture of the full proposal will be defined by the participants in compliance with the IMI2 JU rules and with a view to the achievement of the project objectives. The allocation of a leading role within the consortium will be discussed in the course of the drafting of the full proposal to be submitted at stage 2. To facilitate the formation of the final consortium, until the roles are formally appointed through the consortium agreement, the proposed project leader from among EFPIA beneficiaries/large industrial beneficiaries shall facilitate an efficient negotiation of project content and required agreements. All beneficiaries are encouraged to discuss the project architecture and governance and the weighting of responsibilities and priorities therein.

Industry contribution

The EFPIA participants are companies with extensive, ongoing interests in skin diseases and have come together to address this topic in a collaborative manner aligned with the goals of the IMI programmes. The contributions are framed across the needs of the work-flow and include management support, methodological expertise and training, access to specimens and samples and data-management and data control. The specifics of each partner are as follows:

- Sanofi (lead)

  Sanofi aim to provide the overall scientific leadership needed to support the programme and to ensure the work is of the highest novelty and innovation. Sanofi will also support the alliance management needed to

support the successful execution of this project (including project monitoring and problem resolution) to meet expectations, goals and timelines. From a non-administrative contribution, Sanofi proposes to provide access to advanced, precision based technologies and bioinformatic capabilities. Sanofi will also provide clinical and translational expertise and access to resources that are necessary for regulatory oversight and ethics.

- Boehringer Ingelheim

  Boehringer Ingelheim will provide contributions that will financially support data generation and input in the form of postdoctoral scientists embedded within members of the consortium. This will provide training and career development for individuals. In addition, Boehringer Ingelheim also will support work packages that utilise immune cell assays, both as activities on prospective samples being collected by the consortium, as well as retrospective samples using appropriate methodologies.

- Pfizer

  Through access to samples from ongoing prospective clinical trials within their own programmes, Pfizer will support the work packages aimed at using advanced technologies (e.g. single cell analysis from skin, lipidomics, epigenetics) that cannot be performed on retrospective samples. Pfizer will also provide contributions to the clinical and molecular profiling needs important to assessing endotypes of AD and Pso.

- UCB

  UCB will provide Full Time Equivalent (FTE) support that will be important for the clinical and molecular profiling needs of the program. UCB will also provide support for the data management and capture needs of the programme.

Expected Applicant consortium contribution

The Applicant consortium contributions include access to existing samples relevant to the skin disease topic (especially AD and/or Pso), as well as access to *de novo* samples from ongoing collection. They will provide access to clinical epidemiology information related to skin diseases through comprehensive medical records. They will provide highly specialised techniques of relevance to the overall topic and science of skin and inflammation, including microbiome assessment, and bulk and/or single-cell analysis of transcriptomics, lipidomics, metabolomics; inclusion of precision-based approaches to this is considered a strength. The applicant consortium can provide state-of-the-art approaches to studying skin biology, including 3D organotypic cultures. The applicant consortium contribution should also include advanced modelling of human diseases based on multi-parameter data streams

Reference

[1] Lötvall J, Akdis CA, Bacharier LB, Bjermer L, Casale TB, Custovic A, Lemanske RF Jr, Wardlaw AJ, Wenzel SE, Greenberger PA. Asthma endotypes: a new approach to classification of disease entities within the asthma syndrome. J Allergy Clin Immunol. 2011 Feb;127(2):355-60. doi: 10.1016/j.jaci.2010.11.037.

[2] Matsusaka M, Kabata H, Fukunaga K, Suzuki Y, Masaki K, Mochimaru T, Sakamaki F, Oyamada Y, Inoue T, Oguma T, Sayama K, Koh H, Nakamura M, Umeda A1, Ono J, Ohta S, Izuhara K, Asano K, Betsuyaku T. Phenotype of asthma related with high serum periostin levels. Allergol Int. 2015 Apr; 64 (2): 175-180.

Topic 3: The value of diagnostics to combat antimicrobial resistance by optimising antibiotic use

Topic details

Topic code	IMI2-2017-13-03
Action type	Research and Innovation Action (RIA)
Submission and evaluation process	2 stages

Specific challenges to be addressed

Antimicrobial-resistant (AMR) bacterial strains killed 25 000 people in the EU in 2007 and cost the economy €1.5 billion a year. Many antibiotics that were once thought to put an end to infectious diseases are no longer working. Huge amounts of antibiotics are prescribed and consumed unnecessarily in almost all healthcare systems. The misuse of antibiotics has created a huge global health crisis. Prudent use of antibiotics is urgently required in order to protect the efficacy of our currently available antibiotics. We can reduce their unnecessary use in many ways; nevertheless diagnostics have the potential to provide more targeted, accurate use of antibiotics which is in the best interest of patients and the wider population. Diagnostics play a critical role in guiding treatment in infectious diseases. However, the value of diagnostics as a critical component of antimicrobial stewardship programmes is not fully established throughout Europe, with guidelines, funding and policy varying in each country. This hinders the adoption and use of currently available diagnostic tests by health professionals, as well as the development of advanced or innovative diagnostic tools. Therefore, a pan-European approach is required, to demonstrate the medical, economical and public health value of diagnostics for combating AMR: rapid and reliable characterisation of pathogens and their antibiotic resistance characteristics along with host susceptibility biomarkers. One way to determine the full value of diagnostics, and the optimal means of addressing the multitude of obstacles for their creation, valuation and deployment, is to analyse all these aspects in a standardised clinical trial network.

The overuse of antibiotics and the underuse of diagnostics occur within the entire breadth of healthcare: primary care, as well as hospitals with acute care, rehabilitation facilities and long-term care facilities, where most of the emerging antibiotic-resistant pathogens can be found. In Europe, 30-50% of antibiotics are prescribed unnecessarily, according to estimates from the European Centre for Disease Prevention and Control (ECDC). It is also well-described that the largest volume of antibiotics for human use is prescribed in the community setting (e.g. physician offices, clinics), most often for respiratory complaints and suspected respiratory tract infections – and over half of the time unnecessarily. Better diagnostic capabilities and more aggressive antimicrobial stewardship are amongst the top five unmet medical needs in strategies to combat antibiotic-resistant infections.

One of the most convincing means of demonstrating the value of diagnostics is to conduct prospective clinical trials and data collection which evaluate their impact in real-life patient-care settings. Due to the need for large numbers of patients in such analyses, a network of well-defined patient-care settings is necessary to carry out the type and extent of studies needed to demonstrate the value of diagnostics. The goal for setting up a network of clinical sites is to assess the impact of ‘standardised care and management algorithms’ using well-defined diagnostics in a proscribed manner in a well-defined and common infectious syndrome, compared to ‘usual care’. The choice of the targeted infectious disease is expected to be community-acquired acute respiratory tract infection (CA-ARTI) since it best reflects an area of importance where the over-prescribing of antibiotics is most flagrant. Possible outcomes which could be measured include, among others: i) doses or days of antibiotics prescribed, ii) proportion of patients not receiving antibiotics, iii) development of antibiotic-resistant colonisation post antibiotic therapy, iv) selection of pathogens with a resistant phenotype during or post therapy, v) emergence of antibiotic resistance among ‘normal’ intestinal flora during or after therapy.

There is currently a dearth of studies which can provide the evidence of the value of diagnostics in well-characterised situations, and the lack of such evidence has been a hindrance for diagnostic innovation. Furthermore, the current financial framework (i.e. inadequate reimbursement of diagnostics, reimbursement based on technology rather than medical value) does not encourage innovation related to *in vitro* diagnostic tests. The current *in vitro* diagnostic business model – focused on technology used, lab activity measures, and complexity indicators – is antiquated, and should change to focus on patient outcomes and health-economic

benefits to incentivise the creation and utilisation of high-medical-value diagnostics. Moreover, regulatory approval has historically been based on analytical performance, rather than on clinical effectiveness. Inserting patient-based benefits into the regulatory process would advantage diagnostics which confer the most benefit to individuals and the healthcare system.

More background information is available in the following list of publications:

[1][2][3][4][5][6][7][8][9][10][11][12][13][14][15][16][17][18][19][20][21][22][23][24][25][26][27][28][29][30][31][32][33][34][35][36][37][38][39][40][41][42][43][44][45][46][47][48][49][50][51][52].

Need and opportunity for public-private collaborative research

The urgent action to address the escalating problem of antibiotic resistance requires cooperation amongst industry, academia, patients and patient groups, policymakers, public health experts and healthcare decision-makers in order to implement critical solutions, including impactful diagnostics, which will allow preserving the efficacy of the antibiotics currently available or in development. Multiple diagnostics already exist which can be used to accurately and efficiently guide and improve antibiotic prescribing, but they are under-utilised across Europe. A public-private project is required to address the barriers which prevent the uptake and development of diagnostics for antimicrobial stewardship, which include studies, policy development, funding and reimbursement formulae and schemes, physician education and patient awareness, psychosocial factors, appropriate and innovative assessment (e.g. modern HTA which uses latest technology-specific methods of health technology assessments that include economic and health outcomes in order to assess comprehensively the value of these technologies and not only the clinical effectiveness), and disparate regulatory requirements.

Scope

The main objective of this action is to understand, demonstrate, and quantify the value of diagnostics and the obstacles to their adoption and use in the framework of a Standardised Care Network in order to combat antimicrobial resistance (AMR) by optimising antibiotic use in Europe.

The overuse of antibiotics and the underuse of diagnostics occur within the entire breadth of healthcare. It is a major issue especially in the ‘community’ setting (e.g. non-hospital clinics, private physician offices, para-medical clinics) where the majority of human antibiotics are used, most of which are inappropriately and unnecessarily prescribed. It is crucial to demonstrate both the economic and clinical value of diagnostics to health systems and purchasers. Governments and healthcare systems need to understand the wider value of diagnostics – including how their use can help them to achieve reductions in AMR and healthcare costs.

Health economic models for the use of diagnostics must be developed to:

- address the costs and benefits of the use of diagnostics and their impact on antibiotic prescribing;
- propose funding models (e.g. research incentives, reimbursement framework, adoption motivation) which would facilitate the development, introduction, deployment and use of diagnostics into routine medical care.

A global roadmap, aligned with the essential diagnostics list from the World Health Organisation (WHO) (likely to be disclosed at the end of 2017) must be defined to promote the use and development of diagnostic tools that would have distinct and clearly defined objectives: (i) avoiding unnecessary antibiotic use; (ii) optimising patient treatment and antibiotic use; (iii) identifying high-risk patients and/or pathogens for targeted and personalised antibiotic therapy; (iv) using diagnostics in clinical trials for supporting the development of new anti-infective approaches (prophylactic or therapeutic); (v) boosting innovation for new diagnostic development.

This project aims at providing clinical evidence to demonstrate the medical value, healthcare benefit and economic viability of diagnostic tests for combatting antibiotic resistance and improving patient outcome in conditions such as community-acquired acute respiratory tract infection (CA-ARTI).

Four objectives need to be addressed in this project:

Objective 1

The first objective is to establish a health-economic framework to assess and demonstrate the impact – for individual patients and public health in general – of increasing the use of diagnostics to reduce or optimise antibiotic prescription and ultimately combat the development of antibiotic resistance.

The framework should build on existing evidence from extensive research work and literature in the field as well as experiential knowledge and expertise from key stakeholders in, for example, traditional and innovative value-based evaluation methods, reimbursement schemes, research incentives, evaluation models, policies etc. Results should be disseminated in an adapted way to all stakeholders, including policymakers, clinicians and patients.

Objective 2

The second objective is to establish a Standardised Care Network (pre-existing or new) in order to conduct clinical trials evaluating the value of diagnostics. This network should include high-, medium- and low-antibiotic-use countries in Europe with an antibiotic stewardship programme in place. At a minimum, it should include five high-income EU countries representing a large population base, and five upper or lower middle-income countries from the EU Member States and H2020 Associated Countries. A business model must be constructed which will assure the sustainability of the Standardised Care Network after the IMI project completion. In addition, within this network, a bank of appropriate clinical specimens – properly annotated and curated – must be kept for the duration of the project and a model proposed to sustain the biobank *a posteriori* in cooperation with the diagnostics industry.

Objective 3

A third objective is to design and implement clinical studies to demonstrate the value of diagnostics in the optimal management of community-acquired acute respiratory tract infections (CA-ARTIs), by using the outputs, measures and deliverables defined in the health-economic framework (Objective 1). The study must use combinations of 'host-based' and 'pathogen-based' diagnostic tests in order to determine the optimal testing algorithm for reducing inappropriate antibiotic use and the subsequent development of antibiotic-resistant bacteria (colonisation and/or infection).

Objective 4

The fourth objective is to explore, define and attempt to resolve the many aspects which prevent the more widespread adoption of diagnostics when delivering healthcare to the population. Focus will be necessary on patient and healthcare provider education, psychological, ethical, organisational and social barriers in order to understand and address this complex issue.

Expected key deliverables

Main deliverables include (i) a defined framework to assess and demonstrate the value of diagnostics to optimise antibiotic therapy and reduce antibiotic resistance, taking into account all expected evidences from key stakeholders; (ii) a sustainable Standardised Care Network representing the different countries mentioned above and encompassing the entire range of healthcare establishment from community clinics to long-term care, able to collect and share thorough information on pathogen, patients status, treatment regimen and outcome; (iii) comprehensive clinical studies on the value of diagnostics in community-acquired acute respiratory tract infection (CA-ARTI) by using outcomes and measures specified in the framework; and (iv) a definition and better understanding of the psychosocial aspects preventing widespread adoption of diagnostics during healthcare delivery, focusing on education, psychological, organisational, ethical and social barriers, as well as pragmatic obstacles.

- A framework has to be set up for demonstrating how the use of diagnostics can help to achieve reductions in antibiotic use and the emergence of AMRs. It requires a precise and shared methodology agreed and defined with main stakeholders to:
    1. benchmark the standard of care and identify the most promising opportunities for improvement,
    2. specify the required clinical evidence for the adoption of the best practice and define measurable clinical outcome and success parameters,
    3. describe necessary standards and quality controls to allow the use of the generated evidence for IVD registration,

4. review the current regulatory environment and recommend improvements for product approvals to accelerate their time to market,
5. propose funding models facilitating the introduction and application of diagnostics into primary care,
6. develop a health economic model acceptable to payers for establishing value-based reimbursement for innovative diagnostics,
7. develop an education and dissemination programme to facilitate the implementation of the framework.

- Standardised Care Network comprising high-, medium- and low-antibiotic use countries in Europe, including at least five high-income EU countries that represent a large population base and five upper or lower middle-income countries from the EU Member States and H2020 Associated Countries, should be established to:
  1. perform extensive characterisation of clinical samples and pathogens isolated from patients,
  2. create and maintain a biobank of samples associated with a database and repository of information,
  3. propose an information flux architecture for data sharing and analysis,
  4. define a business concept to sustain the infrastructure for future rapid benchmarking and translation of innovative diagnostics and/or other process changes.

- A multi-country and multi-centre clinical study must be designed and conducted on the value of diagnostics in community-acquired acute respiratory tract infection (CA-ARTI) in order to:
  1. establish the optimal combination of pathogen-based and host-based diagnostics to achieve the outcomes being measured,
  2. define measurable clinical and other outcomes as well as success parameters to support quantification of the clinical impact and value of diagnostics.

- A thorough exploration and analysis of the psychosocial obstacles preventing widespread adoption of diagnostics when delivering healthcare to the population should be conducted to:
  1. define the psychosocial obstacles related to adoption of diagnostics by healthcare providers and patients, and,
  2. provide pragmatic solutions to each of the obstacles outlined, as well as evidence-based methods for their resolution within a European framework.

Expected impact

Expected impact will be the reduction of antibiotic use and AMR resulting in improved patient care through better routine use of diagnostics. It should be adapted according to national/regional requirements and maintained based on a sustainable business model beyond the proposed funding period. A decrease of antibiotic-prescribing rates should further happen in countries involved in the study. This would happen thanks to a raised awareness of health professionals and patients on the necessity to effectively replace empiric therapy by avoidance of antibiotics where unnecessary and definitive targeted therapy when required, particularly for acute respiratory tract infections (ARTIs) with short-term health benefits for patients, short-term economic benefits for the healthcare system, and mid-term / long-term benefits on reducing antibiotic resistance.

The main expected impacts should be: (i) optimum use of diagnostic tests in CA-ARTI for achieving improved patient outcomes, reduction in the inappropriate use of antibiotics, and decrease in the incidence of key antibiotic-resistant pathogens; (ii) wide dissemination of evidence-based conclusions that will sensitise the medical and patient communities, as well as decision makers, to the clinical and economic value of diagnostics; (iii) incorporation of guidance using diagnostic tests and testing algorithms in national and international guidelines; (iv) assistance to regulatory bodies to facilitate adoption of diagnostic tests into wider routine practice; (v) assistance to health technology assessment (HTA) bodies to enable appropriate, fit-for-purpose assessment of the clinical value of diagnostics; (vi) reform of pricing policies (including reimbursement) related to diagnostic tests, according to the demonstrated or anticipated medical value and health outcomes.

New health economic models demonstrated through the project will lead to new pan-European guidelines and algorithms to facilitate the widespread introduction, deployment, adoption and reimbursement of existing and new diagnostics to guide appropriate antibiotic use and reduce unnecessary antibiotic prescribing. Economic models will illustrate to governments, third-party payers and healthcare providers the economic feasibility and benefits of utilising diagnostics to guide appropriate antibiotic prescribing in various healthcare settings.

This evidence should then be published, disseminated, and adopted in order to sensitise the medical, political, regulatory and patient communities to the value of diagnostics in the targeted condition, and promote adoption of the diagnostic tests and testing algorithms into national and international guidelines. Additionally, it is expected that interactions will occur with European (and other) regulatory bodies to assist in the timely approval of diagnostic tests for quick introduction into routine clinical practice.

Health technology assessment (HTA) bodies will be also consulted separately and/or via EUnetHTA Joint Action 3 (European network for Health Technology Assessment, http://www.eunethta.eu) in order (i) to facilitate future, fit-for purpose assessments of the clinical value of diagnostics and (ii) to enhance, improve and reformulate information on the financial decision of diagnostic tests according to their medical value and the health outcomes which they confer.

Applicants should indicate how they will strengthen the competitiveness and industrial leadership of Europe by, for example, engaging suitable small and medium-sized enterprises (SMEs). They can benefit from this project in many ways: (i) choice of their diagnostic for the trial; (ii) clarification of HTAs and other aspects of diagnostic implementation which benefits all diagnostic companies; (iii) connect to laboratories for easier access to blood samples from patients across Europe and clinical data from multi-site European studies, tools that are normally beyond the reach of small companies; (iv) set-up and deployment of education programs; (v) exploitation/expansion opportunities: possibility of spin-off creations, trademark, licensing deals, results implementation by industry, sustainability plans, commercialisation, patent applications, increase in company size/workforce, etc.

Potential synergies with existing consortia

Applicants should take into consideration, while preparing their short proposal, relevant national, European (both research projects as well as research infrastructure initiatives), and non-European initiatives. Synergies and complementarities should be considered in order to incorporate past achievements, available data and lessons learnt where possible, thus avoiding unnecessary overlap and duplication of efforts and funding.

For example, the initiatives listed below might be relevant in that respect:

- **COMBACTE-Net** and **New Drugs for Bad Bugs (ND4BB) programme** (www.combacte.com): This IMI project has established large clinical investigator site and laboratory networks comprising more than 800 clinical sites and more than 600 laboratories across more than 40 European countries. Where possible, this project could build upon the established ND4BB networks and explore synergies. Applicants should note however that there is no requirement to include partners currently engaged in ND4BB in their proposal, but partners should be chosen to best match network needs and the objectives of this call topic.
- **DRIVE-AB**: The IMI project DRIVE-AB (Driving re-investment in R&D and responsible use of antibiotics) (http://drive-ab.eu/) is assessing the present and future burden of antibiotic resistance, defining the value of new antibiotics, and proposing new economic models for antibiotic development, bearing in mind innovation, stewardship, and access.
- **ND4ID** (http://www.nd4id.eu/): the H2020 project ND4ID (New Diagnostics for Infectious Diseases) is addressing the current shortcomings in the training of IVD researchers through an inter-sectorial, multidisciplinary and translational approach by transversal researchers to close the apparent gap between the clinical perspective and the technological perspective on IVDs.
- **ECRIN** (The European Clinical Research Infrastructure Network - http://www.ecrin.org/) is facilitating clinical research in Europe.
- **Enpr-EMA** (European Network of Paediatric Research at the European Medicines Agency - http://www.ema.europa.eu/ema/index.jsp?curl=pages/partners_and_networks/general/general_content_000303.jsp).
- **PREPARE** (Platform for European Preparedness Against (Re-)emerging Epidemics - www.prepare-europe.eu) and its associated GRACE network.

- Upcoming **pan-European Paediatric Clinical Trials Network** (part of the 10th Call for proposals of IMI2 JU)
- The UK Department of Health project Innovate UK AMR is focused on creating an infrastructure that will fast-track the research, development, evaluation and commercialisation of new drugs, diagnostics and vaccines, also, establishing a global multi-centre clinical trials network for drugs, diagnostics and vaccines, with a focus on antibiotic resistance.
- **CARB-X** (http://www.carb-x.org/) mostly devoted to drug development, but new diagnostic technologies are in scope.
- **JPIAMR** http://www.jpiamr.eu/: The scientific research agenda and recommendations of JPIAMR are aligned with the objectives of this project. Synergies with JPIAMR should therefore be explored.
- **Joint action Antimicrobial Resistance and Health Care Associated Infections** (European Commission, 3rd Health Programme - http://ec.europa.eu/chafea/health/actions-2016.html).
- Results and learnings of the following past EC-funded projects (now completed) might potentially be useful:
    - **C4L** (http://cordis.europa.eu/project/rcn/102035_en.html) developed rapid diagnostic tests to link antibiotic prescription with evidence-based diagnosis. Combining the Multiplex Ligation-dependent Probe Amplification (MLPA) and microfluidic technologies allows determination of viral or bacterial origin, as well as bacterial resistance mechanisms.
    - **PARCIVAL** (https://www.up2europe.eu/european/projects/partner-network-for-a-clinically-validated-multi-analyte-lab-on-a-chip-platform_15872.html) developed an integrated and automated multi-analyte lab-on-a-disk platform for the fast and reliable sample-in / answer-out diagnosis of highly infectious respiratory pathogens, resistance patterns and biomarkers for individual severity of the infection.
    - **ROUTINE** (http://cordis.europa.eu/project/rcn/104172_en.html) developed a test that integrates sample preparation, DNA amplification and a fluorescent-based read-out on one platform to allow direct detection of bacteria causing upper respiratory tract infection and the associated antibiotic resistances within 30 min.
    - **RiD-RTI** (http://cordis.europa.eu/project/rcn/104050_en.html) developed and evaluated diagnostic tools for the rapid (< 2 hrs) diagnosis of pneumonia. The diagnostics products are 'near patient', reliable, cost-effective and user friendly allowing for detection, identification, and quantification (for selected targets) and molecular drug susceptibility testing of RTIs.
    - **RAPP-ID** (https://www.uantwerpen.be/en/projects/rapp-id/) developed some of the technologies and innovations needed to speed up the development of rapid diagnostics tests such as a prototype of a breath sampler for influenza and a prototype of the ventilator-associated pneumonia (VAP) test (development of chips which help isolate the DNA of these bacteria from aspirates of VAP patients).

Industry consortium

The industry consortium is composed of the following EFPIA partners:

- bioMerieux (lead)
- Janssen Diagnostics
- Abbott (rapid diagnostics division)

In addition, the industry consortium includes the following IMI2 JU Associated Partners[142]:

- Accelerate Diagnostics
- Bio-Rad

[142] Moreover, MedTech Europe (http://www.medtecheurope.org/), as the European trade association of medical technology industries, will support this project in a role of an informal advisor.

- BD
- The Wellcome Trust

The Wellcome Trust has an interest to better demonstrate the value of diagnostics (both clinical and economic value) to health systems and purchasers. This evaluation can serve as the evidence base to inform a coordinated international advocacy. The Wellcome Trust aims to stimulate the development of new ways for diagnostics to be delivered into care pathways, and trail blaze diagnostics development which can be used in low- and middle-income countries (LMICs). The Wellcome Trust participates in the present topic as Associated Partner to IMI2 JU, contributing EUR 3 400 000.

The industry consortium will provide financial and/or in-kind contributions that altogether address the following area:

- pathogen and host-based assays and equipment
- clinical design and medical affairs expertise
- point-of-care data connectivity solutions, software and expertise
- data analytics (e.g. diagnostic biostatistics and bioinformatics)
- market access / pricing / reimbursement expertise
- health economics
- biobanking capabilities and pathogen characterisation (e.g. antibiotic susceptibility testing, clinical annotations)
- training facilities and modules (assays, data privacy).

Indicative duration of the action

The indicative duration of the action is 48 months.

Indicative budget

The indicative in-kind and financial contribution from EFPIA partners and IMI2 JU Associated Partners is EUR 6 800 000.

This contribution comprises an indicative EFPIA in-kind contribution of EUR 1 945 000 and an indicative IMI2 JU Associated Partners in-kind and financial contribution of EUR 4 855 000, of which EUR 3 805 000 financial contribution to the beneficiaries receiving JU funding in the selected action.

The financial contribution from IMI2 JU is a maximum of EUR 6 800 000.

The total financial contribution available to applicants for proposed activities in relation to the objectives of this action is therefore EUR 10 605 000. Therefore, applicants may allocate up to EUR 10 605 000 in the budget of their short proposals.

Applicants should however note that the final allocation of the financial contribution will be further discussed during the preparation of the full proposal for stage 2 between the applicant consortium selected at stage 1, the EFPIA partners and the IMI2 JU Associated Partners (full consortium).

Applicant consortium

The applicant consortium will be selected on the basis of the submitted short proposals. The applicant consortium is expected to address all the objectives and make key contributions to the defined deliverables in synergy with the industry consortium which will join the selected applicant consortium in preparation of the full proposal for stage 2. This may require that the applicant consortium satisfies the following conditions and mobilises, as appropriate, the following expertise or capabilities:

- health economists experienced in diagnostic studies;
- experience and know-how in conducting clinical trials including clinical operations and clinical programme management;
- access to a large population suffering from CA-ARTI across all age groups and differing healthcare environments (i.e. community, acute-care, rehabilitation, long-term care, home care);
- physicians and other healthcare providers experienced in working with the use of standardised procedures and processes in all clinical trials, uniform training of all research personnel, assistance in the design of clinical trials, inclusion of the patient/parent perspective in clinical trials, and the sharing information related to clinical trials;
- payers / prescribers / regulatory organisations able to actively contribute to the development and standardisation of study procedures and processes (e.g. creation of study documents, patient/parent information);
- psychologists, social workers, educators and other social science experts skilled in the analysis of psychosocial barriers to health intervention implementation;
- expertise in advocacy;
- expertise in information technology/data management;
- expertise in legal and clinical compliance/ICH GCP (International Council for Harmonisation – Good Clinical Practice) aspects;
- strong project management and communication expertise, office administration and website management.

Applicant consortia will be expected to include experts and sites in a ‘community’ setting such as non-hospital clinics, private physician offices, para-medical clinics, etc. (where the majority of human antibiotics are used), as well as hospitals, rehabilitation facilities and long-term care facilities (where most of the emerging antibiotic-resistant pathogens can be found).

SMEs can be of great benefit to IMI projects and, inter-alia, strengthen the competitiveness and industrial leadership of Europe. Their involvement might offer a complementary perspective to industry and the academia, and help deliver the long-term impact of the project. For these reasons, applicants should consider engaging SMEs throughout the proposal. SMEs could provide in particular, but not exhaustively: (i) diagnostic tests, regulatory registered or in the registration process, including novel validated biomarkers; (ii) services, information systems or software for data sharing, storage and analysis; (iii) infrastructures, logistics and services for bio-banking and deep characterisation of pathogens or samples; (iv) project management and dissemination tools including set-up of education programs and training modules to advocate on the value of diagnostic to combat AMR.

Suggested architecture of the full proposal

The applicant consortium should submit a short proposal which includes their suggestions for creating a full proposal architecture, taking into consideration the industry participation including their contributions and expertise. The final architecture of the full proposal will be defined by the participants in compliance with the IMI2 rules and with a view to the achievement of the project objectives.

In the spirit of the partnership, and to reflect how IMI2 JU call topics are built on identified scientific priorities agreed together with EFPIA beneficiaries/large industrial beneficiaries, these beneficiaries intend to significantly contribute to the programme and project leadership as well as project financial management.

The final architecture of the full proposal will be defined by the participants in compliance with the IMI2 JU rules and with a view to the achievement of the project objectives. The allocation of a leading role within the consortium will be discussed in the course of the drafting of the full proposal to be submitted at stage 2. To facilitate the formation of the final consortium, until the roles are formally appointed through the consortium agreement, the proposed project leader from among EFPIA beneficiaries/large industrial beneficiaries shall facilitate an efficient negotiation of project content and required agreements. All beneficiaries are encouraged to discuss the project architecture and governance and the weighting of responsibilities and priorities therein.

The consortium is expected to have a strategy on the translation of the relevant project outputs into policy, regulatory, clinical and healthcare practice. A plan for interactions with decision makers, regulatory agencies/health technology assessment bodies with relevant milestones and allocated resources should be proposed to ensure this.

A plan for aspects related to sustainability, facilitating continuation beyond the duration of the project should also be proposed.

The architecture outlined below for the full proposal is a suggestion. Different innovative project designs are welcome, if properly justified.

It is anticipated that industry contribution would include:

- project management support (project design and continuous follow-up);
- legal expertise, health economics expertise;
- clinical operations, data management, and clinical expertise to support regular review of deliverables;
- training and support of professionals to use/run new diagnostic assays;
- co-leadership to contribute to consortium governance structure and meetings.

Work package 1 – Implementation of diagnostics

It aims at designing and testing a framework for establishing a sustainable infrastructure for the evidence based translation of innovative diagnostics into standard-of-care. The framework should assess and demonstrate the value of diagnostics both for individual patients and for public health. The framework should build on the available evidence and utilise an extensive consultation with key stakeholders.

A diagnostic test needs to provide the clinician with sufficient information to decide on the most appropriate antibiotic strategy or to deviate from prescribing antibiotics altogether. This need differs between various infectious diseases, between different clinical settings and between geographies within Europe and beyond. The project team and public/private partnership should elaborate further on a roadmap including the points outlined below.

- **User requirement specifications** outlining the minimal and optimal requirements of a diagnostic test from an end-user perspective. A separate document could be generated per clinical setting specifying regional differences with clear indication on how the specifications drive clinical utility. Such a document requires an extensive outreach to the various stakeholders, integrating their viewpoints. A number of case studies can be used to anchor these concepts in concrete examples.
- **Proposals of clinical algorithms** for use of diagnostics within various clinical settings. Such use should be based on what is considered 'responsible use' of antibiotics and should integrate in a first instance the result of one or more diagnostic tests with the results of the clinical evaluation of the patient. To this end, the different viewpoints held by different stakeholders should be mapped and linked to current and future (ideal) diagnostic concepts.

This study should reveal shortcomings in the currently available diagnostic tests – even if currently underused, which should feed a technological roadmap, aligned with the essential diagnostics list from WHO, addressing both bioassay content (host and pathogen biomarkers, probes, antibodies, metabolic substrates, etc.) and device/instrument gaps. Indeed, investments into novel technologies that might result in new returns could be considered to incentivise new technology development.

Key tasks:

1. establish a consulting network including physicians, European in vitro diagnostics (IVD) regulators, HTA and other assessment programmes, reimbursement experts, third-party payers, health economists, medical educators and psychosocial experts;
2. undertake a systematic review of the existing (peer-reviewed) literature and ongoing European AMR-related activities;
3. analyse the implementation process for innovative diagnostics into standard of care in CA-ARTI, describe key hurdles and propose actions to systematically drive their evidence based implementation, especially;
4. provide a description of the framework for a rapid evidence based implementation of innovative diagnostics into routine based on a Standardised Care Network;
5. facilitate the decisions regarding the implementation of the best practice process into routine with the key stakeholders;
6. establish and define the measurable clinical and other outcomes and success parameters with which to measure the clinical impact and value of diagnostics;
7. establish a list of shortcomings of currently available tests and propose high level requirements for new products that further improve the practice to tackle AMR challenge in CA-ARTI.

Work package 2 – Establishment of a Standardised Care Network

The purpose is to establish a Standardised Care Network (pre-existing or new) in order to conduct clinical trials evaluating the value of diagnostics. This network should include high-, medium- and low-antibiotic-use countries in Europe, including countries with and without an antibiotic stewardship programme in place. The network should include at least five high-income EU countries that represent a large population base and five upper or lower middle-income countries from the EU Member States and H2020 Associated Countries. A business model must be constructed which will assure the sustainability of this network after the IMI2 JU project completion.
In addition, within this network, a bank of appropriate clinical specimens – properly annotated and curated – must be kept for the duration of the clinical trial, and a sustainability plan should be proposed.

Key tasks:

1. define and set-up a network of well-defined patient-care settings, in order to demonstrate and quantify the value of diagnostics for CA-ARTI management:
   - covering countries mentioned above,
   - encompassing the entire range and spectrum of healthcare establishments from community clinics to long-term care, including physician offices,
   - being coordinated and led through a single entity or group and providing a one-stop point of access,
   - establishing and sharing standardised care procedures and algorithms both for usual care and prospective clinical trial to generate data that feed criteria and evidences specified in work package 1,
   - leveraging or synergising with existing European networks or clinical research infrastructures (IMI, others) in a collaborative effort to shorten set-up time and expand access to patients and samples;
2. conduct multi-center prospective/randomised clinical trials in order to demonstrate and quantify the value of diagnostics for CA-ARTI and their impact in real-life patient-care settings:
   - respecting the frame of clinical studies defined in work package 4,
   - comparing use of novel diagnostics and procedure with usual care in a standardised manner,
   - ensuring relevant patient and sample data collection and storage in agreement with work package 3 requirements;
3. perform extensive characterisation of clinical samples and pathogens isolated from patients:
   - including both isolated pathogens, commensal flora and patient (host) sample analysis,
   - using reference (phenotypic) and state-of-the-art deep characterisation methods (whole genome sequencing, mass spectrometry, epidemiological tools) for pathogen analysis (identification, antibiotic resistance),
   - evaluating host status and response (immune profile, biochemical and genetic markers),
   - covering all antibiotic resistance traits encountered and allowing the identification of new markers or mechanism of resistance;
4. create and maintain a biobank of samples, clinical specimens and pathogens isolated from patients:
   - constituting a comprehensive collection of microorganisms and primary clinical samples with high quality standards (redundancy, traceability, storage),
   - constantly curated and updated based on latest results (new samples, patient follow-up) to allow reliable analyses (statistical performance, regulatory evaluation);
5. propose and validate a scheme and business model to allow the created Standardised Care Network to be sustainable and permanently accessible in Europe for further studies with an emphasis on diagnostics for infectious diseases in order to reduce global antibiotic use and AMR, and so:
   - broadening diagnostic evaluation to other clinical situations,
   - allowing long-term analysis of diagnostic value (patient outcome, infection and resistance recurrence).

Work package 3 – Data Analysis

The purpose is to provide tools and organisation suitable for the analysis of the data from the clinical study undertaken in the Standardised Care Network, including surveillance data, 'best practices' which are based on optimal patient outcomes, and all of the outcomes, measures and deliverables outlined in work package 1.

Key tasks:

1. establish a database and repository of information:
   - gathering results and information obtained in clinical studies (work package 4) performed in the Standardised Care Network (work package2),
   - containing all detailed information on isolated pathogens (identification, resistance traits, epidemiology, prevalence),
   - interfaced with laboratory / hospital information system,
   - connected with patient electronic record / retrieving key (anonymised) information relevant for the project,
   - collecting treatment information related to patient care (drug prescribed, treatment regimen, posology, antibiotic stewardship),
   - consolidating health-care associated expenses by category (hospital stay duration, cost of antibiotic treatment, complementary care, cost of testing…),
   - providing inter-operability features to allow connections between laboratory information systems and partners, and favoring information exchange across laboratories of the consortium),
   - with a user interface suitable for clinicians and healthcare professionals of the network to load, consult or extract information;
2. allow (meta) data analysis including:
   - data mining relevant to evidence and criteria expected from work package 1,
   - extraction of information of clinical studies managed in work package 4;
3. propose a data flux information architecture suitable for:
   - future decision-support tools to implement optimal treatment and management of patient for healthcare professionals,
   - clinical context use to implement / optimise use of diagnostic solutions.

Work package 4 – Clinical study on the value of diagnostics in community-acquired acute respiratory tract infection (CA-ARTI)

The objective is to design and implement clinical studies to demonstrate the value of diagnostics in the optimal management of community acquired – acute respiratory tract infections (CA-ARTIs), by using the outcomes, measures and deliverables outlined in work package 1 within the Standardised Care Network of Work package 2. The studies must use combinations of 'host-based' and 'pathogen-based' diagnostic tests in order to determine the optimal testing algorithm for reducing inappropriate antibiotic use and the development of antibiotic-resistant bacterial strains.

Key tasks:

1. design a multi-country and multi-centre clinical study within the Standardised Care Network as set out in work package 2, to demonstrate the value of diagnostics in the optimal treatment of community acquired – acute respiratory tract infections (CA-ARTIs);
2. implement the clinical study with the following objectives:
   - evaluate the impact of the use of diagnostics in relation to their impact on antibiotic prescribing rates,

- assess the defined measurable clinical outcome and success parameters (clinical utility) which will be derived from the results of work package 1,
- include combinations of 'host-based' and 'pathogen-based' diagnostic tests,
- evaluate and test the implementation process for new devices (change management and sustainability) as derived from work package 1,
- include parameters to evaluate the health economic models as derived from work package 1;

3. implement a system for collecting, monitoring and validating measurable / data as set out above;
4. periodically report the status, results to date and progress;
5. analyse, interpret and publish the results of the study in a peer-reviewed journal.

Work package 5 – Education & advocacy

Key stakeholders who can influence practice, policy and prescribing culture must be made aware of the available research, evidence, clinical utility and societal value (i.e. optimisation of antibiotic prescription and reduction of subsequent antibiotic resistance) of diagnostics. A thorough exploration and analysis of the obstacles preventing widespread adoption of diagnostics when delivering healthcare to the population should be conducted. The social, ethical, organisational, environmental, economic, and psychological factors, that influence the perception and adoption of new diagnostic technologies and their delivery into health systems, should be identified. With the input and help from behavioural and social sciences this work package should address barriers for acceptance of diagnostic tests and help understanding motivational factors which may help overcoming hurdles to effectively use these tests in patient management. This work package should also study how patients and populations can be empowered to become value-conscious beneficiaries of diagnostic tests. Coordinated education and awareness raising will facilitate this.

Regulation and policy can largely influence the development and use of IVD tests regarding AMR. Currently, a coordinated advocacy effort is missing to help all stakeholders (regulators, payers, policymakers, others) to define a new framework that incentivises the use of diagnostics. IVD industries and non-industry actors have a common interest in providing evidence to policymakers resulting from the different activities of the project.

The European Commission has published a new AMR Action Plan and most countries are defining or have defined their national AMR plans. A coordinated public-private action through an advocacy platform is needed to analyse existing policies, identify examples of good practice and evidence regarding diagnostics and surveillance of AMR, discuss with stakeholders and establish concrete recommendations. Advocacy actions should not only target the European level, and collaboration with international associations and initiatives should be envisaged. A public-private partnership will efficiently address the barriers which prevent the uptake of diagnostics and their use in antimicrobial stewardship, which include policy, funding, awareness and disparate regulatory requirements. Economists, public health bodies, healthcare groups and other public bodies are all required to demonstrate independently from industry the value and benefits of rapid diagnostics in antimicrobial stewardship, in order to guide policy, awareness campaigns and funding models.

The advocacy effort performed for middle-income countries from the European continent could be extended to low and middle-income countries (LMICs).

Key tasks:

1. mapping of stakeholders and policies;
2. establishment of an advocacy platform;
3. analysis of existing policies and good practice;
4. sharing of evidence provided in other work packages;
5. organisation of events and meetings with stakeholders and decision makers;

6. analysis of the many obstacles preventing widespread adoption of diagnostics;

7. education and communication programme for all stakeholders.

Work package 6 – Project management

The objective is to establish a framework to optimise resources and ensure delivery of results in due time and/or mitigate the risks associated to the project, maximising interaction and cross-fertilisation across the various work packages.

Project management should furthermore ensure the strategic alignment of efforts to key deliverables. It should also oversee, coordinate, manage and facilitate the project and its work packages among the consortia members and with IMI2 JU.

Key tasks:

1. set-up a joint governance structure for the project;
2. define charters and clear accountabilities;
3. provide coordination and support to work package leaders;
4. define work plan, timelines, deliverables, dates, adherence to budget and review progress;
5. identify project interdependencies, stakeholders, risks and mitigation plan;
6. verify that partners are committed and engaged;
7. ensure meetings and interactions between work packages, sub-groups, and consortium governance;
8. ensure internal and external communication.

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Topic 4: Mitochondrial Dysfunction in Neurodegeneration

Topic details

Topic code	IMI2-2017-13-04
Action type	Research and Innovation Action (RIA)
Submission and evaluation process	2 stages

Specific challenges to be addressed

Neurodegenerative diseases such as Parkinson's disease (PD) are of growing public health concern in developed countries, and the need for novel effective treatments continues to increase. Neurodegenerative diseases take many forms, reflecting the degeneration of different populations of neurons at different times and from distinct causes, but many of them also share common features. Amongst the commonalities are bioenergetic failure and oxidative stress, both of which reflect the dysfunction of mitochondria within neural and glial cells [1][2][3][4]. As such, a detailed understanding of mitochondrial dysfunction in the brain in the context of ageing, injury by misfolded protein toxicity, and genetic factors associated with neurodegeneration holds much promise for the development of therapeutic interventions that could impact multiple neurodegenerative disease states.

While mitochondria are found in most cell types, they have a distinct involvement in the brain and in neurodegeneration and especially in neuronal cells. Indeed, in diseases caused by mutations in the mitochondrial genome (thus in principle systemic, in all cells), the typical disease phenotype is dominated by neuronal dysfunction [5]. In addition, many mitochondrial toxins (such as rotenone or 3-nitroproprionic acid) delivered systemically result in selective injury to the central nervous system [6][7]. Thus, while the brain may be selectively vulnerable to mitochondrial dysfunction, this also implies that the nervous system may preferentially benefit from mitochondrial-targeted therapeutics.

Mitochondria are not static organelles. They constantly undergo fission and fusion; their genome also replicates in post-mitotic cells; and they move to different cellular locations up to the end of the neuronal axon [8-10]. Neuronal injury has been associated with cessation of mitochondrial movement and sometimes dramatic alterations in mitochondrial morphology [11], but the impact of altered mitochondrial structure and function on neurodegenerative disease is yet to be fully elucidated. Some of the key modifiers of mitochondrial dynamics have been identified, such as fission and fusion promoting proteins [10][12], as well as proteins that regulate mitochondrial movement [13][14][15][16][17], but the specific role of these proteins in the context of neurodegeneration has not been established.

Mitochondrial dysfunction may be due to abnormal respiratory function, biogenesis, dynamics (axonal transport, fission, fusion) or mitophagy. It can affect several different cellular activities, including abnormal cellular energy generation encompassing oxidative phosphorylation, the citric acid cycle and beta-oxidation. On the other hand, dysfunction can emerge from perturbations in key functions which are energetically distinct yet intimately related to mitochondrial function as they ensure overall cellular metabolic health. Examples are iron-sulphur cluster biogenesis, organisation of the Endothelial Reticulum (ER)-mitochondria network, mitochondrial quality control (mitophagy), and synthesis of mitochondrial proteins and lipids [1]. It is widely believed that neuronal health is reliant on the proper positioning of the mitochondrial network within long axonal projections, and therefore insults to the ever-adapting nature of mitochondrial networks are seen as a key turning point in the aetiology of many neurodegenerative indications [18].

The overall aim of this topic is to develop an unprecedented appreciation of the evolution of mitochondrial dysfunction in models of PD in order to understand if dysfunction is a driver of disease progression. A key goal is to develop an unprecedented appreciation of mitochondrial function in an *in vivo* model of neurodegenerative disease, which is currently lacking. Other challenges to be addressed within this topic are to quantitatively dissect changes in mitochondrial function in *in vitro* and *in vivo* models (including brain slices) and through mechanistic computational models of PD; and to understand the impact on the degeneration of neurons and/or glia. There is a growing appreciation of the impact of glial cells (astrocytes, oligodendrocytes and microglia) in neurodegeneration, so this topic may include investigations of mitochondrial dysfunction in several cell types [19]. There is also the opportunity to investigate mitochondrial function in neural cells derived from human sources, both from patients and unaffected individuals [20]. Identification of the key molecular drivers of

mitochondrial dysfunctions in the disease models will provide a unique scaffold to enable the discovery and development of new therapeutics to halt neurodegenerative disease progression. It is anticipated that the topic will lead to the identification of key molecular drivers which will provide a foundation for the identification and validation of new drug targets, facilitating innovative therapeutic approaches within the neurodegeneration field. Moreover, mitochondrial abnormalities serve as a connecting theme between several neurodegenerative diseases, with a direct link to several processes known to be impaired in neurodegeneration such as bioenergetics and misfolded protein toxicity [21]. Therefore, the learnings are anticipated to also feed into the understanding of the role of mitochondrial dysfunctions in other neurodegenerative diseases such as Alzheimer's disease (AD).

Need and opportunity for public-private collaborative research

Neurodegenerative diseases are complex entities that demand cross-disciplinary investigation. Successful development of methodologies and technologies will require quantitative assessment of mitochondrial dysfunction *in vitro* and *in vivo*; identification of mitochondrial dysfunction in robust neurodegenerative disease models; and the understanding of the impact this dysfunction has on disease progression. These insights will enable significant advances in strategies to expand the repertoire of targets and encourage renewed investment to develop treatments for neurodegenerative disorders.

It is beyond the reach of a single company or institution to fully understand the magnitude and complexity of the roles of mitochondria in health and disease. Because of the scale and scope of this endeavour, success will require the collaboration of a cross-functional/cross-institutional consortium of academic, small- and medium-sized enterprises (SMEs)/biotech and industrial scientists covering a large variety of scientific expertise.

State of the art *in vitro* and *in vivo* models (brain slice cultures, transgenic and models based on the 'prion-like hypothesis') developed in industry and already used in the research and development (R&D) process, along with creative new disease models and novel methodologies to quantify mitochondrial dysfunction from academia and innovative SMEs, will create synergies that would otherwise likely be unobtainable.

Scope

The overall scope of the project generated by this topic is to identify and understand the impact of mitochondrial dysfunction in *in vitro* and *in vivo* models of neurodegenerative diseases, incorporating core characteristics of neurodegeneration such as protein misfolding. Understanding if dysfunction is a driver of disease progression, and the detailed mechanisms responsible for it, will enable the exploration of novel targets for therapeutic approaches to neurodegenerative diseases.

The scope will be reached by a scientifically robust strategy building on established and innovative PD models, and the appropriate technology experience within the consortium. More specifically, this will include addressing the following objectives:

In vitro

- In established and innovative *in vitro* models of PD in neurons, microglia, oligodendrocytes and/or astrocytes, understand the impact of mitochondrial dysfunction (such as respiratory function, biogenesis, trafficking, fission, fusion and mitophagy) on the development/severity of the disease phenotype and identify key molecular drivers of these dysfunctions. Assessment of correlation between morphology and function should be included to ease later interpretation of morphological observations *in vivo*.

- Among others, the *in vitro* phenotype would ideally include a demonstration of mitochondrial dysfunction induced by α-synuclein or tau in a humanised model system such as induced pluripotent stem cells (iPSCs) which allow the study of both neurons and glia (astrocytes, oligodendrocytes and microglia) individually, but also in co-cultures to study interactions and cross-talk. These cellular models would then be further developed into a robust model for therapeutic target identification. Models could potentially include organotypic slice cultures including those incorporating prion-like spreading of misfolded proteins. Assessment of correlation between morphology and function should be included to ease later interpretation of morphological observations *in vivo*.
- Neurodegeneration is a phenomenon directly associated with ageing, yet most *in vitro* cell-based models use neonatal tissues as a source of primary cells. Moreover, iPSCs essentially have their biological clock

reset, thus eliminating elements of ageing in the model. Incorporating a component affecting mitochondrial ageing as a model variable would be a valuable addition to the *in vitro* approach.

In vivo

- In a well characterised, robust *in vivo* PD model, investigate if mitochondrial dysfunction can be identified. Understand the impact of these changes on disease progression such as neuronal and synaptic health, as well as the potential for their therapeutic modulation. While many *in vivo* models of PD exist, convenient models using transgenic animals already aged before the start of the project or injection of fibrillary forms of disease-associated proteins as a seeding mechanism to trigger neurodegeneration would be the most appropriate [22]. These models typically develop disease pathology over a time frame suitable for the studies proposed here.
- ***In silico***

  Reconstruct a mechanistic computational model of mitochondrial function to account for the gene products of each gene associated with mitochondria [23] and closely associated organelles. Integrate the experimental data from the *in vitro* and *in vivo* experiments to generate control and neurodegenerative computational models. Quantify the relative contribution of abnormal respiratory function, biogenesis, dynamics (axonal transport, fission, fusion), and mitophaghy to mitochondrial dysfunction.

Key deliverables

The applicants should develop a translational framework for the study of mitochondrial dysfunction *in vitro* and *in vivo* that will provide mechanistic insight into the role of mitochondria on disease pathology progression. This should be achieved by the delivery of the following.

- Development of robust tools and assays to study and quantitatively address mitochondrial dysfunction in well characterised *in vitro and in silico* models of neurodegenerative and trauma-associated nervous system diseases, and *in vivo* models of neurodegeneration, with an emphasis on PD.
- Identification of mitochondrial dysfunction in established and well-characterised models using *in vitro, in silico* and *in vivo* approaches.
- Understanding the role of the mitochondrial dysfunction identified on disease progression/severity.
- Validation of the experimental robustness of the mitochondrial dysfunction identified and the quantitative detection of the endpoint. This is a pre-requisite for application of the model system in pharmaceutical research.
- Identification of the mitochondrial dysfunction in each of the cellular populations involved in the disease: neurons and glia.
- Understanding of the role of misfolded proteins and unfolded protein response associated with PD on mitochondrial dysfunction*, in vitro* (including organotypic brain slice cultures) and *in vivo*.
- Identification of key molecular drivers of mitochondrial dysfunction promoting neurodegenerative diseases. This will provide an unprecedented foundation for the pharmaceutical industry to identify and validate innovative drug targets in the field of neurodegeneration.
- Establishment of a European multidisciplinary research platform of excellence of mitochondrial dysfunction in neurodegeneration facilitating the understanding of neurodegenerative disease aetiology, thus ensuring the sustainability of project outcomes.

Expected impact

Progressive neurodegenerative diseases represent a large and growing burden. Despite a considerable investment in research aimed at understanding and treating neurodegeneration, the lack of disease-modifying therapies remains notable. Recognising this gap, the treatment of neurodegenerative disease is a clearly-identified goal of IMI2 JU, and the expected impact of the project to be generated by this topic is closely aligned with the overall goal.

There is considerable evidence implicating mitochondrial dysfunction in the pathogenesis of a number of progressive neurodegenerative diseases, including Parkinson's disease, but no efficacious treatments have been developed based on this knowledge.

By developing a set of validated cellular assays, organotypic brain slice models and *in vivo* tools, the project will remove an important barrier that has limited the systematic exploration of mitochondrial dysfunction in neurodegenerative disease. A clear identification of the specific mitochondria dysfunctions (such as respiratory function, biogenesis, trafficking, fission, fusion or mitophagy) contributing to neurodegeneration will enable the discovery of novel targets for intervention.

By taking advantage of recent advances in the understanding of mechanisms that control mitochondrial dynamics and using innovative technologies to access mitochondrial dysfunction (e.g. axonal transport and fusion/fission in highly relevant model systems), this approach should provide unprecedented insights into the causal link between mitochondrial dysfunction and neurodegeneration.

SMEs can be of great benefit to IMI2 JU projects and, inter alia, strengthen the competitiveness and industrial leadership of Europe. Their involvement might offer a complementary perspective to industry and academia, and help deliver the long-term impact of the project. For these reasons, applicants should consider engaging SMEs throughout the proposal.

The project learnings will strongly aid neurodegenerative disease understanding and the identification of novel targets, giving academics/SMEs/pharmaceutical companies new options for treatments of diseases with mitochondrial dysfunction, such as PD. Moreover it would encourage a renewed investment in developing drugs for neurodegenerative disorders for which there is a high unmet medical need. In particular, biotech SMEs will be able to 'stress-test' their technologies in a non-competitive, open innovation environment, which will greatly facilitate the development of novel and important therapeutics.

Thus, it can be anticipated that the results of the project will benefit patients and society through the accelerated discovery of new drugs and therapies for neurodegenerative diseases.

Potential synergies with existing consortia

While preparing their short proposal, applicants should take into consideration relevant national, European (both research projects as well as research infrastructure initiatives), and non-European initiatives. Synergies and complementarities should be considered in order to incorporate past achievements, available data and lessons learnt where possible, thus avoiding unnecessary overlaps and duplication of efforts and funding.

The project generated from this topic in particular should, among others, consider:

IMI/IMI2 JU projects

- **IMPRiND**: Inhibiting Misfolded protein Propagation in Neurodegenerative Diseases (https://www.imprind.org/)

Relevant with regard to both *in vitro* and *in vivo* model systems for spreading and seeding processes in PD and AD

- European Lead Factory (https://www.europeanleadfactory.eu/) – relevant for assays, and targets for NDDs
- **EBiSC**: European Bank for induced pluripotent Stem Cells (https://www.ebisc.org/)

Relevant with regard to IPSC lines from patients

- Michael J. Fox Foundation: **LRRK2 Cohort Consortium** (https://www.michaeljfox.org/page.html?lrrk2-cohort-consortium

Relevant for samples, cellular and animal models

- Michael J. Fox Foundation: **Parkinson's Disease Research Tools Consortium** (https://www.michaeljfox.org/page.html?tools-consortium)

Relevant for cellular and animal models of protein misfolding in PD

- **MIND MAPS**: Molecular Imaging of Neurodegenerative Disease – Mitochondria, Associated Proteins & Synapses consortium (https://mitochondrialdiseasenews.com/2017/04/05/imanova-mrc-funding-mind-maps-study/)

Relevant for imaging mitochondrial dysfunction in patients with AD and PD

- H2020 project **SYSMEDPD**: Systems Medicine of Mitochondrial Parkinson's Disease (http://sysmedpd.eu/)

Relevant for cellular and animal models of protein misfolding in PD
Ongoing and planned activities of the Joint Programming Neurodegenerative Diseases: Pre-clinical research on Parkinson's disease - relevant for cellular and animal models of protein misfolding in PD, and research on mitochondria in neurodegeneration to ensure complementarity and avoid duplication (http://www.neurodegenerationresearch.eu/?s=mitochondria)

- H2020 project **MEFOPA**: European Project on Mendelian Forms of Parkinson's Disease (http://cordis.europa.eu/result/rcn/149388_en.html)

Relevant for cellular and animal models of protein misfolding in PD.

Industry consortium

The industry consortium is composed of the following EFPIA companies:

- Teva (lead)
- UCB
- H. Lundbeck A/S

In addition, the industry consortium includes the following IMI2 JU Associated Partner:

- Parkinson's UK

The industry consortium will contribute the following expertise and assets:

- Access to *in vivo* and *in vitro* disease models:
    - Well established *in vivo* α-synuclein seeding models in wild type (WT) rodents, including: the SNCA-OVX Tg mouse model (expressing human α-synuclein (SNCA) locus WT α-synuclein at disease-relevant levels) [24], pre formed fibrils (PFF) mouse and rat model [25, 26] and an α-synuclein rat model (AAV-A53T-α-synuclein rats; showing protein aggregation, dystrophic axonal morphology and progressive loss of dopaminergic neurons in the substantia nigra pars compacta and glial responses) [27, 28], including assay protocols, seed material based on recombinant α-synuclein fibrils, and α-synuclein pathology endpoint analysis.
    - Well established α-synuclein seeding models in WT or F28 (human α-synuclein expressing mice) [25, 26] primary neurons, assay protocols, seed material based on recombinant α-synuclein fibrils, pregnant F28 mice for establishment of the cultures and α-synuclein pathology endpoint analysis.

- Access to iPSC lines, iPSC neuronal progenitors and protocols for differentiation into neurons and into glia, including microglia. Protocols and tools for viral transduction and siRNA knockdown of proteins in iPSC neurons.
- Access to human tissue samples for validation studies from a collection of ~1 000 PD cases and 200 controls from which formalin fixed and flash frozen brain tissue is available.
- Evaluation of consistency and robustness of mitochondrial dysfunction key molecular endpoints to ensure future application for target identification/validation.
- Industry will also support communication, dissemination and project management.

Indicative duration of the action

The indicative duration of the action is 36 months.

Indicative budget

The indicative industry in-kind contribution is EUR 3 288 000 .

This contribution comprises an indicative EFPIA in-kind contribution of EUR 3 120 000 and an indicative IMI2 JU Associated Partners in kind contribution of EUR 168 000.

Due to the global nature of the participating industry partners, it is anticipated that some elements of the contributions will be non-EU/H2020 Associated Countries in-kind contributions.

The financial contribution from IMI2 JU is a maximum of EUR 4 500 000.

Applicant consortium

The applicant consortium will be selected on the basis of the submitted short proposals.

The applicant consortium is expected to address all the research objectives and to make key contributions to the defined deliverables in synergy with the industry consortium which will join the selected applicant consortium in preparation of the full proposal for stage 2.

This may require mobilising, as appropriate, the following expertise and resources:

- Expertise in using *in vivo* models of PD, and the capability to enable easy transfer of industry models to the applicant laboratories. This includes necessary animal facilities and handling experience.
- Expertise using *in vitro* models of PD, including access to models which exhibit a robust and well characterised disease phenotype with a strong link to the pathology in patient brains, i.e. protein aggregation. The applicant laboratories must have relevant cell culture facilities and strong know-how on the proposed model systems (primary cultures, organotypic brain slice cultures or iPSCs) regardless of whether the model system is already running in their laboratories or they will be transferred from an industry partner.
- The use of *in vitro* and/or *in vivo* PD models that involve introduction of seeding proteins to trigger disease processes may be an advantage.
- Expertise in the evaluation of key elements of mitochondrial function *in vitro*, including bioenergetics, ROS production, biogenesis, fission, fusion and mitophagy.
- Expertise in, and tools for, *in vitro/in vivo* imaging for the investigation of mitochondrial morphology and trafficking. This could include expression of mitochondrial-targeted fluorescent proteins in relevant cell populations.
- Know-how and tools for manipulation of mitochondrial function. For morphology this could be through the expression of proteins such as DRP1, mitofusin 2, OPA1 or Miro or other tools. Small molecules would also be helpful.
- Know-how and an innovative mind-set for the development of new tools and assays to study and quantitatively address mitochondrial dysfunction in *in vitro* and *in vivo* models of PD.
- Expertise in multi-scale mechanistic modelling of biochemical networks.
- Expertise in approaches to model mitochondrial ageing and/or trauma in *in vitro* models; expertise in the evaluation of the role and influence of the different cell populations affected by the disease: neurons and glia (astrocytes, oligodendrocytes and microglia).
- Expertise in communication, dissemination, project management and coordination of research activities.
- Applicants should indicate how they will strengthen the competitiveness and industrial leadership of Europe by, for example, engaging suitable SMEs. Thus, participation of SMEs with relevant know-how and standardised technologies and assays is strongly supported

Suggested architecture of the full proposal

The applicant consortium should submit a short proposal which includes their suggestions for creating a full proposal with an effective and simple architecture, taking into full consideration the deliverables, and the contributions and expertise of the industry consortium.

In the spirit of the partnership, and to reflect how IMI2 JU Call topics are built on identified scientific priorities agreed together with EFPIA beneficiaries/large industrial beneficiaries, these beneficiaries intend to significantly contribute to the programme leadership and project and financial management.

The final architecture of the full proposal will be defined by the participants in compliance with the IMI2 JU rules and with a view to the achievement of the project objectives. The allocation of a leading role within the consortium will be discussed in the course of the drafting of the full proposal to be submitted at stage 2. To

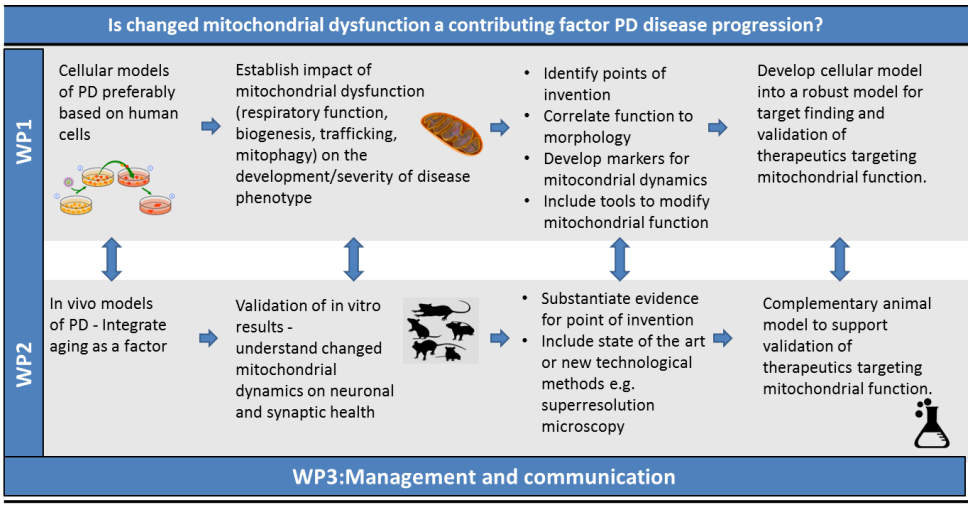
facilitate the formation of the final consortium, until the roles are formally appointed through the consortium agreement, the proposed project leader from among EFPIA beneficiaries/large industrial beneficiaries shall facilitate an efficient negotiation of project content and required agreements.

All beneficiaries are encouraged to discuss the project architecture and governance and the weighting of responsibilities and priorities therein.

A plan for aspects related to sustainability, facilitating continuation beyond the duration of the project should also be proposed.

The architecture outlined below for the full proposal is a suggestion. Different innovative project designs are welcome, if properly justified.

It is suggested to organise the work plan into three main themes, each corresponding to a specific work package (WP):



Work package 1 – Evaluation of mitochondrial dysfunction in cellular models of Parkinson's disease

- Identification of specific mitochondria dysfunctions (respiratory function, biogenesis, trafficking, fission, mitochondrial DNA maintenance, fusion or mitophagy) in established *in vitro* PD models which exhibit a robust and well characterised disease phenotype with a strong link to the pathology in the patient brains, i.e. ex. protein aggregation.
- Establishment of quantitative detection of the mitochondrial dysfunction endpoints and demonstration of robustness of the parameters. This could ideally include implementation of tools (proteins, reagents) modulating the relevant mitochondrial functions.
- Understanding the role of the mitochondrial dysfunction identified on disease phenotype progression/severity. Potentially, understand the contribution of mitochondrial damage due to misfolded proteins. The latter would include the establishment of relevant tools and cellular models exhibiting relevant manifestations of ageing.
- Identification and quantification of the relative contribution of key molecular drivers of the mitochondrial dysfunctions identified using data-driven, mechanistic computational modelling of mitochondria. Prediction of targets to ameliorate mitochondrial function *in vitro*.
- If relevant, transfer of model systems from industry partner/s to applicant consortium partner/s.
- As necessary, development of new robust tools and assays to study and quantitatively address mitochondrial dysfunction *in vitro*.
- In innovative organotypic brain slice models of PD, including those incorporating prion-like spreading of misfolded proteins, understand i) the impact of mitochondrial dysfunction on the development/severity of the disease phenotype; and ii) the reciprocal impact of intracellular protein misfolding on mitochondrial dysfunction. Assessment of the correlation between morphology and function should be included to ease later interpretation of morphological observations *in vivo*.

With these methods in hand, the goal is to provide a detailed characterisation of the contribution of mitochondrial dysfunctions to PD-related degeneration of the relevant cell types. Identification of the key molecular drivers of the dysfunctions identified is of particular interest. Tools modulating the abnormal mitochondrial parameters, such as fission or mitophagy, may provide the opportunity to identify mitochondrial targets for therapeutic intervention. Moreover, it would be advantageous to have the opportunity to understand the contribution of mitochondrial damage due to misfolded proteins, trauma and ageing to neurodegenerative disease progression and severity.

The industry contribution will include contributions of cellular models, tissue from animal models and protocols as well as the development of mitochondria dysfunction assays and quantitative detection of mitochondrial functional levels. Technologies to be contributed may include high content screening, bioenergetics assays and iPSC derived models.

The expected Applicant consortium contribution will include development of novel tools and models to assess the impact of ageing, trauma and misfolded proteins on the manifestation of mitochondrial dysfunction, as well as the development of additional novel mitochondrial dysfunction assays.

Work package 2 – Evaluation of mitochondrial dysfunction using *in vivo* models of Parkinson's disease

- Identification of specific mitochondria dysfunctions (respiratory function, biogenesis, trafficking, fission, fusion or mitophagy) in robust and well established *in vivo* PD models, e.g. *in vivo* seeding models. This would imply following the changes in mitochondrial function over the course of the development of the neuropathology to understand if a sub-acute time course could be identified, and then allow mitochondrial dysfunction to be tracked before and during the development of neurodegeneration.
- Establishment of quantitative detection of mitochondrial dysfunction endpoints and demonstration of robustness of the parameters. This could ideally include the development of ways to modify the parameters either genetically or pharmacologically.
- Understanding the role of the mitochondrial dysfunction identified on disease phenotype progression/severity.
- Identification of key molecular drivers of the mitochondrial dysfunctions identified.
- If relevant, transfer of model systems from EFPIA partners to Applicant consortium partners.
- If required, development of new, robust tools and assays to study and quantitatively address mitochondrial dysfunction *in vivo*. It could for example be methods for imaging of mitochondrial dynamics in mouse models.

The industry contribution will include the contribution of animal models of neurodegenerative diseases, with a focus on seeding models of disease, together with relevant protocols and the assessment of mitochondrial functional endpoints in these models.

The expected Applicant consortium contribution will include the development of tools and assays to quantitatively assess mitochondrial dysfunction endpoints *in vivo*, and implementing them to enable longitudinal of mitochondrial function in relevant models of diseases and correlation to disease phenotype and severity.

Work package 3 – Project and data management.

- Define work expectations of different work streams, deliverables, dates and activities and review progress regarding adherence to budget, timelines and quality (by all consortium members).
- Ensure legal and contractual management.
- Ensure the set-up of a joint governance structure (by all consortium member).
- Ensure appropriate communication/dissemination within the consortium and with the external scientific community and the public.
- Develop and manage communication via avweb portal and other social media tools with a repository of key documents.
- Quality assessment of documents.

- Define project interdependencies, stakeholders and risks.
- Ensure ethics management.

The industry contribution will include co-leading this work package, including management of legal, contractual, ethical and quality assessment aspects, and developing and executing a detailed communication and dissemination plan, all to be achieved in partnership with all remaining consortium members, who will also work together to define the governance structure and full work plan.

The expected Applicant consortium contribution will include co-leadership and input to all structures and activities needed for decision-making, monitoring and project management, and jointly develop the governance structure and full work plan.

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Topic 5: Support and coordination action for the projects in the neurodegeneration area of the Innovative Medicines Initiative

Topic details

Topic code	IMI2-2017-13-05
Action type	Coordination and Support Action (CSA)
Submission and evaluation process	2 stages

Specific challenges to be addressed

Dementia affects over 47 million people globally. As populations age, this figure is projected to increase to 75.6 million by 2030, and more than triple by 2050. The overall number of people living with dementia in European Union countries is expected to rise from 9.6 million in 2015 to nearly 15 million in 2035[143]. The disease places a huge and growing burden on health and social care systems as well as on the families and carers of those affected. Yet despite decades of research and large investments, there is still neither treatment nor cure for the disease and success in clinical trials remains elusive.

There are significant medical, scientific, ethical, regulatory, and operational issues around the question of what can be done to support biomedical research and health innovation for the delivery of the required diagnostics and disease-modifying treatments for Alzheimer's disease (AD) and other dementias.

After the G8 meeting in London in December 2013[144], a significant increase was observed in the number of initiatives focused on advancing the field of dementia research. While geographically diverse, these initiatives are mostly either of public-private nature with the aim to optimise pre-competitive collaboration and knowledge generation or large collaborative public efforts which deliver innovative results that would benefit from further translation into practice (see figure 1). The Innovative Medicines Initiative (IMI) projects 'European Medical Information Framework' (**EMIF -** http://www.emif.eu/), 'Organising mechanistic knowledge about neurodegenerative diseases for the improvement of drug development and therapy' (**AETIONOMY -** https://www.aetionomy.eu/en/vision.html) and 'European prevention of Alzheimer's dementia consortium' (**EPAD -** http://ep-ad.org/) stated their willingness for collaboration in March 2015, creating the IMI Alzheimer's Research platform[145]. After that, and in just the first three years of its activities, IMI2 JU implemented eight new projects in the area of neurodegeneration and more are in the pipeline. These initiatives have been launched either via the Strategic Governing Group Neurodegeneration (**SGG ND -** https://www.imi.europa.eu/about-imi/governance/strategic-governing-groups#strategic-governing-groups-collapsible-3), or as part of platforms such as the Remote assessment of disease and relapse (**RADAR -** https://www.radar-cns.org/ and http://ec.europa.eu/research/participants/portal/desktop/en/opportunities/h2020/topics/imi2-2017-12-01.html) and Big Data for Better Outcomes (**BD4BO -** http://bd4bo.eu/).

These diverse initiatives now cover the research and development (R&D) value chain from bench to bedside (see figure 1). Although several of these initiatives have started leveraging on one another, an operational coordination of the activities promoted by all these actors is missing, and despite the growing number of initiatives, there are no agreed metrics to show their value in advancing research and removing bottlenecks toward the delivery of innovative treatments to patients.

There is a constant need for strengthening the information flow and enhancing the exchange of experience on on-going and future European and international research and innovation activities concerning neurodegeneration, at IMI level and beyond, as well as for maintaining continuous dialogue between all stakeholder groups and initiatives to allow an evaluation on how the investment is impacting the area.

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[143] http://www.oecd-ilibrary.org/social-issues-migration-health/health-at-a-glance-europe-2016/dementia-prevalence_health_glance_eur-2016-20-en

[144] https://www.gov.uk/government/publications/g8-dementia-summit-global-action-against-dementia/g8-dementia-summit-global-action-against-dementia-11-december-2013

[145] http://www.imi.europa.eu/news-events/press-releases/innovative-medicines-initiative-alzheimers-disease-projects-launch-joint

Effective and efficient collaboration and coordination among the IMI/IMI2 JU portfolio of projects in the area of neurodegeneration and related national, European and global initiatives is the key success factor for the important public-private investment to achieve its full impact, as also highlighted at a recent meeting hosted in Brussels by the IMI2 JU[146].

It also is evident that projects share several areas of common interest (e.g. modelling and simulation, imaging) and have developed best practices that would be very useful for other ongoing and upcoming initiatives, but due to the silo-like structure of the individual initiatives, the opportunity for real and effective cross-fertilisation is limited and based on the 'good will' of enthusiastic individuals. Indeed this has been the case with the IMI Alzheimer's Research Platform, which links three projects which have some specific complementarities, however now the portfolio of IMI projects has grown significantly and it is much more diverse in scope and focus, creating the need for a more tailor-made and structured support structure.

Projects would also benefit from support (including access to learnings from other projects) towards the submission of results for regulatory and/or health-technology assessment (HTA) to ensure that important results can impact regulatory practice and the healthcare system in a timely manner. Often the data to support a regulatory/HTA submission are only fully available in the very final phase of the projects, or even after their official end, which may hamper their submission and subsequent follow up.

A significant challenge in collaboration is the burden required to develop agreements and good practices for sharing and reuse of data, biological tools (e.g. cell lines) and other materials, activities that are normally either not or only minimally resourced under individual initiatives and can be labour intensive and require expertise (e.g. legal, ethical) not always readily available for each project.

All projects face the challenge of sustainability of their results, and the lack of a source of advice and support in finding/choosing relevant solutions beyond the project lifetime. There is therefore a clear need for support to ensure that collaboration and coordination become intentional and structural to the portfolio of projects in the IMI strategic area of neurodegeneration, by providing the necessary resources and framework.

Last but not least, there would be a very high value in having a framework to facilitate collaboration and coordination of the many initiatives focused on neurodegeneration, in and beyond IMI, and to develop some metrics to show their value in advancing research and removing bottlenecks toward the delivery of innovative treatments to patients.

[146] http://www.imi.europa.eu/news-events/events/collaboration-alzheimers-disease-beyond

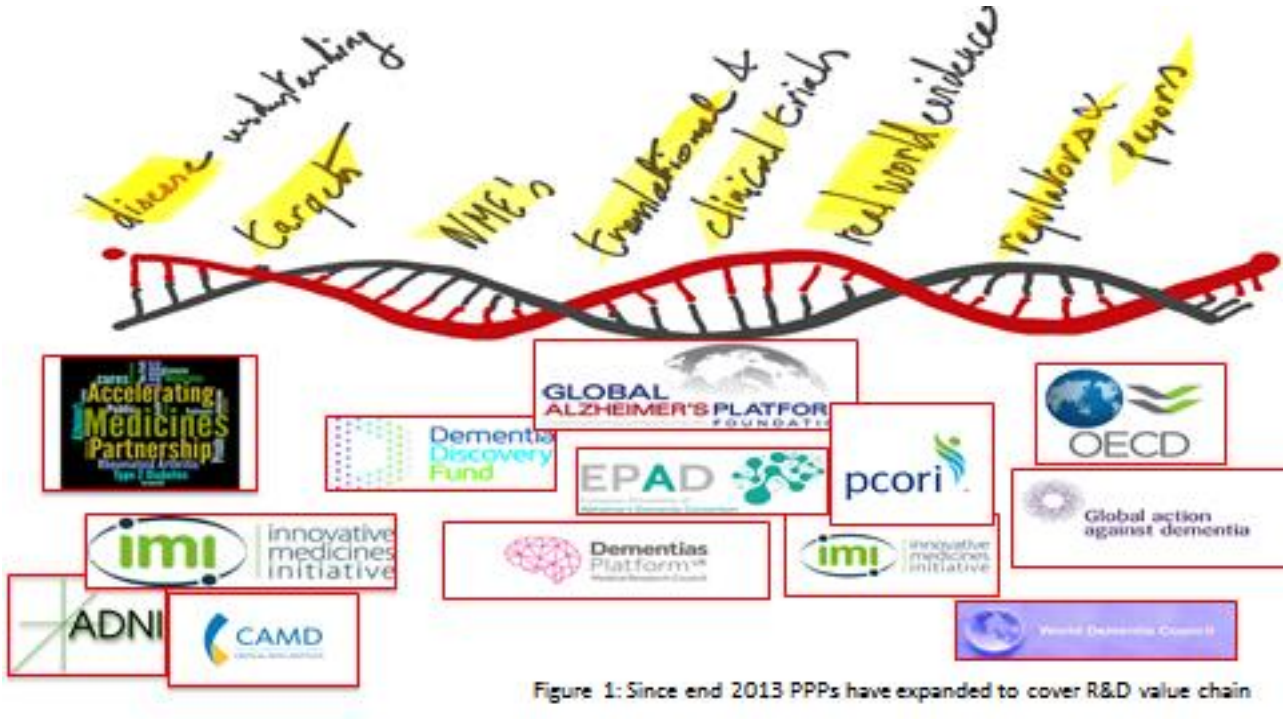

Figure 1: Since end 2013 PPPs have expanded to cover R&D value chain

JPND research

Human Brain Project

Scope

The overall scope of the coordination and support action is to provide the necessary overall framework and resources to achieve effective and efficient coordination and collaboration among the ongoing and future projects in the IMI strategic area of neurodegeneration. This will include:

- developing a framework to coordinate and support the operational alignment of the IMI neurodegeneration research portfolio, including a process to ensure that projects make appropriate use and can access existing infrastructures;
- providing expert advice and other support to facilitate sharing of and access to data, biological tools and other materials among projects;
- providing expert advice and support in preparing for regulatory and/or HTAs interactions (e.g. legal support, access to relevant expertise, funding to pay submission fees) to ensure that appropriate regulatory input is provided when most valuable and also beyond the timeframe of a project;
- establishing and managing workshops designed to share common approaches/best practices across IMI projects and beyond;

- developing a framework to coordinate and efficiently support the operational alignment of IMI-led actions with other relevant partnerships and initiatives at national, European and global levels (e.g. DPUK[147], DZNE[148], JPND[149], CAMD[150], NIH/AMP[151], WHO[152], GAP[153], World Dementia Council[154]);
- creating a platform to enable the mapping of partnerships and collaborative efforts that have supported over the past years research in Alzheimer's disease to capture their contributions and identify the remaining gaps and develop metrics and benchmarks to measure value, including socio-economic impact;
- developing outreach and engagement actions with other international/national/regional initiatives including patient organisations to promote and increase the value of trans-national and international research collaborations;
- communicating and disseminating joint activities and initiatives in the field of neurodegenerative diseases;
- seeking alignment and coordination on issues of common interest such as ethical, legal and social implications of clinical neurodegenerative disease (especially Alzheimer's disease) research, where several learnings are already available but disperse.

Expected key deliverables

- An operational platform to coordinate and support the activities of the IMI neurodegeneration projects, including new relevant IMI2 JU actions and international collaborations. Ensure that cross-project dependencies/synergies are operationally supported enabling actual delivery on them. Such platforms should be developed including consideration for self-sustainability beyond the funding of this action.
- Relevant support to enable timely and effective interaction with regulatory authorities and HTAs.
- A series of guidelines and good practices for the access and sharing of data, biological tools and other materials among projects, as well as a resource to facilitate the process.
- An advisory board and an up-to-date and dynamic catalogue of potential solutions for sustainability of project results.
- A series of workshops and relevant proceedings to share common approaches/best practices across IMI projects.
- Metrics and benchmarks to measure success.
- A public depository (to be self-sustainable after the end of the action) for protocols, deliverables, white papers, etc. produced by the action and by relevant IMI projects to insure their optimal dissemination to the wider scientific community.
- A relevant programme of outreach activities.
- Joint white papers to provide an aligned and educated perspective of all key stakeholders on key issues in the area of neurodegeneration research, including regulatory and HTA perspectives.
- A map of the partnerships and collaborative efforts that have supported over the past years research in Alzheimer's disease to capture their contributions and identify the remaining gaps.

Expected impact

The expected impact would be:

- enhancing impact of the individual projects by creating structural synergy and collaboration;

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[147] DPUK – D ementias Platform UK: https://www.dementiasplatform.uk/
[148] DZNE – Forschungszentrum für neurodegenerative Erkrankungen: http://www.dzne.de/home.html
[149] JPND – Neurodegenerative Disease Research: http://www.neurodegenerationresearch.eu/
[150] CAMD – Coalition Against Major Diseases: https://c-path.org/programs/camd/
[151] NIH/AMP – National Institutes of Health / Accelerating Medicines Partnership: https://www.nih.gov/research-training/accelerating-medicines-partnership-amp
[152] WHO – World Health Organization: http://www.who.int/en/
[153] GAP – Global Alzheimer's Platform: http://globalalzplatform.org/
[154] World Dementia Council: https://worlddementiacouncil.org/

- an enhanced visibility of IMI's significant public and private investment in the area of neurodegeneration; ensuring that the results of relevant IMI projects are developed optimally for the benefit of patients and health systems including strategies for sustainability and uptake;
- an optimisation of the impact of IMI projects' activities in neurodegeneration toward the achievement of the IMI2 JU Council Regulation objectives and in particular those aiming to:
    - increase the success rate in clinical trials of priority medicines identified by the World Health Organisation;
    - where possible, reduce the time to reach clinical proof of concept in medicine development, such as for cancer, immunological, respiratory, neurological and neurodegenerative diseases;
    - develop new therapies for diseases for which there is a high unmet need, such as Alzheimer's disease;
    - develop diagnostic and treatment biomarkers for diseases clearly linked to clinical relevance and approved by regulators.
- an analysis of the scientific results and achievements delivered by various partnerships in neurodegeneration so far, and an understanding of their translation into more efficient and faster development of new medical products in this area and of critical factors for a successful translation;
- an overview and a framework to inform future collaborative research globally and facilitate the translation to innovative treatments for patients.SMEs can be of great value to IMI projects and, inter-alia, strengthen the competitiveness and industrial leadership of Europe. Their involvement might offer a complementary perspective to industry and the academia, and help deliver the long-term impact of the project. For these reasons, applicants should consider engaging SMEs throughout the proposal.

Potential synergies with other consortia

Applicants should take into consideration, while preparing their short proposal, relevant national, European (including research projects, research infrastructure initiatives, projects and joint actions funded through the Programme for the Union's action in the field of health (2014-2020) such as EUnetHTA Joint Action 3), and non-European initiatives. Synergies and complementarities should be considered in order to incorporate past achievements, available data and lessons learnt where possible, thus avoiding unnecessary overlap and duplication of efforts and funding.

The action will have to build strong links with the portfolio of IMI projects in the area of neurodegeneration[155] to ensure that the activities are in good synergy with those potentially already ongoing within individual initiatives.

It is also expected to leverage and build on efforts and lessons learnt from other initiatives and organisations at national, European and global levels (e.g. DPUK, DZNE, NIH/AMP, JPND, CAMD, WHO, GAP, World Dementia Council, among others).

Finally the action should build synergies and complementarities with other relevant coordination activities in IMI and H2020:

CSA HCO-10-2018 topic in the SC1 work programme that was recently pre-published (https://www.horizon2020.services/calls/)

IMI2 DO-IT (http://bd4bo.eu/index.php/portfolio/do-it/)

IMI2 ADAPT-SMART (http://adaptsmart.eu/)

Industry consortium

The industry consortium is composed of the following EFPIA companies:

- Janssen (lead)

[155] http://www.imi.europa.eu/projects-results/project-factsheets

- Eli Lilly
- Roche
- Takeda
- Sanofi

In addition, the industry consortium includes the following IMI2 JU Associated Partner:

- Parkinson's UK

The industry consortium will contribute the following expertise and assets:
- contribution to project and meeting management;
- measurement and analytical tools;
- regulatory affairs;
- data privacy law and related legal aspects;
- medical affairs and healthcare communication;
- contribution to website management;
- data/knowledge management, repository of knowledge;
- experts time in different relevant scientific areas.

The industry consortium will also provide their expertise in the conduct and follow up of management tasks to secure this overall programme platform (including any IT system to help the work of the platform and the communication between partners) as well as provide the necessary resources for programme management, e.g. from defining strategic priorities to the organisation of meetings / workshops / teleconferences.

Indicative duration of the action

The indicative duration of the action is 36 months.

Indicative budget

The indicative industry in-kind contribution is EUR 1 200 000.

This contribution comprises an indicative EFPIA in-kind contribution of EUR 1 056 000 and an indicative IMI2 JU Associated Partner in kind contribution of EUR 144 000.

Due to the global nature of the participating industry partners, it is anticipated that some elements of the contributions will be non-EU/H2020 Associated Countries in-kind contributions.

The financial contribution from IMI2 JU is a maximum of EUR 1 200 000.

Applicant consortium

The applicant consortium will be selected on the basis of the submitted short proposal.

The applicant consortium is expected to address all the objectives and make key contributions to the defined deliverables in synergy with the industry consortium which will join the selected applicant consortium in preparation of the full proposal for stage 2. This may require mobilising expertise in:

- project management and coordination;
- organisation and logistics of workshops and international meetings;
- knowledge and expertise in legal, ethics and data privacy aspects of sensitive, personal-level data management and biological tools management , including intellectual property (IP) considerations;
- data hosting and maintenance;
- regulatory science;

- health economics;
- medical/scientific writing;
- outreach and communication targeted for the different stakeholders and public at large;
- development of effective communication tools including websites and social media, platforms to create awareness of the programme and disseminate findings;
- expertise to create training and communication materials based on results of the programme.
- Additionally, applicants should indicate how their proposal will strengthen the competitiveness and industrial leadership of Europe by, for example, engaging suitable SMEs.

Suggested architecture of the full proposal

The applicant consortium should submit a short proposal which includes their suggestions for creating a full proposal architecture, taking into consideration the industry participation including their contributions and expertise.

In the spirit of the partnership, and to reflect how IMI2 JU call topics are built on identified scientific priorities agreed together with EFPIA beneficiaries/large industrial beneficiaries, these beneficiaries intend to significantly contribute to the programme and project leadership as well as project financial management.

The final architecture of the full proposal will be defined by the participants in compliance with the IMI2 JU rules and with a view to the achievement of the project objectives. The allocation of a leading role within the consortium will be discussed in the course of the drafting of the full proposal to be submitted at stage 2. To facilitate the formation of the final consortium, until the roles are formally appointed through the consortium agreement, the proposed project leader from among EFPIA beneficiaries/large industrial beneficiaries shall facilitate an efficient negotiation of project content and required agreements. All beneficiaries are encouraged to discuss the project architecture and governance and the weighting of responsibilities and priorities therein.

The architecture outlined below for the full proposal is a suggestion. Different innovative project designs are welcome, if properly justified.

Work package 1 – Platform for coordination and collaboration (including sustainability)

This work package will focus on:

- set up and maintenance of a website including relevant webpages tailor made for the different stakeholders, with special attention to patients;
- implementation of the operational platform to coordinate and support the activities of the IMI neurodegeneration projects and international collaborations. Ensure that cross-project dependencies/synergies are operationally supported, enabling actual delivery on them;
- running of workshops and production of relevant proceedings to share common approaches/best practices across IMI projects;
- establishment and maintenance of a public depository for protocols, deliverables, white papers, etc. produced by the action and by the IMI projects to ensure their optimal dissemination to the wider scientific community;
- establishment of an advisory board and set up and maintenance of an up-to-date and dynamic catalogue of potential solutions for sustainability of project results.

Industry consortium contribution:

- strong programme management skills;
- expertise in value-based healthcare, real-world evidence (RWE);
- network with leaders of IMI projects (BD4BO and others);
- governmental affairs and public policy.

Expected applicant consortium contribution:

- strong programme management skills, including road mapping tools;
- experience in coordinating projects of similar complexity/ scale/ sustainability;
- expertise in initiatives related to health outcomes and value-based healthcare.

Work package 2 – Support for regulatory and/or HTA interactions

This work package will focus on:

- establishment of a resource (including all relevant support and best practices) to enable timely and effective interaction with regulatory authorities and HTAs.

Industry consortium and applicant consortium contribution:

The types of resources will be similar from both sides of the consortium since we anticipate there will be a need for a variety of specific roles, including information/knowledge management skills, project management, business analysis, healthcare systems expertise, expertise in outcome definition, measurement tools, etc. for standardisation of methodologies across diseases, Health Economics and Outcomes Research (HEOR) expertise, knowledge about health funding models and various coordinating activities.

Work package 3 – Communication, dissemination and outreach

This work package will focus on:

- alignment of dissemination and communication strategies across the projects;
- joint white papers to provide an aligned and educated perspective of all key stakeholders on key issues in the area of neurodegeneration research, including regulatory and HTA perspectives;
- creation of material for internal and external communication;
- setting up of social media platforms and inventory of communication;
- support publication and other dissemination activities of IMI neurodegeneration projects' findings, including through training activities;
- a relevant programme of outreach activities.

Work package 4 – Mapping and impact analysis

This work package will focus on:

- analysis of the socio-economic impact of the IMI portfolio in neurodegeneration including in EU countries with different economic status;
- implementation and maintenance of a map of the partnerships and collaborative efforts that have over the past years supported research in Alzheimer's disease to capture their contributions and identify the remaining gaps.

Industry consortium contribution:

- communication (communication strategies, media, social media);
- website set up and management;
- science writers;
- events organisation;
- stakeholder engagement expertise at national and EU level with all relevant stakeholders, including but not limited to HTAs, regulators, payers, patients, medical societies, and providers;
- organisation of multi-stakeholder meetings, workshops or forums to foster stakeholder engagement.

Expected applicant consortium contribution:

- communication strategies and tools;

- health economics impact analysis;
- development/adaptation of tools, models and methods for monitoring and measuring impact
- science writers;
- creating communication materials;
- creating training materials and delivering trainings;
- appropriate resource and expertise from HTAs, regulators, payers, providers, patient organisations, medical societies and other appropriate stakeholders;
- organisation of multi-stakeholder meetings, workshops or forums to foster stakeholder engagement, especially with additional healthcare systems' stakeholders beyond the consortium.

Work package 5 – Standards and guidance for the use and reuse, access, and sharing of human samples, biological tools and data

This work package will focus on:

- implementation of a resource, including expert advice, sharing of learnings, writing of guidelines and other support, to facilitate sharing of and access to data, biological tools and other materials among projects;
- development of minimum standards (templates) for ICFs for clinical studies and other research studies;
- development of guidance documents to facilitate the work with the generated ICF templates, including their terminology and application, and provision of guidance on related aspects of data privacy laws and regulations (e.g. concept of anonymisation) for IMI/IMI2 projects and non-IMI related addressees;
- development of standards, training and educational guidance on aspects of data privacy laws and regulations, data protection mechanisms and consequences of their application for IMI/IMI2 projects as well as non-IMI related addressees (e.g. patients).

Industry consortium contribution:

- legal expertise in connection with data privacy and related legal matters.

Expected applicant consortium contribution:

- knowledge and expertise in legal, ethical and data privacy aspects of sensitive, personal- level data management from several angles: 1) from an academic perspective as well as from the perspective of groups of academic research organisations; 2) from the perspective of healthcare SMEs, in particular biobanking SMEs or health-IT companies; 3) from the perspective of national and international supervisory/regulatory authorities dealing with data protection in the healthcare context on a regular basis (ideally one participant from each interest groups);
- understanding of patient and physician concerns such as in patient organisations and medical associations;
- ethical considerations as relevant in ethics committees.

Topic 6 : A sustainable European induced pluripotent stem cell platform

Topic details

Topic code	IMI2-2017-13-06
Action type	Research and Innovation Action (RIA)
Submission and evaluation process	2 stages

Specific challenges to be addressed

Since their introduction in 2007 [1] human inducible pluripotent stem cells (human iPSCs) have been rapidly and broadly incorporated into research to understand their potential for disease and are a very powerful tool for translational research. This has substantiated interest to incorporate this resource into drug discovery pipelines, prospective patient stratification, recruitment for clinical trials and post-clinical drug assessment of safety issues following rare event reporting. In addition, human iPSCs can potentially provide unlimited autologous cells for therapy and therefore hold great promise for regenerative medicine [2]. The evolution of these applications depends on facilitated and unfettered access to a standardised and well characterised iPSC resource to help avoid dissemination of unauthenticated or substandard cell lines to the research community.

iPSCs are cells derived from somatic cells of the body and reprogrammed by introducing specific transcription factors in order to re-establish pluripotency [1] [3] iPSCs can be differentiated into the three germ layers, the mesoderm, endoderm, and ectoderm, which form the organs during embryonic development. The continued optimisation of protocols now allows producing large quantities of differentiated, human cells in a reliable and reproducible manner. Human iPSCs are established from patients with the promise to capture in cell models specific human disease phenotypes which cannot be revealed in animal models, and to allow studying these in a human context. With the advent of gene editing technologies like the -Clustered Regularly Interspaced Short Palindromic Repeats/associated (Crispr/Cas)-system, specific mutations relevant for a certain disease are being introduced into human iPSCs to again model specific phenotypes and compare with the isogenic parental line. While these efforts will foreseeably improve the consistency with which new cell lines will be developed they will not necessarily foster the standardised and scalable distribution of pre-established or new lines to the wider hiPSC research community.

The rising demand by academia and industry has instigated a number of large scale public and privately funded disease and/or population oriented human iPSC banking initiatives in the US, Japan and UK [4]. However, ‘several issues should be overcome to advance the field quickly. First, it will be critical to network iPSC resources around the world to create an iPSC library of both normal and diseased cells using a common quality standard. Second, a systematic approach to develop an iPSC library in conjunction with a clinical database, tissue bank and genome-wide association study (GWAS) would be most useful. Third, further development of efficient and standardised *in vitro* iPSC differentiation protocols into many more cell types is essential for progress in the field. Forth, continuous effort to recapitulate phenotypes of late-onset diseases *in vitro*, at least partly, would be critical to extend their applications. Lastly, reducing complexity of culture methods will be important to make the system more easily applicable to high throughput screening’ (cited from [5]). Several efforts are ongoing worldwide to address these matters, but still in a highly fragmented way.

In Europe, the **EBiSC** project (https://www.ebisc.org/) funded by the Innovative Medicines Initiative Joint Undertaking (IMI JU) has demonstrated the feasibility and challenges of coordinating existing organisational capacities across Europe to fast track the establishment of a centralised network and facilities to access a standardised resource of established hiPSC lines and data. EBiSC has established a unique European-based iPSC repository and has delivered harmonised and publically accessible Standard Operations Procedures (SOPs) for tissue procurement, bio-sample tracking, iPSC expansion, cryopreservation, qualification and distribution to the research community. These were implemented to create a quality managed foundational collection of lines and associated data made available for distribution [6].

The critical challenge addressed by this topic is to build on these important infrastructure, capabilities and knowledge to create a fully sustainable European hiPSCs distribution platform with worldwide reach.

Need and opportunity for public-private collaborative research

The complexity of setting up the logistics and infrastructure to secure continued housing, support, and distribution of an iPSC collection in general, and to secure availability of iPSC assets established within public private partnerships including EBiSC plus associated information, needs to be addressed by a public-private-partnership involving a variety of stakeholders as it cannot be accomplished by an individual research group or company and will require a strong collaborative effort to be successful.

Only a collaborative endeavour bringing together academic laboratories and small and medium-sized enterprises (SMEs) with access to and ownership of necessary hiPSC lines, technologies and logistics, and EFPIA partners that closely interact with the hiPSC banking entity, advising and supporting the further expansion of the hiPSC repository, will ensure that therapeutically relevant areas will continue to be addressed and that consistency and quality of preparations meet the needs of drug development campaigns. EFPIA will provide critical feedback on quality and differentiation potentials of iPSC lines and precursor cells provided by the bank facility. Information and data obtained from certain iPSC lines will be added to the banking entity's information management to disseminate knowledge on disease understanding and facilitate development of screening models to be used in drug development.

This engagement of EFPIA will uniquely enable to capitalise on existing capabilities and knowledge to reach the ultimate goal of self-sustainability of the hiPSC banking entity.

Scope

A European iPSC repository that operates on a non-for-profit basis and allows researchers access to a continuously expanding number of well-characterised and fully quality controlled (QC) iPSC lines with clarified access information is mandatory to fuel basic research and development and drug development campaigns. Although previous activities have prepared the ground for such a banking entity, significant aspects listed below remain to be addressed.

The overall objective of the action generated from this topic is therefore to establish a fully self-sustainable European human iPSC banking facility, that has to be operational within the first three months of the action by seamlessly building on and incorporating existing cell lines, knowledge and infrastructure established within former European-wide initiatives (e.g. EBiSC). The bank has to be able from the start to handle and deliver a minimum of approximately 500 quality-controlled, disease-relevant (in particular for neurodegeneration, Alzheimer's disease and other tauopathies, Parkinson's disease, cardiovascular disease, safety, diabetes, and auto-immune and selected monogenic diseases), research-grade iPSC lines, with integrated data and cell services which will be further built on as part of the research and technology work of the action. The ultimate goal is to transform significant pre-existing European banking infrastructures into a sustainable resource for European research and development. The applicant consortium at stage 2 will have to document in the full proposal that this can be achieved efficiently and in the expected timelines as a first go/no go milestone.

Thus the following has to be accomplished:

- transfer of assets established in previous large standardised European collections with linked data and SOPs to the new bank where appropriate technology is in place to handle cells and guarantee seamless continuation of banking and distribution operations;
- secure continued housing, expansion and QC of the existing iPSC collection generated in such previous initiatives;
- ensure a continued and efficient distribution infrastructure with a European and worldwide reach within the first half year after start of the funding period;
- provide long-term storage capacity for up to 10,000 iPSC-vials with a minimum of 3 replicates each under liquid nitrogen gas phase and automated handling. Capability for long-term storage of biosamples;
- banking entity and mirror bank certified to operate according to ISO 9001 standards;
- secure and further optimise established QC-procedures and SOPs by incorporating newly established and accepted methodologies that become available during this undertaking;
- ensure a continued Information Management System to monitor the iPSC line status and keep track of iPSC line data, complement available information related to existing lines (e.g. mutation confirmation and exome sequencing), and incorporate relevant information including clinical records to new entries;
- develop the technology and establish efficient and reproducible protocols for parallelised production of bulk quantities of iPSCs and/or precursor cells in response to drug developers or future costumer

demands. Within the project, the cells will be subject to analysis at the participating EFPIA companies in order to establish disease models and screening assays;

- further expand the repository by incorporating additional iPSC lines (patient-derived and gene-edited) that:
  - will be established by the consortium during the lifetime of the action. It is expected that the consortium will support cell line commissioning projects including gene editing technologies, like the Crispr/Cas-system, that are requested by the consortium (public and industry partners) as well as relevant members of the external research community to fuel the repository with iPSC lines relevant for research of benefit to patients and community. Such requests will be reviewed by the consortium board consisting of the EFPIA group and the public partners and approved if the deliverables are of relevance for the scientific community and pharmaceutical industry,
  - will become available in other publicly-funded consortia with a focus on iPSC technology. It is expected that the consortium will actively reach out to other cell line owners or publicly-funded consortia in the process of establishing iPSC lines to discuss and secure integration of new lines into the repository. In addition, reaching out to other biobanking entities to complement offering to the scientific community and/or avoid duplication of work is encouraged,
  - are already available in the scientific community;
- ensure ethical and legal matters are in place for incorporation of iPSC lines into a public accessible bank to allow freedom to operate for research and development purposes;
- establish clinical networks that allow access to well-described patient biosamples for the establishment of iPSC lines and, where the ethical and legal ground is established, allow fast access to samples relevant for academic and industrial research;
- implement all necessary activities to ensure that by the end of the action the repository is fully self-sustainable.

Expected key deliverables

The key overall deliverable of the action is the establishment of a self-sustainable iPSC banking facility that fully leverages significant pre-existing infrastructures and know-how. Key deliverables and goals are:

- establish within the first three months of the action a European standardised and at-scale human iPSC banking facility by successfully transferring existing iPSC lines, knowledge and infrastructure established within relevant pre-existing European wide banking (e.g. EBiSC) initiatives to this collaboration;
- establish and maintain a cell line housing facility with the capacity to handle existing lines and be extendable to incorporate new ones;
- establish and maintain a mirror cell line bank at capacity;
- apply and continuously improve SOPs to achieve highest standards in iPSC technology. QC criteria will be defined for characterisation of newly established, expanded, and differentiated iPSC lines;
- establish and maintain a European and worldwide distribution infrastructure;
- throughout the runtime of the project, the consortium is expected to strive for self-sustainability of the iPSC repository. Therefore, applicants need to formulate in their proposals, deliverables, and milestones related to a business plan that details the operations after the funding period. The repository will have to be fully self-sustainable by the end of the action;
- ensure a continued iPSC-line Laboratory Information Management System;
- establish efficient and reproducible protocols/SOPs to produce bulk quantities of precursor cells that can be differentiated into cells from all three germ layers;
- further expand the repository by incorporating additional iPSC lines:
  - reach out to governmental funding bodies and the scientific community to discuss and secure integration of new iPSC lines into the repository,
  - to support the cell line commissioning projects requested and partially funded by the EFPIA group or the scientific community,
  - establish clinical networks that will facilitate the establishment of iPSC lines from well described patients of relevance to the EFPIA partners and the scientific community,

- reach out to and network with other biobanking entities to capitalise on synergisms;

- support the iPSC banking entity with regard to ethical and legal aspects to secure freedom to operate and unlimited use of iPSC lines in research and developmental processes.

It is expected that applicants address all the above objectives in the Short proposal (within the available duration and budget) and demonstrate a relevant strategy for achieving them, through partnership with the industry consortium.

Expected impact

iPSC research and banking continues to be fragmented across a broad spectrum of institutions in Europe, and lacks sufficient scale to support the current and anticipated demands of academic and industrial research and development. In Europe, the IMI JU project EBiSC[156] has prepared the ground for establishment of a self-sustaining banking entity by creating a QC'ed iPSC repository of currently several hundred iPSC lines with ethical and legal standards in place. These lines represent important disease areas among them neurodegenerative diseases (Alzheimer's disease, other tauopathies like frontotemporal dementia, and Parkinson's disease), diabetes, neuropathic pain, and cardiovascular diseases that the participating drug developers are actively researching to provide novel treatments to patients.

Availability of iPSC lines derived from patients, as well as of a broad spectrum of lines from healthy donors of different ages, standardised according to how they were made and their *in vitro* behaviour, and the possibility of linking a gene code to cell line phenotype reflective of the disease, will enable the research community to refine original clinical diagnosis into one based on disease stratification and thereby design more precise experiments to discover novel pathogenic pathways, drug targets and new medicines. This is expected to significantly advance research and development activities across Europe by accelerating the progress of understanding certain disease aetiologies, as well as finding potential cures, thereby strengthening European competitiveness.

This European iPSC repository will be uniquely positioned to serve as the central European iPSC repository hub to accelerate and facilitate European research and development activities. Therefore, the consortium will have to continuously monitor the sale of cells produced by the banking entity, and its trend in order to develop in the runtime of the project a plan as to how to transform the repository into a self-sustainable business. Ultimately this will secure that the public and private investment will establish a resource that beyond the runtime of the project continues to support and fuel European basic research as well as drug development campaigns in pharma companies.

Applicants should indicate how their proposal will strengthen the competitiveness and industrial leadership of Europe by, for example, engaging suitable SMEs.

Potential synergies with existing consortia

Applicants should take into consideration, while preparing their short proposal, relevant national, European (both research projects as well as research infrastructure initiatives), and non-European initiatives. Synergies and complementarities should be considered in order to incorporate past achievements, available data and lessons learnt where possible, thus avoiding unnecessary overlap and duplication of efforts and funding.

More specifically, the applicants have to demonstrate awareness of the most current iPSC landscape across Europe, to be able to reach out to relevant programs to be incorporated or supported in order to ensure that the new banking initiative fully leverages previous significant public and private investments and infrastructures. In Europe, a unique repository of hiPSCells has been created by the IMI JU **EBiSC** project (https://www.ebisc.org/). Also, the IMI JU StemBANCC collection of iPSC lines has become part of the repository during the lifetime of the previous IMI JU EBiSC project. Other examples of IMI/IMI2 JU research collaborations with a strong iPSC focus are **ADAPTED** (https://www.imi-adapted.eu/), **PHAGO** (http://www.phago.eu/), or **IMPRiND** (https://www.imprind.org/). Additional actions related to or employing iPSC technology will be created in response to the topic launched in the IMI2 JU 12th Call for proposals. Coordination with the European Strategy Forum on Research Infrastructures (**ESFRI**, https://ec.europa.eu/research/infrastructures/index_en.cfm?pg=esfri) is to be considered.

[156] https://www.ebisc.org/

Other European wide or national initiatives are:

- the **Human Induced Pluripotent Stem Cell Initiative** (http://www.hipsci.org/);
- the **Human Pluripotent Stem Cell Registry** (https://hpscreg.eu/);
- national initiatives such as **El Banco de Líneas Celulares de Barcelona** (https://www.cmrb.eu/banco-lineas-celulares/que_es.html);
- the **UK Stem Cell Bank** (http://www.nibsc.org/ukstemcellbank);
- the **German Stem Cell Network** (http://www.gscn.org/en/HOME.aspx);
- the **Stem Cell Network NRW** (http://www.stemcells.nrw.de);
- several projects within the funding measures related to the Action Plan 'Individualized Medicine', e.g. 'Innovative stem cell technologies for personalized medicine' (https://gesundheitsforschung-bmbf.de/de/innovative-stammzelltechnologien.php).

Furthermore, it will be mandatory for the applicants to monitor collaborative activities across the European R&D landscape to make the infrastructure available to governmentally-funded scientific projects in the iPSC area.

Industry consortium

The industry consortium is composed of the following EFPIA companies:

- Janssen (lead)
- Bayer
- Eli Lilly
- Lundbeck
- Novo Nordisk
- UCB
- Pfizer
- Takeda
- Fujifilm
- Servier

The industry consortium will contribute the following expertise and assets:

- facilitation of transfer of capabilities and knowledge from EBiSC to reach the ultimate goal of self-sustainability of the iPSC banking entity;
- test of the consistency and quality of iPSC lines as well as preparations of bulk quantities of precursor cell preparations;
- interaction to ensure banking of iPSC lines which will aid in disease understanding and development of screening models to be used in R&D;
- establishment of robust and reliable iPSC disease models and screening assays demonstrating proof of concept for the use of iPSCs for disease and pharmaceutical research;
- support for research activities focusing on:
    - differentiating and analysing iPSC-derived neurons. This will include efforts to shorten the time to achieve electrophysiologically mature neurons with the goal to replace rodent, primary neuron preparations. A focus will be on the analysis of iPSC lines derived from patients suffering from neurodegenerative diseases or gene-edited to carry certain risk genes or mutations that are linked to neurodegeneration,
    - producing iPSC-derived cardiomyocytes and analysing effects of e.g. pro-arrhythmogenic mutations or pharmacological treatments on the electrophysiological characteristics of cells,

- producing and analysing iPSC-derived pancreatic cells to study the underlying mechanisms of diabetes and beta cell dysfunction,
- producing iPSC-derived cells from auto-immune and selected monogenic diseases, as well as defined disease phenotypes with known genetic background,
- they will further support the adaptation of the iPSC technology to automated screening technology by employing precursor cells provided by the consortium.

Indicative duration of the action

The indicative duration of the action is 36 months.

Indicative budget

The indicative EFPIA in-kind contribution is EUR 4 000 000.

Due to the global nature of the participating industry partners, it is anticipated that some elements of the contributions will be non-EU/H2020 Associated Countries in-kind contributions.

The financial contribution from IMI2 JU is a maximum of EUR 4 600 000.

Applicant consortium

The applicant consortium will be selected on the basis of the submitted short proposals.

The applicant consortium, which should include SMEs with relevant expertise and experience in iPSC line derivation and QC, is expected to address all the research objectives and make key contributions to the defined deliverables in synergy with the industry consortium which will join the selected applicant consortium in preparation of the full proposal for stage 2. SMEs can be of great benefit to IMI2 JU projects and, inter-alia strengthen the competitiveness and industrial leadership of Europe. Their involvement might offer a complementary perspective to industry and the academia, and help deliver the long-term impact of the project. For these reasons, applicants should consider engaging SMEs throughout the proposal.

Significant experience, knowledge and know-how in logistics and infrastructure to operate a European-wide cell line repository, including a mirror iPSC bank according to ISO 9001 standards are prerequisites. In addition, this may require mobilising, as appropriate, the following expertise on:

- storage and distribution of cells;
- the procurement of biosamples for iPSC generation;
- long-term storage of biosamples to build a clinically relevant source of primary material and allow re-derivation of iPSC lines;
- reprogramming of human-derived cells using state-to-the-art technologies;
- gene-editing approaches to generate isogenic pairs of iPSC cells;
- comprehensive QC of established iPSC lines;
- knowledge in long term storage of biosamples;
- knowledge in reprogramming of somatic cells to generate pluripotent stem cells;
- state-of-the-art gene editing technology (Crispr/Cas);
- handling, expansion and QC of iPSC lines;
- technology and know-how to handle large-scale iPSC cultures as well as the ability to produce bulk quantities of precursor cells or cells with a mature phenotype for distribution;
- database management to monitor status of the cell bank and maintain and amend information available to each cell line;
- knowledge in establishing and maintaining an online portal for purchasing iPSC lines;
- experience in ethical and legal affairs related to the derivation and use of iPSCs;

- business or economics experience to transform the iPSC repository into a self-sustainable business;
- scientific / industrial expertise to guide the expansion of the iPSC repository in therapeutically relevant disease areas;
- general project management (ability to consistently set and achieve milestones on time and within budget; managing varying interests of multiple stakeholders) and professional communication expertise (expertise in communication tools and systems for project management purposes).

It may also require mobilising, as appropriate, the following resources:

- a pre-existing, European-wide, quality-controlled foundational collection of iPS cell lines representing specific disease backgrounds with a focus on neurodegeneration (Alzheimer's disease and related tauopathies, Parkinson's disease), diabetes and cardiovascular diseases and healthy controls including associated data made available for distribution;
- IT capabilities to maintain and support the laboratory infrastructure management system that hosts iPSC-related information and to make the catalogue and the associated data accessible via the internet;
- capacities to allow online ordering and payment of iPSC lines;
- support on legal and ethical matters;
- commercial / industrial application of iPSC-derived assets generated within such a consortium including large-scale production of iPSCs or cell derivatives for medium-/high- throughput screenings;
- access to logistics and infrastructure to operate a cell-line repository including a mirror iPSC bank;
- a fully automated storage system allowing handling of cell lines in the gas phase of liquid nitrogen for long-term storage purposes.

An established distribution pipeline to deliver cell lines to customers and being operational at the outset of the action.

Suggested architecture of the full proposal

The applicant consortium should submit a short proposal which includes their suggestions for creating a full proposal architecture, taking into consideration the industry contributions and expertise provided below.

In the spirit of the partnership, and to reflect how IMI2 JU call topics are built on identified scientific priorities agreed together with EFPIA beneficiaries/large industrial beneficiaries, these beneficiaries intend to significantly contribute to the programme and project leadership as well as project financial management. The final architecture of the full proposal will be defined by the participants in compliance with the IMI2 JU rules and with a view to the achievement of the project objectives. The allocation of a leading role within the consortium will be discussed in the course of the drafting of the full proposal to be submitted at stage 2. To facilitate the formation of the final consortium, until the roles are formally appointed through the consortium agreement, the proposed project leader from among EFPIA beneficiaries/large industrial beneficiaries shall facilitate an efficient negotiation of project content and required agreements. All beneficiaries are encouraged to discuss the project architecture and governance and the weighting of responsibilities and priorities therein.

In summary, the work plan should enable activities aiming at:

- managing the existing iPSC collection, including storage, QC, banking, expansion, and distribution of cell lines;
- further expanding the iPSC collection by providing technology to derive and establish iPSC lines, reaching out to the European scientific community and consortia (being operational or in the process of becoming operational) to make use of synergies and support logistics necessary to secure continued access to iPSC-related assets generated within these consortia;
- continuous refinement and optimisation of protocols, QC criteria, and SOPs supporting the operation of the banking activities;

- provide gene editing capabilities to generate iPSCs with specific relevant mutations and creation of reporter cell lines;
- develop the technology and establish efficient and reproducible protocols to produce bulk quantities of iPSCs, precursor cells or cells with a mature phenotype to fuel industrial screening campaigns. Definition of QC criteria to deliver consistent quality of expanded or differentiated iPSCs.

The call topic specifically aims to achieve sustainability as well as further development and maturation of a European-based iPSC repository that includes assets that have been developed by previous public-private iPSC collaborations. One of the key outcomes of this action will be to build on existing assets, and, in the runtime of this project, outline a business plan that will allow the future European iPSC banking entity to continue operations beyond the runtime of the project to support the European research & development activities. The scientific challenges that will be addressed in the action to be generated by this topic will further add technology, differentiation protocols, and iPSC lines, including data attached to individual lines to increase the value of the repository.

The bank has to be self-sustainable by end of the action.

The below architecture for the full proposal is a suggestion; different innovative project designs are welcome, if properly justified.

Work package 1 – Project management

This work package will focus on:

- grant administration;
- communication (within the consortium and with relevant external collaborators);
- dissemination of scientific results and research data;
- sustainability plan facilitating continuation beyond the duration of the action.

Industry contribution
Co-leadership and the overall coordination of the project.
Expected applicant consortium contribution
All of the above. Preparation of a business plan to run iPSC banking operations in a self-sustainable fashion after funding period to achieve sustainability and continue to serve the European research community with access to iPSC technology.

Work package 2

This work package will focus on:

- continuation, expansion, and further optimisation of banking operations. This includes European and worldwide reach of sales to reach self-sustainability;
- incorporation of iPSC assets developed in previous public-private partnerships;
- refinement of existing SOPs for QC of cell lines;
- facilitate integration of appropriate new iPSC lines generated in other scientific projects (IMI2 JU as well as non-IMI2 JU projects);
- establishing connection to clinical networks, biobanks, and other iPSC banking entities, allowing timely access to patient/donor fibroblasts attached to full donor consent, free distribution for research and development, and freedom to operate.

Industry contribution
Supporting above activities. Supporting iPSC line establishment by advising which cell lines are of interest.
Expected applicant consortium contribution
Banking operations as outlined above.

Work package 3

This work package will focus on:

- establishment of bulk production capabilities / SOPs for generating iPSCs or precursor cells to fuel screening campaigns;
- definition of QC criteria for expanded and differentiated iPSCs.

Industry contribution
Advice and identification of cell lines to be subjected to bulk production.
Expected applicant consortium contribution
- Development of protocols for bulk production of iPSC lines and precursor cell lines for all three germ layers.
- Adaptation of differentiation and maintenance protocols.

Work package 4

This work package will focus on:

- proof of concept experiments across industry consortium partners using cell lines produced in work packages 2 and 3 and focusing on the following areas:
    - neurosciences:
        - explore accelerated maturation and/or aging in iPSC-derived neurons with electrophysiological relevant readouts (multi electrode assays or patch clamp analysis),
        - co-cultivation with astrocytes and / or microglia to explore effect of clinically relevant mutations (Alzheimer's disease, Parkinson's disease) on neuronal function,
        - establish brain organoid cultures suitable for high-content imaging analysis,
        - establish *in vitro* or xenograft models for pathology seeding relating to Alzheimer's disease or Parkinson's disease;
    - diabetes:
        - explore technologies to support the adaptation of established protocols for large-scale production,
        - molecular and functional analysis of pancreatic progenitors as well as mature pancreatic cells,
    - cardiovascular diseases:
        - establish standardised differentiation and maturation protocols for derivation of cardiovascular, iPSC-derived cells (including cardiomyocytes, endothelial cells, smooth muscle cells etc.),
        - establish functional assays and readouts to analyse compound/drug efficacy in iPSC-derived cardiovascular cells; harmonise readouts with FDA-approved activities (e.g. in CiPA),
        - assess ability of iPSC-derived cardiovascular cells for patient stratification (drug efficacy depending on common genetic variation),
        - analyse proteomics/metabolomics in iPSC-derived CV cells;
    - gene editing using e.g. Crispr/Cas system to establish disease-relevant iPSC lines;
    - reprogramming of patient derived somatic cells using state-of-the-art technologies (non- integrating technologies).

Industry contribution
- Support in differentiating and analysing iPSC-derived neurons. This will include efforts to shorten the time to achieve electrophysiologically mature neurons with the goal to replace rodent, primary neuron preparations. A focus will be on the analysis of iPSC lines derived from patients suffering from neurodegenerative diseases or gene-edited to carry certain risk genes or mutations that are linked to neurodegeneration.
- Support in producing iPSC-derived cardiovascular cells and analysing effects of e.g. arrhythmogenic mutations or pharmacological treatments on the (electrophysiological) characteristics of cells.

- Support in differentiating and analysing iPSC-derived pancreatic cells to study the underlying mechanisms of diabetes. This includes molecular as well as functional assays. Focus will be on establishing large-scale cell culture capabilities as well as competences in gene editing in collaboration with the relevant partners.
- The industry group will further support the adaptation of the iPSC technology to automated screening technology by employing precursor cells provided by the consortium.

Expected applicant consortium contribution

Already established and QC'ed hiPSCell lines for all the above disease areas; support of industry consortium activities by producing iPS-cells and / or precursor cells at quantity to allow screening and other R&D activities. Knowledge and capabilities in gene-editing and reprogramming of somatic cells to derive iPSCs.

Reference

[1] Takahashi K, Tanabe K, Ohnuki M, Narita M, Ichisaka T, Tomoda K, Yamanaka S. Induction of pluripotent stem cells from adult human fibroblasts by defined factors. Cell. 2007;131(5):861-72.

[2] Lu X, Zhao T. Clinical therapy using iPSCs: hopes and challenges. Genomics Proteomics Bioinformatics. 2013 Oct;11(5):294-8. doi: 10.1016/j.gpb.2013.09.002. Epub 2013 Sep 21.

[3] Phillips BW and Crook JM. Pluripotent human stem cells: A novel tool in drug discovery. BioDrugs. 2010 Apr 1;24(2):99-108.

[4] McKernan R, Watt FM. What is the point of large-scale collections of human induced pluripotent stem cells? Nat Biotechnol. 2013 Oct;31(10):875-7.

[5] Hankowski KE, Hamazaki T, Umezawa A, Terada N. Induced pluripotent stem cells as a next-generation biomedical interface. Lab Invest. 2011 Jul;91(7):972-7.

[6] De Sousa PA, Stee R, Wachter E, Bruce K, King J, Hoeve M et al. Rapid establishment of the European Bank for induced Pluripotent Stem Cells (EBiSC) - the Hot Start experience. Stem Cell Res. 2017 Apr;20:105-114.

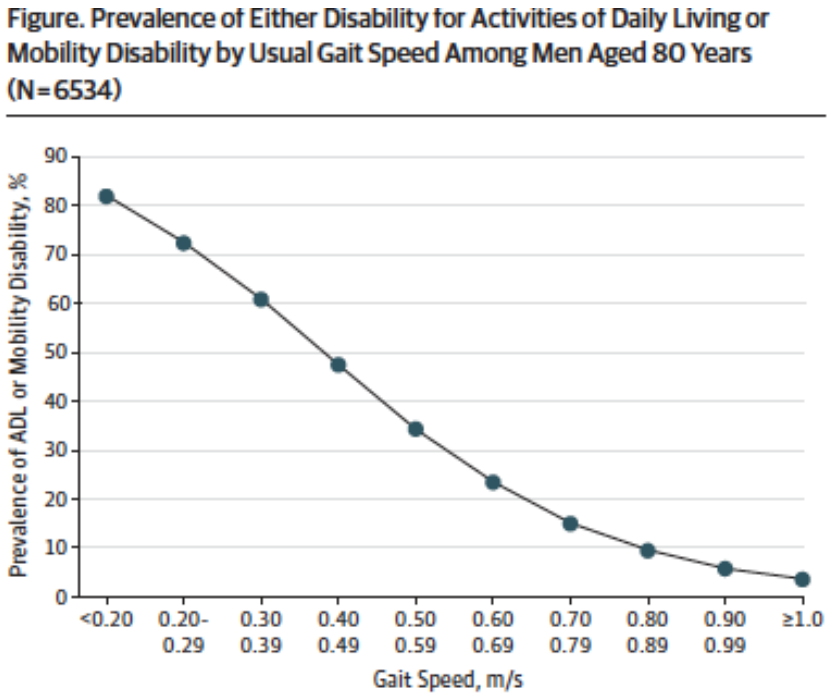
Topic 7: Linking digital assessment of mobility to clinical endpoints to support regulatory acceptance and clinical practice

Topic details

Topic code	IMI2-2017-13-07
Action type	Research and Innovation Action (RIA)
Submission and evaluation process	2 stages

Specific challenges to be addressed

Loss of mobility is a growing unmet medical need, driven by chronic illness and frailty in the elderly and by injury in the young (Figure 1). Loss of mobility is a key morbid effect of diseases of various organ systems, including chronic obstructive pulmonary disease (COPD), heart failure, multiple sclerosis, neurodegenerative diseases, etc. New therapeutic approaches target restoration of function and mobility in patients with degenerative diseases, acute injuries, and age-related disabilities, such as muscle anabolic drugs, cartilage regeneration approaches, and other therapies targeting the musculoskeletal system.



However, current primary endpoints that measure mobility are either based on patient reported outcome or performance testing, both of which have significant shortcomings. Emerging digital technologies can now measure many aspects of mobility in the 'real world' on a long-term basis. Preliminary results suggest that those technologies have the potential to fundamentally change clinical trials across the development pathway and eventually, medical practice, much the way that Holter monitoring revolutionised the assessment of cardiac arrhythmias decades ago. However, full acceptance and integration of digital mobility assessment into clinical trials and utilisation as primary or secondary endpoint requires rigorous validation and linkage to clinically relevant 'hard' endpoints, such as death, disability, falls, or other complications.

The proposed project will validate digital mobility assessment, focusing on 'real-world walking speed' (RWS) as a primary endpoint for a more sensitive, objective measurement in patients' native environment over longer periods of time and with greater granularity than is currently feasible. RWS is chosen because it requires shorter periods of observation (and lower patient compliance) than 24-hour step counts, fall detection, etc.; and because observed gait speed is already linked to mortality, falls, and hospitalisations in multiple populations. Emerging data suggest that RWS can be detected using digital inertial sensors, with or without global positioning (GPS) capability, using centre of mass (i.e. belt or skin-worn) devices. Secondary outcomes of additional digital mobility assessment (walking parameters including total time, step counts, gait characteristics, gait cadence, estimated energy expenditure of physical activity, etc.) should be assessed as

well. More background information is available in the following list of publications: [1][2][3][4][5][6][7][8][9][10][11][12][13][14][15][16][17][18][19][20][21][22][23]0.

Need and opportunity for public-private collaborative research

Most pharmaceutical companies are grappling with how to apply emerging digital technology to clinical development programmes and post-marketing authorisation assessment of drug efficacy or safety. However, for digital endpoints to truly transform research, regulatory recognition is required. In addition, expertise from pharmaceutical companies and partners with expertise in digital data collection and analysis, use of wearable devices, 'big data' handling and analysis, and data privacy will be required. This expertise is not prevalent among EFPIA partners and will require engagement of companies that are already experienced in the field of continuous monitoring. We believe that physical activity monitoring using inertial sensors is the most advanced technology relevant to pharmaceutical development, and that RWS is the most advanced endpoint that could be validated within a 2-3 year period. By achieving surrogate endpoint qualification, this will harmonise the approach to digital endpoint development, create a powerful regulatory precedent, drive innovation in both pharmaceutical and technology markets, and potentially transform clinical practice relating to frail, elderly, and chronically ill populations. Such an approach can only be done by multiple companies, including small and medium-sized enterprises (SMEs) working with governmental, academic, and patient advocacy groups, to create a harmonised approach.

Scope

The purpose of the action is to measure in three chronically ill or frail populations:

- as a primary outcome, real world walking speed (RWS);
- as secondary outcomes, additional digital mobility assessment (step counts, time walking, gait characteristics, time sitting/standing/walking, cadence, estimated energy expenditure of physical activity, etc.) to be collected and compared (or combined) with RWS to identify outcomes of maximum predictive power[157].

The action will demonstrate that RWS or one of the other gait parameters predicts relevant medical outcomes (falls, injurious falls, hospitalisations, loss of activities of daily living [ADLs], death), and achieve regulatory recognition of RWS as a surrogate endpoint independently of underlying disease diagnosis. To do this, regulatory submission for qualification opinion is anticipated.

The applicant will decide on the three populations to study, and demonstrate that the participants in the applicant consortium have adequate access to such populations for the purposes of this action (e.g. heart failure, multiple sclerosis, Parkinson's disease, COPD, frailty/sarcopenia, post-hip fracture).

The project is envisioned as having two parts:

Part A, a 1-2 year technical validation part that will develop an algorithm for quantifying RWS in the relevant population of slow walkers; and **Part B**, a 3-year validation programme that will demonstrate that the algorithm predicts relevant clinical outcomes (e.g. falls, injurious falls, hospitalisations, disability, and mortality).
The successful applicant consortium will include academic centres and private entities that have expertise in development of digital sensor solutions. The consortium will identify and engage existing longitudinal cohort studies in three relevant populations and support application of digital sensors to the participants with ongoing follow-up for key regulatory endpoints (death, falls, hospitalisations, institutionalisation, loss of ADLs over several years). Linkage of these novel digital methods and readouts to these clinically relevant outcomes is mandatory for uptake of these methods by the medical community, regulators, and payers.

The specific aims are to develop and apply algorithms that will subsequently become publicly available, so that the validated endpoint consists of the measurement algorithm, the analytic method, and the range of normal or abnormal results that predicts relevant clinical outcomes. This construct should support a variety of wearable hardware and inertial sensor types, and provide design-control characteristics that allow any manufacturer to receive medical device approval by demonstrating comparable performance characteristics to the tested device (i.e. a CE mark and reimbursement approval in the EU or 510(k) process in the USA). For the purposes of the action, however, the successful consortium will only be asked to demonstrate the validity of a single device-algorithm pairing; expansion to subsequent devices will be outside the scope of this action.

[157] http://www.oarsijournal.com/article/S1063-4584(17)30253-4/abstract

For simplification, the following parameters are recommended, although arguments in favour of alternative approaches may be made.

- Devices that capture data from the body centre of mass or lower extremities are preferred to those positioned at the wrist.
- Preference will be given to medical-grade devices over consumer-grade devices, although consumer-grade devices that have adequate documentation of performance characteristics can meet clinical data quality standards, and make raw data available (x, y, z accelerations) in addition to summary outcomes provided by the device firmware, are acceptable.
- The technical specifications of the device – hertz rate of signal acquisition, battery life, presence or absence of feedback to subject – should be described.
- The device must be able to accurately record wear-time to get an estimate of compliance.
- The algorithm to be developed should include step detection, gait speed assessment, and other relevant parameters; any information relating to detection thresholds should be described.
- The method for capturing reference data, i.e. ground truth and other annotations, for Part A (algorithm development) should be stated (e.g. GaitRite, observed 6 minute walk, 400 m walk, etc.). Preference will be given to applications which provide granular and real-world relevant information.
- The development population must be clinically relevant (i.e. gait speed 0.4-1.0 m/s, not only healthy volunteers, although early testing in healthy adults is acceptable). Consideration may be given to remote (internet-based) recruitment and/or follow-up of subjects, with appropriate consent and tracking procedures.
- Once a beta-version of the algorithm-device pair is available, human factor and wearability testing should be performed in a relevant population. Wearability should be tested for at least 7 days, and reliability of measurements when data are collected for fewer days should be assessed to determine the minimal number of days of wear that would constitute adequate collection. In addition, usability testing by patient interview should be conducted.

In addition, important confounding variables should be considered. A key decision is how much gait asymmetry will be acceptable in the study populations, and how much the algorithm can accept without excessive error. In general, the goal of the project is to validate low gait speed and/or inadequate walking as a whole-body function, rather than gait asymmetry due to arthritis, neurological deficits (stroke, etc.) that affect primarily one limb or joint. However, these are not always clear distinctions, and some overlap is expected, especially in elderly populations. In addition, environmental factors limit physical activity to different extents in different geographical locations, depending also on the patient's medical condition (ability to go outside, etc.). Applicants should describe their approach to these confounding variables, including but not limited to:

a. postural stability
b. balance
c. dizziness
d. symmetry of gait
e. medications
f. comorbid conditions
g. weather/external conditions/location.

The regulatory approach, already under discussion with the European Medicines Agency (EMA), will be analogous to multi-indication approval for drugs, where demonstration of efficacy in two or more populations can lead to a broad approval for an indication. Engagement of EMA and the U.S. Food and Drug Administration (FDA) by the successful consortium will be a key aspect of the plan. The aim is to gain approval of mobility assessment as an endpoint, not to certify any particular device. The output of the consortium will be validation of RWS or other endpoints with cut-offs for predicting increased risk of the clinical endpoints for 1) surrogate primary or secondary endpoints for clinical trials carried out under oversight of EMA, FDA, or other competent authorities; 2) recognition by payers and health technology assessment (HTA) bodies of the validity of RWS and application of cut-offs to support pharmacological or other interventions; 3) clinical decision-making outside of clinical trials.

Sustainability of the project beyond the 5-year period should also be considered. Additional work to validate, promulgate, and expand on the use of the algorithm(s) developed during the project period may be considered for separate funding.

Expected key deliverables

The key deliverables for the project include:

Part A

- Development of the appropriate algorithm and one (or more) digital mobility assessment devices to use in the subsequent validation studies. Assessment of algorithm precision and accuracy should be carried out using a reference method (wheel-based speed assessment, video step analysis, GaitRite analysis, shoe insole systems, etc.) in a relevant population of slow walkers (gait speed approximately 0.4-1.0 m/s). The algorithm must be able to function across the relevant range of gait speeds associated with poor clinical outcomes (e.g. 0.4-1.0 m/s). The sensitivity and specificity of the algorithm to detect bouts of purposeful walking should be assessed.
- Human factors and wearability testing in a relevant population.
- Consensus on data collection, database structure, data quality, and analysis algorithms that will be publicly available and can function across multiple devices.
- Ongoing collaboration with and submission of algorithm validation for mobility assessment to health authorities and HTA bodies.

Part B

- Identification of ongoing longitudinal cohort studies in relevant populations, in which the outcome measures are being or can be collected.
- Digital mobility and clinical outcome assessment over 2-3 years in each of three populations (for example, COPD, heart failure, multiple sclerosis, neurodegenerative diseases, sarcopenia/frailty, hip fracture recovery, etc.). The choice of populations is up to the applicant, but applications will be judged in part on the detail and quality of the population cohorts selected. Sufficient detail should be provided about each cohort to demonstrate that there is a stable population, effective follow-up, and adequate data collection. Applicants must be mindful that it is their responsibility to demonstrate in their proposals that clinical sites chosen are able and willing to participate.
- Define the duration and frequency of digital gait assessment needed (e.g. one week every six months?) to successfully predict the endpoints.
- Analysis of the predictive capacity and thresholds for increased risk of clinical outcomes (falls, hospitalisations, loss of ADLs, death) in multiple populations. Definition of what constitutes a meaningful change (e.g. responder definition or minimum clinically relevant difference) in gait parameters in each population studied (e.g. is 0.1 m/s the smallest difference that represents a meaningful change in how the patient feels, functions or survives)?
- Meta-analysis of mobility across populations as a predictor of adverse clinical outcomes. Does RWS or a secondary endpoint predict outcomes equally across all three populations? Are meaningful differences of the same magnitude? What is the minimal device wear time that gives a stable estimate of each predictive parameter?
- Submission of data to health authorities and HTA bodies for consideration as a surrogate endpoint for clinical trials, and for payer recognition of the endpoint for clinical use, respectively.

For guidance regarding timing, it is suggested that years 1-2 (Part A) may consist of algorithm and device selection, algorithm validation, development of clinical protocols and consent forms, coordination with clinical study sites, etc. Years 3-4 may be focused on validating data collection; year 5 on data analysis, and regulatory and HTA submission. Applicants are free to modify this suggestion as they think best. It is recognised that HA and HTA review and feedback will probably continue after the end of the project, and results exploitation will be part of the planning in year 5. As RWS is already in use with pilot data in multiple populations, and several pharmaceutical companies have already initiated discussions with EMA and FDA, the goal of full surrogate endpoint validation should be realistic.

Expected impact

The mission of IMI is to improve health by speeding development of, and patient access to, innovative medicines, particularly in areas of high unmet medical or social need. As the fastest-growing population in Europe is that of people over 80 years of age, and many previously fatal illnesses have been converted into chronic diseases, mobility disability is going to continue to grow in the 21st century. The first step in treating loss of mobility and preventing disability is detecting it effectively, with methods that do not require highly complex, hospital-based solutions. By making mobility assessment feasible, and indeed an integral part of medical care, the consortium could enable development of novel solutions (pharmacological, digital, nutritional, exercise-based) to a major public health problem – the increasing prevalence of mobility disability due to the aging of the population and chronic diseases. The digital assessment of mobility is such a method, and has the potential to revolutionise the care of frail populations and of the development of drugs to treat them.

Successful demonstration that digitally-detected low mobility predicts relevant clinical outcomes will have major impact on drug development and clinical care of the target populations. We anticipate that many additional projects will emerge if the output of the proposed action is successful, for example, demonstration of RWS predictive power in additional populations; further studies required for surrogate endpoint recognition; applications to clinical settings in various national health care system contexts, etc.

Applicants should also indicate how they will strengthen the competitiveness and industrial leadership of Europe by, for example, engaging suitable SMEs.

Potential synergies with existing consortia

Applicants should take into consideration, while preparing their short proposal, relevant national, European (both research projects as well as research infrastructure initiatives), and non-European initiatives. Synergies and complementarities should be considered in order to incorporate past achievements, available data and lessons learnt where possible, thus avoiding unnecessary overlap and duplication of efforts and funding.

Applicants should consider any relevant related projects from IMI, FP7, Horizon 2020 and other relevant initiatives outside the EU. For the collaboration with HTA bodies, interaction with EUnetHTA Joint Action 3 (European network for Health Technology Assessment - http://www.eunethta.eu/) should be considered.

Because the project does not focus on a single clinical disease, there is great potential for synergy with existing IMI projects in:

- COPD **(PRO-Active)** (http://www.imi.europa.eu/projects-results/project-factsheets/pro-active)
- multiple sclerosis **RADAR-CNS** (www.radar-cns.org)
- age-related sarcopenia **SPRINTT** (www.mysprintt.eu).

Conversely, there is potential synergy with other IMI projects that focus on digital medicines (e.g. **EMIF** - www.emif.eu , **eTRIKS** - www.etriks.org , **EHR4CR** - www.ehr4cr.eu), especially in regard to learnings about data management, privacy, transfer, and analysis; and capture of clinical outcomes. Finally, consideration should be given to collaborating with non-IMI projects, such as the Clinical Trials Tranformation Initiative (**CTTI**) project 'Developing Novel Endpoints Generated by Mobile Technology for Use in Clinical Trials' (https://www.ctti-clinicaltrials.org/projects/novel-endpoints). Such agreements would enhance the ability of various types of digital data to be captured, analysed, and shared with greater efficiency, and would be an additional boon to the field.

Industry Consortium

The industry consortium is composed of the following EFPIA partners:

- Novartis (lead)
- Amgen
- AstraZeneca
- Bayer
- Grünenthal
- Merck KGa
- Pfizer

- Roche
- Sanofi
- Takeda
- Teva
- Microsoft
- ERT
- ICON

EFPIA participants are already working with actimetry in their own clinical trials, and are working on analysis and measurement algorithms to various extents. This project will utilise this expertise through close collaboration with EFPIA participants. EFPIA participants will also help select a Scientific Advisory Board that will meet regularly throughout the study. EFPIA members may also offer in-kind contributions of expertise and analysis capacity based on their internal research experience with digital devices in general and mobility assessment in particular. Technology companies are expected to bring additional and greater expertise in the data handling and analysis aspects.

Indicative duration of the action

The indicative duration of the action is 60 months.

Future project expansion

Potential applicants must be aware that the Innovative Medicines Initiative 2 (IMI2) Joint Undertaking may, if exceptionally needed, publish at a later stage another Call for proposals restricted to the consortium already selected under this topic, in order to enhance and progress their results and achievements by extending their duration and funding. The consortium will be entitled to open to other beneficiaries as they see fit.

Specific areas of activity may include additional meta-analyses across the study populations; longer follow-up beyond the initial study period; secondary data analyses for additional endpoints; exploratory analyses of subpopulations, etc. Additional activities for further publication of the results, dissemination of the algorithm, and application to additional digital devices may also be in scope for sustainability.

Indicative budget

The indicative EFPIA in-kind contribution is EUR 24 700 000.

Due to the global nature of the participating industry partners it is anticipated that some elements of the contributions will be non-EU in-kind contribution.

The financial contribution from IMI2 JU is a maximum of EUR 25 500 000.

Applicant Consortium

The applicant consortium will be selected on the basis of the submitted short proposals.

The applicant consortium is expected to address all the research objectives and make key contributions to the defined deliverables in synergy with the industry consortium. Relevant technology companies, in particular SMEs, should be part of the successful consortium, along with academic medical centres or other organisations that have access to ongoing longitudinal cohort studies of the patient populations of interest (geriatrics, heart failure, COPD, multiple sclerosis, Parkinson Disease, or other populations with high event rates for mortality, serious morbidity/complications, and falls). Expertise on complex data management and analysis and specifically in validation of technology-related medical tools are also required. It is imperative that at least one technology company with expertise in wearable technologies for activity monitoring be part of all applicant consortia. Experience with medical device registration is also an advantage. It is envisioned that regulatory and HTA bodies will be engaged in an advisory capacity, rather than as consortium members. Patient advocacy groups should be included in the consortium and be in the work packages as appropriate.

Suggested architecture of the full proposal

The applicant consortium should submit a short proposal which includes their suggestions for creating a full proposal architecture, taking into consideration the industry contributions and expertise provided below.

The final architecture of the full proposal will be defined by the participants in compliance with the IMI2 JU rules and with a view to the achievement of the project objectives.

In the spirit of the partnership, and to reflect how IMI2 JU call topics are built on identified scientific priorities agreed together with EFPIA beneficiaries/large industrial beneficiaries, these beneficiaries intend to significantly contribute to the programme and project leadership as well as project financial management. The final architecture of the full proposal will be defined by the participants in compliance with the IMI2 JU rules and with a view to the achievement of the project objectives. The allocation of a leading role within the consortium will be discussed in the course of the drafting of the full proposal to be submitted at stage 2. To facilitate the formation of the final consortium, until the roles are formally appointed through the consortium agreement, the proposed project leader from among EFPIA beneficiaries/large industrial beneficiaries shall facilitate an efficient negotiation of project content and required agreements. All beneficiaries are encouraged to discuss the project architecture and governance and the weighting of responsibilities and priorities therein.

The below architecture for the full proposal is a suggestion; different innovative project designs are welcome, if properly justified.

The consortium is expected to have a strategy on the translation of the relevant project outputs into regulatory, clinical and healthcare practice. A plan for interactions with regulatory agencies/health technology assessment bodies with relevant milestones and resources allocated should be proposed to ensure this (e.g. qualification advice on the proposed methods for novel methodologies for drug development, qualification opinion).

A plan for aspects related to sustainability, facilitating continuation beyond the duration of the project should also be proposed. For example, if the project is successful, how will dissemination of the results to support use in clinical practice be proposed?

Work package 1 – Project management and oversight

This work package will address the strategy, management, and implementation of the project. Work package (WP) 1 will create regular meetings and interaction between sub-groups and teams, to coordinate and follow up on the work effort. This WP will also be responsible for post-project result sustainability and exploitation planning.

Industry contribution

- Support for project management, including planning, budgeting, follow up and tracking, and consolidation of work package reports to IMI. Project risk management and comprehensive communication and dissemination of its progress and its milestones are important additional elements of EFPIA contribution. In-kind contribution of legal support as feasible for intellectual property (IP) discussions.

Expected applicant consortium contribution:

- Providing detailed follow up and tracking, via regular work package reports, early report of any unexpected organisational or structural issue or delay with respect to the project deployment and intermediate objectives. This WP will also organise a Scientific Advisory Board (SAB) and a Data Monitoring Committee (DMC) (if needed) to review and support the studies and give advice to the project. The WP should also engage with patient support groups and ensure patient input to the development and validation process.
- In addition, this WP will ensure that IP of participants is respected and that dissemination of results is not prevented by IP disputes. Primary legal support will be from the applicant coordinator's institution, with input from the EFPIA lead. The applicants are reminded to familiarise themselves with IMI2 JU IP rules applicable both to pre-existing IP needed for the project, and to IP to be developed during the programme.

Work package 2 – Algorithm development and technical validation

Consortium partners will collaborate to select a digital activity detection device, develop or obtain an algorithm for step detection, purposeful walking detection, and walking speed measurement, and pursue technical validation against a reference method.

Industry contribution

- The industry partners will work closely with the consortium to assist in the steps above, and provide research expertise and in-kind contributions to support data capture, analysis, and interpretation.

Expected applicant consortium contribution

- Should include a strong technology company participant that is capable of: carrying out the technical validation procedures and providing the raw digital data; identify a patient population of slow walkers in whom the initial validation can be carried out; develop the study protocols for initial algorithm development (method development) and subsequent initial method validation. Human factor and wearability/usability testing as described above should be included in the development plan. This will be the bulk of Part A of the project.

Work package 3 – Database development and data management

The consortium will develop and host the clinical and technical database to support the project and provide access to all consortium members.

Industry contribution

- Advice and oversight based on member companies' expertise with database development and function, including privacy assurance and data anonymisation experience. Additional contributions may be supported after discussion between industry and applicant participants.

Expected applicant consortium contribution:

- Server hosting, database development and maintenance; creation of processes for data security, privacy, and transfer; provision of data anonymisation procedures when necessary; definition of data standards that can be used for capture of raw and processed data from a range of inertial sensor types and sensor positioning.

Work package 4 – Validation of RWS vs. clinical outcomes and definition and validation of RWS/mobility clinical endpoints

The consortium will jointly identify at least three (3) clinical populations to study; identify the existing longitudinal cohort studies that are available to the consortium to carry out Part B of the study; and develop the protocol for Part B.

Industry contribution

- Making fully available the member companies' expertise in clinical study initiation and conduct, providing oversight over the study management, the accomplishment of overall objectives. EFPIA members will also support study monitoring and participate in data interpretation.

Expected applicant consortium contribution

- Coordinate with existing longitudinal cohort studies to incorporate the digital device into their procedures; agree on a common set of procedures, endpoints, and analytical approaches; develop the data structures and transfer specifications to support digital data analysis; create the appropriate database structures for Part B; develop endpoint definitions and their measures of meaningful change; lead the analysis of the data and report the results in collaboration with WP 6.

Work package 5 – Regulatory, HTA, and payer consensus over operational definitions

The consortium partners will jointly contribute to the overall evaluation of evidence and results from WP 2 and WP 4. This WP will engage with EMA and FDA, as well as with relevant HTA bodies, to develop the administrative and regulatory pathways for digital mobility analysis in parallel with the development of the data to support submissions. The consortium will engage with EMA on a regular basis. As noted earlier, the scope of these discussions is about the endpoint validation, not specific instrument (device) approval.

Industry contribution

- Planning, hosting and organising workshop(s) with regulators and payers, contributing to discussion of available evidence (including unpublished data), literature analysis, publication support, co-authoring of reviews and white paper(s).

Expected applicant consortium contribution

- Participate and actively contribute to constructive discussion with regulators and payers to promote and achieve consensus over operational definitions. (Co)-author reviews and white paper(s).

Work package 6 – Statistical analysis, evaluation of results, and data availability

The consortium partners will collaboratively review the trial results in order to draw the necessary clinical and regulatory conclusions. This WP will also be responsible for creating the project databases, including those which will become publicly available at the conclusion of the project. The WP will also support regulatory review for a qualification opinion, as required.

Industry contribution

- Planning, hosting and organising workshop(s) with regulators; providing regulatory affairs expertise to the consortium; contributing to results discussion via its experts (including biostatisticians); providing technical support (translations, etc.); (co-) authoring of reviews and white paper(s).

Expected applicant consortium contribution

- Analyse the data and collaborate with EFPIA sponsors on data interpretation and publication. Contribute to constructive discussion with regulators to achieve scientific and regulatory agreement over the interpretation of study results. Co-author primary papers, reviews, and white paper(s). Support consolidation of the scientific consensus necessary to achieve project aims.

Work package 7 – Stakeholder information and results dissemination

The consortium partners will contribute over the 5-year project duration to drive public awareness of the project, including presentation to stakeholders and media as appropriate. In collaboration with WP 6, this WP will develop methods for external researchers to access project results at the end of the project period.

The successful applicant is encouraged to take a leading role early on in the project and engage with the scientific community and make data, standards, and software (including underlying raw measurements, source code, APIs etc.) openly accessible using FAIR (findable, accessable, interoperable, reusable) principles. Since in this case the data can be easily anonymised there should be no privacy concerns to prevent an open innovation approach.
In this way, the project would benefit from the rapid developments in the data science community by encouraging other groups to explore the data and develop alternative analysis approaches; contribute to establishing technical interoperability standards in the field; and educate the data science community about the specific technical and regulatory requirements for digital biomarkers.

Industry contribution

- Logistics and organisational support; contribution of EFPIA experts as appropriate; providing technical support (translations, etc.); this will include a dedicated website and organisation of milestone workshops for stakeholders (and the general public as appropriate).

Expected applicant consortium contribution

- Provide the scientific and medical content for building, consolidating and updating information about digital mobility assessments over the project duration; provide personal and collegial contribution to the dissemination programme implementation; support publication of papers in peer reviewed scientific journals.

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Topic 8: Human tumour microenvironment immunoprofiling

Topic details

Topic code	IMI2-2017-13-08
Action type	Research and Innovation Action (RIA)
Submission and evaluation process	2 stages

Specific challenges to be addressed

Despite the initial clinical success of cancer immunotherapy with the advent of checkpoint inhibitors and other immune modulating agents, most patients still do not experience a deep, durable and satisfactory (e.g. with limited side effects) response. Numerous trials are currently ongoing exploring combinations of checkpoint inhibitors with established therapies to increase the response rate. Experts in the field are, however, discussing whether all these trials follow a sound scientific rationale. An improved knowledge on the molecular and cellular composition of the tumour microenvironment and better understanding of the mechanisms by which the immune system and tumours interact will contribute to more informed decisions on combination therapies and help with developing interventions that would enable better management of the disease and even its cure. Though much has been discovered about the nature of tumour-host interactions, the basic understanding of how the mechanisms and the different types of immune cells involved in the anti-tumour immune response interact with each other and with tumour cells, and how they can be monitored and pharmacologically manipulated to better control disease remains somewhat elusive.

To improve therapy, the understanding of the tumour microenvironment needs to evolve. Firstly, the understanding of **tumour/host interaction on the cellular and molecular level in the absence of therapeutic intervention** needs to improve. Both individual tumours and individual hosts are heterogeneous with respect to the quality and degree of immunity. Understanding the cellular and molecular nature of the tumour microenvironment will (i) help us characterise the ability of a patient's immune system to mount an anti-tumour attack and (ii) provide ideas which pharmacological interventions may support or activate the immune cells to attack the tumour cells.

Secondly and in close alignment with the previous paragraph, one needs to understand **how current therapeutic approaches affect the host/tumour interaction** to **have a baseline** from which to improve the current therapeutic paradigm. Such data could be used to further improve currently available treatments or to develop new potential therapeutic strategies.

A multi-modal approach to assess both the tumour and the host is recommended. Recently developed models and systems allow for large information-rich data sets to be created that can be mined to gain insights for the development of therapeutic interventions. Furthermore, access to informatics and machine-learning tools may lead to the development of clinical and scientific hypotheses that could potentially be validated in the clinic.

This IMI2 JU topic is designed to generate an information set to help evolve clinical hypothesis generation that will drive the development of new therapeutic interventions for cancer and to identify patient sub-populations that may respond to specific interventions, in particular to immunotherapy. **The proposed topic, for the first time, will assemble a consortium to generate a data set sufficient to gain a meaningful view of the tumour micro-environment. The generation of such a data set is the core activity of this IMI2 JU topic while the future purposes (improvement of the currently available treatments and development of potential therapeutic strategies) go beyond the frame of this topic.**

Need and opportunity for public-private collaborative research

Given the heterogeneity both in patients' immune systems and tumours, large data sets need to be generated to gain meaningful insights into the tumour microenvironment and the tumour-host interaction both at baseline (without treatment) and under therapy, in particular immunotherapy. This requires access to large numbers of patient samples from numerous clinical centres, collaboration of a number of different partners to analyse them for their molecular and cellular composition. Finally, a collaborative effort is needed to store and integrate patient and sample data according to agreed standards to allow for comparability of data and further analyses. Bioinformatics expertise as well as IT and legal support will be needed. Whilst no single organisation has access to all these resources and expertise (e.g. EFPIA partners: clinical biomarker and drug discovery & development expertise; public partners/clinical centres: patient samples, pathology, histology, etc), all share the same desire and need for a large and standardised dataset on the human tumour microenvironment, making this an ideal setting for a public-private partnership.

Scope

The ultimate aim and core activity is **to create a database containing integrated cellular and molecular data from the tumour microenvironment of patients** treated with both targeted and non-targeted therapy, in particular immunotherapy, **as well as key information from patient history and clinical progression**.

- **Core activity (broad profiling):**

  development of a fully integrated data set of defined immune cell subsets (deliverables (1) and (2)) in samples from patients from specific cancer indications treated with radiotherapy, chemotherapy, targeted therapy and, in particular, targeted immune checkpoint therapy and correlation to the oncogenomic profile of the tumour.
- **Supplemental activities:**
  - in-depth profiling of a subset of samples from patients undergoing immunotherapy using **selected** advanced technologies (deliverable (5));
  - development of a sustainable open-access, royalty-free and precompetitive database that houses such a data set, including the required privacy settings (deliverables (7-9));
  - generation of a biomarker validation platform to identify and start to characterise potential predictive biomarkers for single-agent and combinatorial immunotherapy trials (deliverable (10)).

Expected key deliverables

1) **Deliverable 1**

   A data set on presence and spatial distribution of immune cell subtypes (including T cells, NK cells, B-cells, myeloid-derived suppressor cells, macrophages including polarisation markers, neutrophils, dendritic cells, Ki67), using immunohistochemistry (IHC) or immunofluorescence (IF), in surgical specimen (wherever possible) and biopsies with pathologist-validated tumour content, immune infiltrate and invasive front (wherever possible).
   IHC or IF measurements should ideally be centralised at one of the academic consortium partners. In case IHC or IF measurements will be performed at multiple sites, a data package needs to be provided demonstrating that such assays can be run using harmonised analysis platforms, reagents and protocols. In any case, validated antibodies should be used and staining and slide scanning should be performed at the same site.

2) **Deliverable 2**

   RNAseq analysis of all samples as profiled under (1) using ≥ 100M reads per sample.

Deliverables (1) and (2) will be referred to as 'broad profiling' which is regarded as the core activity of the consortium and is expected to consume a considerable part of the resources.

3) **Deliverable 3**

Obtaining such data from patients with the following specifications:

a. pre- and post-treatment tumour samples whenever possible (pre-treatment: up to six months, preferably immediately prior to treatment and not older than 1 year; post-treatment: should allow informative analyses, e. g. 6-8 weeks after treatment);

b. for immune checkpoint inhibitor (ICI) treatment, pre-treatment samples are mandatory, post-treatment samples are desirable. In case only peripheral samples are available in post-treatment settings, detection of immune cells needs to be performed using suitable methods;

c. for longitudinal studies; collection of samples during the course of therapy (i.e. 1st, line therapy followed by 2nd line therapy, etc.) would be supported and preferred whenever possible;

d. indications, treatments and envisaged sample numbers:

Indication	
Tumour indication*	**No. of patients envisaged** (please justify deviations from numbers in application)
Lung adenocarcinoma	≥ 600
Head & Neck Cancer	≥ 600
Colorectal Cancer *(with known microsatellite (MS) status)*	≥ 600
ICI failures from different indications	≥ 600
Indication as proposed by academic consortium** (not: melanoma)	≥ 100-600 (flexible; based on the proposal)
All	2500-3000
Treatments	
Type of treatment	**% of patients**
Chemotherapy, radiotherapy, non-ICI targeted therapy	≤ 40% (consortium has to show that large enough sample numbers can be collected for any subgroup to achieve statistical power for broad profiling data set)
ICI therapy (Either post prior therapies or as first line therapy)	≥ 60%
Retrospective versus prospective analysis	
Retrospective (samples max 2ys old, paraffin slides are not sufficient, tumour blocks need to be available)	≤ 30%
Prospective	≥ 70%

*Indications 1-4 are fixed. Lung adenocarcinoma has the highest priority. The consortium should start with this indication and apply any learnings to the other indications.
**This could be a 'classical' tumour indication but could also be a more explorative/subgroup of patients, for example patients who developed cancer under immunosuppressive therapies, e. g. HIV or in a post-transplantation setting.

4) **Deliverable 4**

Established and validated workflow for sample quality control, tracking and storage.

5) **Deliverable 5**

A ‘deep profiling’ data set for a subset of tumour samples (~50-100 per indication) to address a particular hypothesis, from patients having undergone or undergoing ICI therapy, with the goal of comparing pre- versus post-treatment samples as derived from, for example:

a. single cell RNA seq on sorted immune cell population (important);
b. multi-color flow cytometry, especially of surgical specimen, realised by participating partners that have appropriate capabilities using a standardised panel of markers;
c. multiplex-IF including a panel of functional immune-related markers;
d. selected advanced technologies, e. g. CyTOF;
e. microbiome analysis;
f. ctDNA and ctRNA analysis;
g. proximity ligation assay-based approaches for detection of e. g. receptor-ligand interactions.

A selected and well-reasoned set of these technologies should be employed; a reasonable and limited part of the budget should be allocated to ‘deep profiling’ (considerably less than ‘broad profiling’).

6) **Deliverable 6**

For all patients collection and banking of:

a. blood samples including samples for e.g. paxgene blood-RNA or RNA scope as well as plasma;
b. faeces;

matched to immuneprofiled tumours to enable future validation of potential predictive biomarkers in peripheral tissue.

7) **Deliverable 7**

A raw data repository with access for all consortium partners.

8) **Deliverable 8**

Software and bioinformatics packages for full data integration and analysis, for example, gene signatures, gene fusions and latest-generation image processing software for analysis of IHC/IF data.

9) **Deliverable 9**

A sustainable database/IT infrastructure allowing for open-access query of data set and long-term housing of database. The data are initially accessible for consortium partners; following data curation, integration and journal publication, the data will be released into the public domain.

10) **Deliverable 10**

Experimental validation packages and classifier signals for potential predictive biomarkers based on the data collected in the consortium.

Wherever possible, synergies with pre-existing platforms, solutions and databases should be realised.

Expected impact

Immunotherapy, as exemplified by therapeutic antibodies neutralising the immune checkpoint PD1, has been shown to provide sustained survival benefit to patients with melanoma, lung, kidney, and bladder cancers. In general, the response rate in these cancer patients to PD1/PD-L1 blockade is about 20 to 30%. Acquired resistance to immune checkpoint blockade is also likely to be observed in some of these responders. While some biomarkers like PD-L1 expression and IFN-gamma gene signature have been able to predict response to PD-1/PD-L1 targeting therapeutics, the mechanisms of resistance, innate and/or acquired, to immune checkpoint blockade in these cancer patients remains largely unknown.

A comprehensive database, profiling immune cells in the tumour microenvironment (TME) of patients that are responsive to immune checkpoint blockade versus those that are not, is generally lacking at the present time and therefore the creation of such a database is the ultimate aim of this IMI2 JU topic. A searchable database, with integrated tumour genomic information along with matched immune profiles and (immune) therapy outcome, will enable users to identify biological networks involved in, and develop biomarkers to predict response to, immunotherapy. Maximum impact would be achieved by continued integration of clinical outcome data received after the end of the consortium. This IMI2 JU topic is expected to be the basis for future significant impacts but these will go beyond the scope and timeframe of the IMI2 JU topic:

- identification of novel predictive biomarkers and patient selection strategies and thereby improving clinical response rate to current cancer immunotherapy and other therapeutic regimens in oncology; such discoveries and improvements should enhance clinical and healthcare practice;
- understanding mechanism(s) of resistance to current immunotherapy, but also other therapy regimens, to enable identification of new therapeutic targets;
- establishing rational combination immunotherapy strategy (this should strengthen competitiveness and help to address the specific societal challenge of low response rates in cancer patients to current therapies);
- deriving therapy solutions for patients that are insensitive to immune checkpoint blockade (thus generating a positive impact on European cancer patients' health and wellbeing in the long-term);
- understanding molecular effects and potential safety liability of immunotherapy.

Overall, the project is consistent with the IMI2 JU goals of supporting the development of next-generation medicines and treatments for diseases with high unmet medical need as well as treatment biomarkers for diseases clearly linked to clinical relevance.

Potential synergies with existing consortia

Applicants should take into consideration, while preparing their short proposal, relevant national, European (both research projects as well as research infrastructure initiatives), and non-European initiatives. Synergies and complementarities should be considered in order to incorporate past achievements, available data and lessons learnt where possible, thus avoiding unnecessary overlap and duplication of efforts and funding.

Industry consortium

The industry consortium is composed of the following EFPIA companies:

- Merck KGaA (lead)
- AbbVie
- Bayer
- Eli Lilly
- GSK
- Janssen/J&J
- Sanofi
- Servier

- Pierre-Fabre

The industry consortium anticipates contributing the following expertise and assets:

- largely financial contribution (most activities centralised at public partners);
- work package co-leadership;
- contribution to database / IT solutions and bioinformatic analyses;
- contribution to biomarker validation studies.

Indicative duration of the action

The indicative duration of the action is 60 months.

Future project expansion

Potential applicants must be aware that the Innovative Medicines Initiative 2 (IMI2) Joint Undertaking, may publish at a later stage another call for proposals restricted to those projects already selected under this topic, in order to enhance and progress their results and achievements by extending their duration and funding. Consortia will be entitled to open to other beneficiaries as they see fit.

As part of a possible future expansion of this IMI2 JU topic, logical next step activities may be performed that go beyond the time and resource constraints here, e.g. (i) additional tumour indications may be explored, (ii) additional deep-profiling activities may be performed, (iii) advanced biomarker testing and validation activities and discovery platforms may be employed, and (iv) further IT and data analytics activities may be warranted.

Indicative budget

The indicative EFPIA contribution is EUR 16 350 000.

This indicative figure includes EUR 6 300 000 as in-kind contribution and EUR 10 050 000 as financial contribution to the beneficiaries receiving JU funding in the selected action.

Due to the global nature of the participating industry partners, it is anticipated that some elements of the contributions will be non-EU/H2020 Associated Countries in-kind contribution.

The financial contribution from IMI2 JU is a maximum of EUR 17 830 000.

In relation to the above, applicant should be informed that the financial contribution from the IMI2 JU will be supplemented by an approximate EUR 10 050 000 financial contribution from the participating EFPIA companies, thus resulting in an indicative EUR 27 880 000 total financial contribution.

Therefore, at stage 1 applicants should provide a suggested allocation of the total financial contribution (EUR 27 880 000) in the budget of their short proposal in order to achieve the deliverables, ensuring sufficient funding of core activities (i.e. broad profiling, described in deliverables 1 and 2).

The final allocation of the financial contribution for the project deliverables, to be included in the full proposals, will need to be further discussed in preparation of stage 2 between the applicant consortium selected at stage 1 and the industry partners (full consortium).

Applicant consortium

The applicant consortium will be selected on the basis of the submitted short proposals.

The applicant consortium is expected to address **all the research deliverables** (see ‘deliverables’), bearing in mind the core activity of the IMI2 JU topic) and make key contributions to the defined deliverables in synergy with the industry consortium which will join the selected applicant consortium in preparation of the full proposal for stage 2. The size of the applicant consortia should reflect the expertise needed to achieve the proposed objectives within the indicated budget while ensuring the ‘manageability’ of the consortium as well as efficient and effective team work. Therefore, the number of members of the applicant consortium needs to be thoroughly justified in the proposal and all partners involved should make a significant contribution to the project. **The public partners are expected to carry out the vast majority of the hands-on work,** whereas

EFPIA partners contribute in-kind and financially (see above), so that **work can be carried out centrally with clear streamlined processes.** Steering of the individual work packages and content decisions will be done jointly by the public and private partners. To ensure a rapid and efficient start, it is essential that a translational research infrastructure in oncology with demonstrated collaboration across multiple disciplines (e.g. surgeons, trial nurses, medical oncologists, radiologists, pathologists, bioinformaticians, laboratory researchers) is already in place. The consortium is not expected to run dedicated clinical trials.

Specifically, the applicant consortium should be able to demonstrate:

- access to tumour tissue and matched blood samples from untreated and treated patients (as indicated in the table under expected key deliverables), with fixation/storage appropriate for different analysis methods. It is expected that the entire number of patient samples to be profiled in this project will come from the public consortium. Applicants should demonstrate the feasibility of collecting the outlined number of samples (see deliverables). EFPIA companies and private partners may contribute additional individual cohorts of patient samples where possible and appropriate;
- technical expertise to carry out the specified measurements using a harmonised set of platforms, protocols & reagents for all consortium partners;
- established and validated workflow for sample quality control, tracking and storage. If such processes do not exist yet in the manner necessary to centralise essential steps in the consortium as outlined in the deliverables, the ability to set this up should be shown;
- experience (as demonstrated by manuscripts/publications/other study reports) on a core set of 'deep profiling' technologies to be carried out on a subset of samples. Some 'deep profiling' technologies might be established during the course of the project or could be performed by SMEs;
- ability to have a legal frame (informed patient consent forms = IPCF) in place for the full duration of the consortium and beyond that allows:
    - acquisition of samples and experimental & bioinformatics studies outlined in the deliverables,
    - transfer of raw and processed experimental data as well as relevant data from medical history in anonymised fashion into data repository/database and open access for consortium members and later, the greater public,
    - maintenance of documentation of IPCFs,
    - operation under General Data Protection Regulation (EU) 2016/679 (effective May 2018) for European partners, or according to local regulations in case of data from other partners,
    - adherence to any other national laws and regulations;
- experience in handling, analysing and integrating large and complex data sets including housing a database;
- to support standardisation of data, adherence to the FAIR principles (Findable, Accessible, Interoperable and Reusable), as outlined in the standard starter pack developed by **eTRIKS**: https://zenodo.org/record/50825#.Wa5XC7IjHIV;
- ability to technically and legally establish and maintain an open-access database beyond consortium frame;
- a plan for aspects related to sustainability should be proposed, especially ensuring that the database remains accessible and facilitating its population with additional clinical outcome data. This can include a proposal for options transferring the open access database into an existing structure and should include realistic ideas for long-term financial and operational sustainability of the database;
- maximum impact would be achieved if collection of clinical outcome data for at least two years beyond consortium frame and integration of the collected data into the database is possible;
- ability to coordinate a large research initiative and to create a scientific network;
- ability to involve patient advocacy groups in such projects.

The applicant consortium is expected to set up a governance structure that includes the necessary project management skills suitable for the consortium and activities.

This could be ensured by one of the publicly funded partners, who in this case would need to have significant project management and coordination skills as well as the necessary experience in supporting complex – per size and composition – consortia in IMI/EU funded projects.

The resources allocated should be adequate for the complexity and size of the consortium.

Suggested architecture of the full proposal

The applicant consortium should submit a short proposal which includes their suggestions for creating a full proposal architecture, taking into consideration the industry contributions and expertise as provided below.

In the spirit of the partnership, and to reflect how IMI2 JU call topics are built on identified scientific priorities agreed together with EFPIA beneficiaries, these beneficiaries intend to significantly contribute to the programme and project leadership as well as project financial management.

The final architecture of the full proposal will be defined by the participants in compliance with the IMI2 JU rules and with a view to the achievement of the project objectives. The allocation of a leading role within the consortium will be discussed in the course of the drafting of the full proposal to be submitted at stage 2. To facilitate the formation of the final consortium, until the roles are formally appointed through the consortium agreement, the proposed project leader from among EFPIA beneficiaries shall facilitate an efficient negotiation of project content and required agreements. All beneficiaries are encouraged to discuss the project architecture and governance and the weighting of responsibilities and priorities therein.

The public partners are expected to carry out the vast majority of the hands-on work whereas EFPIA partners contribute in-kind and financially (see above), so that work can be carried out centrally with clear streamlined processes. Steering of the individual work packages and content decisions will be done jointly by the public and private partners. In addition to project leadership, industry partners staff efforts will be largely spent on work packages 4-8, with major involvement of industry partners in work package 7. Further details will be worked out between the full consortium, i.e. the industry consortium and the selected applicant consortium, in preparation of stage 2. In particular, the final allocation of the financial contribution for the project deliverables will be discussed and agreed by the full consortium.

All work packages will be co-led by EFPIA and public partners and are expected to have adequate autonomy. A lean governance structure should be put in place.

The architecture outlined below for the full proposal is a suggestion. Different innovative project designs are welcome, if properly justified.

Work package 1 – Management & steering, coordination, sustainability planning; project management office

Industry contribution:

- project leader;
- coordination across different work packages (including overall scientific and strategic oversight).

Expected applicant consortium contribution:

- project coordinator;
- professional project management expertise (daily operational support with project meetings, reporting and internal communication), e. g. through a project management office;
- see section on applicant consortium.

Work package 2 – Communication, public relations, and involvement of patient advocacy groups

Industry contribution:

- communications and patient advocacy expertise.

Expected applicant consortium contribution:

- carry out communication on project overall;
- involve patient advocacy and other groups of interest, e.g. to support patient consent;
- see section on applicant consortium.

Work package 3 – Legal aspects

Industry contribution:

- legal input to support discussions around informed patient consent form & data privacy;
- enable potential synergies with IMI2 JU DO->IT consortium.

Expected applicant consortium contribution:

- ensure legal frame is compatible with deliverable;
- implementation of a legal frame to allow execution of all the deliverables, e.g. clearance by institutional or pan-consortium ethics committees, availability of IPCFs, data privacy, data repository and access, etc;
- see section on applicant consortium.

Work package 4.1 – Broad profiling (core activity)

Industry contribution:

- input and expertise on selection of profiling technologies, antibodies, and immune cell subtypes to be analysed;
- expertise in selected profiling technologies, image analysis and primary data analysis;
- oversight of broad profiling activities and results.

Expected applicant consortium contribution:

- input and expertise on selection of profiling technologies, antibodies, and immune cell subtypes to be analysed;
- applicants are expected to carry out all broad profiling activities, including sample taking, staining, slide scanning, RNAseq, and analysis;
- see deliverables 1-3 and section on applicant consortium.

NOTE: Profiling costs (consumables, RNA seq etc) for all samples outlined in deliverable 3 are expected to consume a substantial part of the cash budget and resources, which should be outlined in the application.

Work package 4.2 – Deep profiling

Industry contribution:

- input and expertise on selection of deep profiling technologies;
- expertise in selected deep profiling technologies and primary data analysis**.**

Expected applicant consortium contribution:

- input and expertise on selection of deep profiling technologies;
- applicants are expected to carry out all deep profiling activities;
- see deliverable 5 and section on applicant consortium.

NOTE: A selected and well-reasoned set of technologies should be employed; a reasonable and limited part of the budget and resources should be allocated (considerably less than ‘broad profiling’).

Work package 5 – Patients/indications: oversight sample banking and management, QC and ethics

Industry contribution:

- expertise in sample logistics and quality control;
- expertise on handling ethical questions and obtaining relevant input;

- input into process and oversight of validated workflow for sample quality control, tracking and storage/banking (deliverables 4 and 6);
- oversight of sample logistics, quality control etc.

Expected applicant consortium contribution:

- possess or deliver workflows for sample collection, quality control, tracking, storage, banking and maintenance, also linked to legal frame, and implement and carry them out for the project;
- see especially deliverables 4 and 6 and section on applicant consortium.

Work package 6 – Biomarker validation

Industry contribution:

- experimental and technical expertise, pharmacological tool agents;
- input into idea generation and oversight on biomarker validation (deliverable 10);
- laboratory and computational approaches related to I/O biomarkers.

Expected applicant consortium contribution:

- input into idea generation and execution of biomarker validation (deliverable 10);
- see deliverable (10) and section on applicant consortium;

NOTE: A reasonable and limited part of the budget and resources should be allocated.

Work package 7 – Data integration and bioinformatics

Industry contribution:

- input into and oversight of bioinformatics, data integration and statistics support;
- support / carry out software and bioinformatics packages for data analysis.

Expected applicant consortium contribution:

- input into and implementation of software and bioinformatics packages for full data integration and analysis;
- carry out data analysis;
- see deliverable 8 and section on applicant consortium.

Work package 8 – Database and IT infrastructure

Industry contribution:

- database expertise;
- input on database infrastructure and testing.

Expected applicant consortium contribution:

- implement a raw data repository, upload and maintain data, make data accessible to different consortium members;
- develop and implement a sustainable database/IT infrastructure as outlined in deliverable 9;
- carry out the activities for deliverables 7 and 9;
- see deliverables 7 and 9 and section on applicant consortium.

Topic 9: ConcePTION – Continuum of Evidence from Pregnancy Exposures, Reproductive Toxicology and Breastfeeding to Improve Outcomes Now

Topic details

Topic code	IMI2-2017-13-09
Action type	Research and Innovation Action (RIA)
Submission and evaluation process	2 stages

Specific challenges to be addressed

Information to guide decision making for the safe and effective use of medications during pregnancy and breastfeeding is a large unmet need that hinders optimal care of women of childbearing potential. Pregnant women with serious illness need medicines, to treat conditions in order to prevent irreversible damage to their health and the health of their unborn child. These patients, together with their healthcare professionals (HCPs), are invariably interested in better information on the risks that their disease and/or medication can pose to the foetus as well as to babies during breastfeeding.

Prescribing information leaflets generally lack clear information to inform decision making. Very often pregnancy is listed either as a contraindication, or a warning or advice to use effective contraception to avoid pregnancy and stop medication in case of pregnancy. It is common to have statements such as, *'[drug] should not be used during pregnancy unless clearly necessary'* and *'It is not known whether [drug] or metabolites are present in breast milk; caution should be exercised when administered to a nursing woman*', rather than useful scientific information [1]. In the absence of scientific data to inform decision making, the treating physicians often take a risk avoidance approach and advise women with chronic diseases to avoid becoming pregnant, or to stop or not start treatment during pregnancy and breastfeeding. In some situations, when the treatment is stopped, the disease itself may cause even more damaging effects for both the foetus and the mother than the medication, and this may lead to a higher disease burden, poor quality of life, and more healthcare costs.

After a marketing authorisation has been granted, pregnancy registries may be proposed by the Marketing Authorisation Holder (MAH) or mandated by the Medicines Agencies or National Competent Authorities to better characterise the foetal risk in a real-world setting. Over time it has become evident that product-specific pregnancy registries often have their own shortcomings, as evidenced by the lack of published data from these sources, and according to the Food and Drug Administration (FDA) review based on 59 pregnancy registries, only a minority (12%) informed the label to adequately advise patients and HCPs [2], notwithstanding huge investments in funds and time by the sponsors.

The major reason why most pregnancy registries end up being non-informative is that they do not achieve the targeted number of pregnant women, and commonly lack internal comparator groups to aid data interpretation. Hence, many compound-specific pregnancy registries close several years after initiation, woefully under-enrolled, despite efforts by the sponsors to increase recruitment. Alternative ways of characterising disease and compound-mediated adverse foetal outcomes, like teratology information services cohorts, retrospective database or case control studies, are increasingly used for hypothesis testing, but there are still gaps in our knowledge about the best methods to use. In addition, there is no consistent standard of data quality (data collection and analytical methods) recognised as warranting inclusion in product labels.

The situation is even worse concerning breastfeeding. There is a large information gap for patients and HCPs on the risk to the breastfed child from medication given to the mother. Often, due to a lack of data, and even when some data exists, due to difficulties with the predictability of animal data to humans, women are advised to avoid breastfeeding, despite the proven benefit of breastfeeding. The majority of current drug labels follow this approach which is more based on risk avoidance than on risk/benefit assessment. However, certain compounds, due to their physicochemical properties, are either not excreted in the milk, or are found at concentrations well below any biologically active concentrations. As there are no broadly accepted ways of generating such data and there is no requirement that such data/calculations are generated, these data are often not available. Although there are many different biological sample banks in the EU, there is no biobank

for human breast milk. Such a biobank, when in place, would increase human milk research as well as the assessment of medication concentrations in human milk.
This topic addresses the unmet need for a science and data driven approach to define the standards for generating data on medicines used during pregnancy and breastfeeding. It will result in better and more complete scientific information on drug effects on pregnancy and lactation and this will be used to inform treatment decisions and will increase the quality of care for women.

Need and opportunity for public-private collaborative research

Historically, the two sources of data about medicine use and effects in pregnancy and lactation have been academia and industry. The former focused more on diseases, the latter more on products. Both sources and approaches combined have essentially failed to fill the knowledge gap with relevant, timely and adequate information. Today there are three new and positive elements that can fundamentally change this current unsatisfactory status quo. Firstly, the expectations of the public and regulators about better information connecting risks associated with disease and medication are rising (Pregnancy and Lactation Labelling Rules (PLLR) in the USA, guidelines in EU are expected). Secondly, new data analytics and data sources, such as electronic health records, allow efficient access to and learning from much larger pregnant populations. And thirdly, there is a growing consensus among all stakeholders in healthcare that collaboration is the way forward when facing a challenge, like this one, that is too large or complex for any one player to address.
The magnitude and complexity of the challenges mentioned above are such that they can only be addressed by a strong and dedicated collaboration between stakeholders, such as academic groups, HCP associations, patient organisations, pharmaceutical companies and other commercial entities, regulators and governments. A public-private partnership involving a variety of stakeholders equipped with complementary areas of expertise and working together with a multi-disciplinary integrated approach provides a unique scientific opportunity in finding game-changing solutions to this huge unmet medical and societal need affecting millions of women world-wide every year. It is important to recognise that the private partners are not restricted to large commercial enterprises, such as drug manufacturers, but can include small and medium-sized enterprises (SMEs) that might provide targeted support or innovations, such as in the development of bioanalytical methods and analysis, web design, communication for patients, project management, and other services.

IMI2 JU provides the ideal neutral framework for such a sensitive matter to ensure maximum transparency and buy-in by all stakeholders, and is an established forum where different stakeholders' needs can be put forward. It also provides the framework to share data in a secure environment as well as for interactions with different health authorities, which is essential to guide and advise on recommendations and consensus papers envisaged by the project, as well as gain broad acceptance of methods and criteria for the predictive models generated as part of the proposed project.

Scope

The scope of this topic is to better inform the use of medicines during pregnancy and breastfeeding. To change current practices, the overall objective is to provide improved tools and methods to generate more valuable, reliable and timely information to HCPs and pregnant and lactating women to enhance optimal care. More specifically the aims are as follows.

- Define more timely and efficient data collection and analytical approaches compared to pregnancy registries to better estimate disease background rates and treatment-related rates of adverse pregnancy and birth outcomes, including long-term outcomes in children. Improved information enables HCPs and pregnant patients to make informed decisions regarding medication use, and enhances care.
- Harmonise data elements collected during routine pharmacovigilance and enhance the collection of spontaneous reports (rate and the quality) of pregnancy cases. The standardised data elements will be also applicable for patients who get pregnant during clinical trials and for use in clinical practice.
- Develop and validate a new animal lactation model in a species that more closely parallels human lactation physiology. Develop a physiologically based pharmacodynamic model for translation between the medication concentration in animal and human breast milk. These data will provide more reliable information for the initial product label than the currently existing prediction based on the presence or absence of medication in human milk mainly using the rat model.
- Establish a non-commercial, Europe-wide breast milk biobank to be built on an already existing biobank setup with existing governmental support and an analytical centre for the analysis of drug concertation in

milk. The biobank will be able to host clinical breast milk samples from healthy breastfeeding volunteers as well as patients taking prescription medications.

- Disseminate through various channels educational material for HCPs on the importance of reporting pregnancy cases through the pharmacovigilance system as well as why the follow up is needed. Educational information will be provided to patients on how to read and interpret relevant sections of the label, how to obtain relevant information from HCPs on treatment during pregnancy and breastfeeding, and why clinical research in this field is needed.

Expected key deliverables

The deliverables are as follows.

- **Moving beyond pregnancy registries to enhance our understanding of disease related pregnancy, birth/infant outcomes, medication use and safety in pregnancy**

  1) Comprehensive catalogue of existing data sources and approaches to capturing maternal medication exposure in pregnancy and subsequent pregnancy and birth outcomes, including long-term outcomes in children building on existing catalogues (like the ENCePP pregnancy special interests groups overview, the European Medicines Agency (EMA) funded catalogue and others) and including a quality assessment of data elements included.
  2) Publication of common data elements across data sources, proposing a common data model for consolidating information across multiple sources, regions and countries.
  3) Consensus on key data elements and analytical methods to allow the assessment of medication utilisation and safety in pregnancy to meet regulatory requirements and standards for inclusion in product labelling.
  4) Proposal for a governance structure to enable de-identified data sharing across participating data sources under the common data model (leveraging experience of relevant IMI projects).
  5) Publication of recommendations outlining data collection and analytical standards for conducting drug utilisation studies in pregnant women and conducting demonstration projects for established and newly-marketed products.
  6) Publication of recommendations outlining data collection and analytical standards for conducting medication safety studies in pregnancy using secondary data approaches (e.g. from claims data or similar large non-registry sources). Conducting demonstration projects for established and newly marketed products.
  7) Publication of recommendations on appropriate disease-based comparators (untreated and standard of care treated) with reference to demonstration projects and a range of diseases of varying prevalence using the literature and patient data from clinical trials, and primary data collected through pregnancy registries.
  8) Publication of overall recommendations on the application of different data approaches and analytical methods to study medicine safety in pregnancy, based on the knowledge gained through the project.
  9) Publication of aligned recommendations on how to prepare for pregnancy and medication use during pregnancy for HCPs, patients and the general public.

It is expected that the deliverables will be regulatory accepted and be considered for implementation in regulatory practice.

- **Enhance safety data collection in pregnancy and the analysis of case reports**

  1) Publication of standardised core data elements (when and what) for pregnancy exposure and follow-up reports, with a specific focus on adverse drug reaction reports, applicable globally across industry and clinical practice.
  2) Publication of a standardised method for data analysis for aggregate reviews across individual cases from different sources (e.g. spontaneous and clinical studies).

It is expected that the deliverables will be regulatory accepted and be considered for implementation in regulatory practice.

- **Enhance data generation about lactation during medicine use and standardise approaches to human lactation studies**

1) Publication of a well characterised *in silico* and/or physiology-based pharmacokinetic (PBPK) model.
2) Translatable animal model to human.
3) Developed standards for conducting animal lactation studies.
4) Best practice document for conducting animal lactation studies.
5) Best practice document on how the results can be implemented when studying medication-related risks during lactation, and develop an algorithm when human lactation studies are indicated.
6) Best practice document on standards developed for conducting human lactation studies.
7) Aligned general recommendations on medication use during breastfeeding for HCPs, patients and the general public.

It is expected that the deliverables will be regulatory accepted and be considered for implementation in the regulatory practice.

- **Establish a non-commercial, Europe-wide breast milk biobank building on an already existing biobank setup with existing governmental support and an analytical centre for the analysis of drug concertation in milk**
  1) A self-sustaining Europe-wide human milk biobank (building on an existing biobank with existing governmental support) for voluntary donor and study collected samples.
  2) Europe-wide human milk sample analytical centre(s) able to comply with quality standards capable of measuring medication concentrations in milk.
- **Dissemination and education for HCPs, pregnant and breastfeeding patients and general public**
  1) Partnering to provide online, centralised and verified information on medicines use during pregnancy and breastfeeding as well as risks associated with untreated diseases.
  2) Network to deliver and maintain accurate and current information on good scientific and registry practice.
  3) Guidelines addressing data privacy, balancing spontaneous comments affecting the benefit-risk profile, use of social media including electronic tools, and ethical questions related to cross-border communication on pregnancy and breastfeeding.
  4) Education and training programmes enhancing HCPs', patients' and the general public's ability to understand / comprehend information provided in labels regarding medication use in pregnancy and breastfeeding.
  5) Aligned general recommendations for medication use during pregnancy and breastfeeding for HCPs, patients and general public.

Expected impact

It is expected that the funded project will deliver: 1) broadly acceptable methodologies for generating event rates of adverse foetal and birth outcomes, including long-term outcomes in children, as well as rates for selected diseases; 2) promote alternatives to traditional pregnancy registries for timely generation of medication-related adverse foetal and birth outcomes, including long-term outcomes in children, to inform the labels; 3) an enhanced and harmonised way for dealing with pharmacovigilance pregnancy reports; 4) an advanced methodology on how compound milk transfer can be better characterised in animals to inform the initial label with more relevant data, and communication on standards for conducting human lactation studies; and 5) an EU centralised breast milk biobank and an analysis centre(s) to enable research on medication transfer into human milk.

According to United Nations statistics [3], there were around 230 million pregnancies worldwide in 2012. According to the Eurostat data [4] in 2014, 5.1 million children were born in the EU-28 and around 6 million in the US (Centers for Disease Control and Prevention, CDC). The proportion of pregnant women using medicines during pregnancy in developed countries varies in the published literature, the estimates being lowest in northern European countries (44% to 47%), around 50% in the US and highest in France (93%) and Germany (85%, [5]). When only conservatively taking the lowest reported proportion of medication use in pregnancy in Nordic counties of 40%, the population which will benefit from the outcomes of this private-public partnership would be around 2 million pregnant women in the EU alone every year.

The short-term impact of the funded project is that regulatory bodies will be able to review data generated by individual sponsors that use the same broadly acceptable methodologies, hence making review of the individual product datasets easier. The faster and more efficient way of producing data to assess medication-related adverse pregnancy outcomes will enable regulatory bodies to include enhanced information in the label, providing prescribers and patients with much needed information to guide treatment decisions for the benefit of women and children. Better characterisation and prediction of the excretion of medicines in breast milk will deliver more reliable data to inform the initial label, and the breast milk biobank and the analytical centre will allow for future milk research regarding drug transfer to human breast milk as well as milk research in general. The project is expected to deliver scientifically sound and validated information for implementation into the regulatory guidelines, which will lead to better information for HCPs and patients, and generally improve the health of our next generation. If the next generation is healthier, this should reduce the health burden on society and contribute to economic growth. In the absence of the information generated through the project, the diseased pregnant and breastfeeding population will continue to be underserved.
Finally, small and medium-sized enterprises (SMEs) can be of great benefit to IMI2 JU projects and can strengthen the competitiveness and industrial leadership of Europe. Solutions that are co-created with SMEs can provide an economic stimulus that can be enduring. Their involvement in the action might offer a complementary perspective to industry and the academia, and help deliver the long-term impact of the project.

Potential synergies with existing consortia

Applicants should take into consideration, while preparing their short proposal, relevant national, European (both research projects as well as research infrastructure initiatives), and non-European initiatives. Synergies and complementarities should be considered in order to incorporate past achievements, available data and lessons learnt where possible, thus avoiding unnecessary overlap and duplication of efforts and funding.

Example of relevant IMI and non-IMI projects include:

- **EUROCAT (http://www.eurocat-network.eu) has existed for decades and includes most Member States in collecting pregnancy and congenital anomalies data. Collaboration with EUROCAT will eliminate any duplicative work on pregnancy registries, collaboration will be synergistic and will provide outcomes that will be more conclusive, timely and less costly for all stakeholders.**
- **EUROMEDICAT (http://euromedicat.eu/) is a European system for the evaluation of the safety of medication use in pregnancy in relation to the risk of congenital anomalies.**
- **IMI EUPATI project (https://www.eupati.eu/) focuses on education and training to increase the capacity and capability of patients to understand and contribute to medicines research and development and also improve the availability of objective, reliable, patient-friendly information for the public.**
- **ISRHML (International Society for Research in Human Milk and Lactation, https://isrhml.net) is a non-profit organisation dedicated to the promotion of excellence in research and the dissemination of research findings in the field of human milk and breastfeeding.**
- **IMI PROTECT project (http://www.imi-protect.eu). Although the project has ended, its legacy lives on in the knowledge and tools for monitoring the benefits and risks of medicines generated by the project.**
- **GAIA Consortium (http://gaia-consortium.net) aims to improve programmes of immunisation in pregnancy by harmonising maternal, pregnancy, foetal, and neonatal health outcome assessment.**
- **European Network of Teratology Information Services (ENTIS) (https://www.entis-org.eu) has the general objective to coordinate the activities of the different Teratology Information Services (TIS), and to collect and evaluate data in order to contribute to the primary prevention of birth defects and developmental disorders.**
- **IMI eTOX project (http://www.etoxproject.eu). The principles developed by the IMI eTOX project for sharing data, both public and private, through the combination of legal (intellectual property, IP), IT and honest broker concepts would be in principle applicable to the project selected under this topic.**

- **IMI eTRANSAFE project (http://www.etransafe.eu/) aims to improve safety in the drug development process by investigating the predictivity of preclinical data for human clinical effects.**
- **IMI EHR4CR project (http://www.ehr4cr.eu) provides adaptable, reusable and scalable solutions (tools and services) for reusing data from electronic health record systems offering large opportunities for the advancement of medical research, improvement of healthcare, and enhancement of patient safety.**
- **To help improve access to these patient-level data, the IMI European Medical Information Framework (EMIF) (http://www.emif.eu) project develops common technical and governance solutions and improves access and use of health data.**
- **Future IMI project resulting from the topic European Health Data Network (EHDN) IMI2 – Call 12 http://www.imi.europa.eu/sites/default/files/uploads/documents/IMI2Call12/IMI2_Call12_CallText.pdf.**
- **The US-based Mommy's Milk Human Milk Research Biorepository (https://mommysmilkresearch.org), the first human milk biobank that makes easier for scientists to perform research with standardised, sterile and indexed human breast milk samples.**
- **BBMRI-ERIC (http://www.bbmri-eric.eu/) operates a pan-European distributed research infrastructure of biobanks and biomolecular resources in order to facilitate access to resources.**
- **IMEDS (https://blogs.fda.gov/fdavoice/index.php/2017/01/introducing-imeds-a-public-private-resource-for-evidence-generation/) framework provides governance that allows private sector entities to gain access to the FDA Sentinel System's distributed data, making the scientific methods and tools available for entities outside of the FDA.**
- **HBM4EU (https://www.hbm4eu.eu/) aims to provide better evidence of the actual exposure of citizens to chemicals and the possible health effects to support policy making.**
- **WHO milk surveys (http://www.who.int/foodsafety/areas_work/chemical-risks/pops/en/index1.html) [6]**
- **LifeCycle (https://lifecycle-project.eu/about-lifecycle/project-summary) is conducting innovative research on the role of novel integrated markers of early-life stressors that influence health across the lifecycle using an open and long-term network of European cohorts that started during pregnancy or childhood.**

Finally consideration should be given to the work currently ongoing at the European Medicines Agency for potential synergy/complementary in particular:

- **ENCePP Special Interest Groups in Pregnancy has a key task to regularly review the of data sources for drug safety in pregnancy research (http://www.encepp.eu/structure/structure_specialInterestGroups.shtml).**
- **EudraVigilance, the system for managing and analysing information on suspected adverse reactions to medicines which have been authorised in the European Economic Area (http://www.ema.europa.eu/ema/index.jsp?curl=pages/regulation/general/general_content_000679.jsp)**

Industry consortium

The industry consortium is composed of the following EFPIA partners:

- Novartis (lead)
- GSK
- Lilly
- BMS
- UCB
- Takeda

- AbbVie
- Sanofi
- J&J
- Merck KGaA
- Covance
- Teva
- NovoNordisk
- Ellegaard
- Pfizer

The industry consortium will bring extensive expertise in pharmacoepidemiology and pharmacovigilance, experience in collecting additional information on spontaneous pregnancy case reports, prospective data collection, statistical analysis of spontaneous reports, legal and ethics experts, extensive expertise in animal lactation studies, reproductive toxicology, physiologically based modelling and simulation expertise, expertise in bioanalytical methods, assay development, sample collection and handling expertise, sampling protocol development, legal, ethical, financial expertise, expertise in medical communications, patient affairs, drug labelling, experience in monitoring social media, experience of translating highly technical information into usable information for health care providers and patients, as well as experience with interacting with regulatory authorities.

More detailed industry consortium contribution is presented under the section ‘Suggested architecture of the full proposal’ (see below).

Indicative duration of the action

The duration of the action is 60 months.

Future Project Expansion

Potential applicants must be aware that the Innovative Medicines Initiative 2 (IMI2) Joint Undertaking may, if exceptionally needed, publish at a later stage another Call for proposals restricted to the consortium already selected under this topic, in order to enhance and progress their results and achievements by extending their duration and funding. The consortium will be entitled to open to other beneficiaries as they see fit.

A restricted Call may be launched as part of a future IMI2 JU Annual Work Plan to carry out the correlation/analysis between animal reproductive toxicology data and human adverse pregnancy outcomes safety data. For instance, the standards developed by the IMI2 eTRANSAFE consortium on the correlation of general toxicology studies with adverse effects in humans may be used in the expansion project in case reproductive toxicity correlation would not be covered in the eTRANSAFE project.

Indicative budget

The indicative EFPIA in-kind contribution is EUR 13 500 000.

Due to the global nature of the participating industry partners it is anticipated that some elements of the contributions will be non-EU in-kind contribution.

The financial contribution from IMI2 JU is a maximum of EUR 15 300 000.

Applicant consortium

The applicant consortium will be selected on the basis of the submitted short proposals.
The applicant consortium is expected to address all the research objectives and make key contributions to the defined deliverables in synergy with the industry consortium which will join the selected applicant consortium in preparation of the full proposal for stage 2. This may require mobilising the following expertise, including from SMEs:

- expertise in design and analysis of existing data sets, electronic health records, epidemiological design and analytics;

- teratology and birth defect experts, scientific societies working with malformations;
- experience in legal, ethics and privacy law across regions;
- expertise in gynaecology and neonatology, representatives of patient's advocacy groups and professional medical associations, breastfeeding advocacy groups;
- expertise in animal and human lactation physiology and physiologically based modelling and simulation, capabilities to develop animal lactation models as well as conducting animal lactation validation studies, ability to host a non-commercial breast milk biobank with already existing governmental support and analytical centre, expertise in assay development and adaptation of medication assays to milk;
- financial experts for advising on sustainability;
- experience in use of different communication channels to reach different interest groups and professional associations, ability to communicate and translate complex medical information into lay language, expertise in handling and dissemination of information through internet and social media, expertise in qualitative analysis of social media feedback, web design and website maintenance experience;
- regulatory expertise, experience dealing with regulatory agencies, professional expertise managing complex multi-stakeholder projects, professional project management capability and experience.

Applicants should consider how they will strengthen the competitiveness and industrial leadership of Europe by, for example, engaging suitable SMEs in the consortium. The expected applicant consortium contribution expertise is presented under the section Suggested architecture of the full proposal (see below).

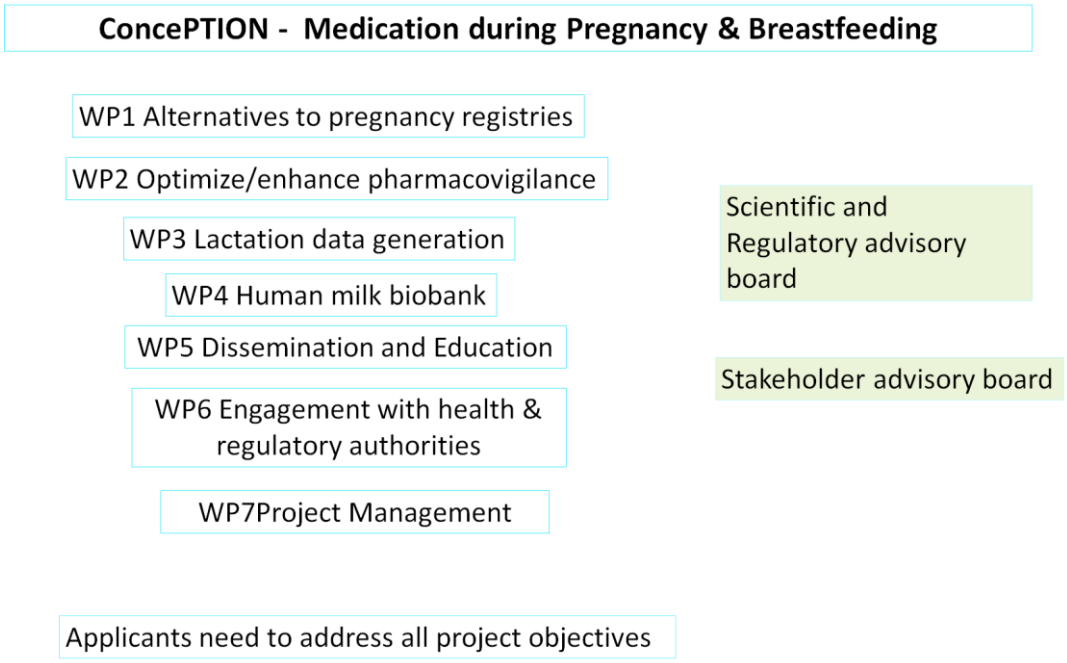
Suggested architecture of the full proposal

The applicant consortium should submit a short proposal which includes their suggestions for creating full proposal architecture, taking into consideration the industry contributions and expertise provided below.

In the spirit of the partnership, and to reflect how IMI2 JU call topics are built on identified scientific priorities agreed together with EFPIA beneficiaries/large industrial beneficiaries, these beneficiaries intend to significantly contribute to the programme and project leadership as well as project financial management.

The final architecture of the full proposal will be defined by the participants in compliance with the IMI2 JU rules and with a view to the achievement of the project objectives. The allocation of a leading role within the consortium will be discussed in the course of the drafting of the full proposal to be submitted at stage 2. To facilitate the formation of the final consortium, until the roles are formally appointed through the consortium agreement, the proposed project leader from among EFPIA beneficiaries/large industrial beneficiaries shall facilitate an efficient negotiation of project content and required agreements. All beneficiaries are encouraged to discuss the project architecture and governance and the weighting of responsibilities and priorities therein.

The architecture outlined below for the full proposal is a suggestion. Different innovative project designs are welcome, if properly justified.



The consortium is expected to have a strategy on the translation of the relevant project outputs into regulatory practices, clinical and healthcare practice. A plan for interactions with regulatory agencies/health technology assessment bodies with relevant milestones and resources allocated, should be proposed to ensure this e.g. qualification advice on the proposed methods for novel methodologies for drug development, qualification opinion.

Sustainability

A plan for aspects related to sustainability, facilitating continuation beyond the duration of the project should also be proposed.

It is important to recognise that certain project deliverables are expected to endure beyond the timescale of the project, and particular emphasis should be put on ensuring the sustainability of these deliverables.

It is important that the following deliverables of the project are made sustainable after the completion of the project:

- human breast milk biobank;
- dissemination and education;
- website and social media communication infrastructure and content support.

The list of activities within the work packages below gives more detailed insight into the activities which are proposed in order to achieve the project objectives.

Work package 1 – Moving beyond pregnancy registries to enhance our understanding of disease-related pregnancy outcomes, medication use and safety of use during pregnancy

The goals of this work package will be to:

1. develop a comprehensive catalogue of existing data sources and approaches capturing maternal medication exposure in pregnancy and subsequent pregnancy outcomes building on existing catalogues and including a quality assessment of data elements included;

2. review and publish common data elements across identified data sources, building a proposal for a common data model for consolidating data across multiple data sources, regions and countries by building on existing knowledge;

3. propose and gain consensus on key data elements and analytical approaches to allow assessment of medication utilisation in pregnancy as well as medication safety data to meet regulatory requirements and standards for inclusion in product labelling;

4. propose a governance structure for de-identified data sharing across participating data sources under the proposed common data model;

5. conduct Strengths, Weaknesses, Opportunities, Threats (SWOT) analysis of approaches to collecting and analysing data for medication utilisation and medication safety in pregnant populations: primary data collection (e.g. product specific pregnancy registries) versus alternative approaches (secondary data collection); hybrid approaches and relevant analytical methods for each;

6. based on SWOT analysis, agree standard data collection and analytical methods and publish recommendations for conducting drug utilisation studies in women of childbearing potential;

7. based on SWOT analysis, agree standard data collection and analytical methods and publish recommendations for conducting medication safety studies in pregnancy using secondary data collection approaches and conduct demonstration projects (case studies) for established and newly marketed products;

8. develop and publish recommendations on appropriate disease-based comparators (untreated and standard of care treated) with reference to demonstration projects and a range of diseases of varying prevalence (e.g. examples for frequent (e.g. hyperemesis); common (e.g. depression); and rare (e.g. breast cancer or lupus));

9. publish recommendations on application of several types of data collection and analytical approaches to study medicine safety in pregnancy based on the knowledge gained through the project;

10. prepare aligned recommendations on how to prepare for pregnancy and medication use during pregnancy for HCPs, patients and general public.

Industry contribution

Expertise in pharmacoepidemiology; drug regulatory experience; legal and ethics expertise; experience conducting databases/registry studies. The industry consortium will share placebo clinical trials pregnancy cases and non-treated/standard-of-care-treated patients data from pregnancy registries (as far as available); experience and challenges as well as roadblocks encountered during primary data collection and use of alternative approaches as well as sharing of experience of what worked well.

Expected applicant consortium contribution

Experience in leveraging alternative data sources; experts in analysis of large data sets like electronic health records; expertise in epidemiological design and analytics, teratology experts; statisticians; data modelling; legal, ethics and privacy law experience; expertise in gynaecology and neonatology; patients' advocacy groups; representatives of professional medical associations; regulatory experience.

Work package 2 – Enhance safety data collection in pregnancy and the analysis of case reports

The goals of this work package will be to:

1. conduct cross-company inventory on handling pharmacovigilance (PV) pregnancy exposure and follow up case reports;

2. develop and standardise core data elements (when and what) for pregnancy and infant follow-up, with specific focus on adverse drug reaction reports. This core set should apply across industry and clinical practice and be applicable globally;

3. develop standardised method for data analysis for aggregate reviews across individual cases from different sources (e.g. spontaneous reports and clinical studies);

4. publish standards for handling PV pregnancy case reports in peer review journal(s);

5. prepare aligned information on importance of reporting pregnancy cases though PV system for HCPs in order to stimulate data reporting and create a safe environment for reporting pregnancy cases with compounds without appropriate safety information in labels.

Industry contribution

Extensive expertise in pharmacoepidemiology and pharmacovigilance; experience in collecting additional information on spontaneous pregnancy case reports; prospective follow up data collection; statistical analysis of spontaneous reports; legal, and ethics experts. The industry consortium will also share pharmacovigilance pregnancy data under the Honest Broker concept to better inform the feasibility of the outcome.

Expected applicant consortium contribution

Expertise in design and analysis of existing data sets; teratology and birth defect experts; legal, ethics and privacy law experience; expertise in gynaecology and neonatology; representatives of patient's advocacy groups and professional medical associations.

Work package 3 – Enhance data generation about lactation during medicine use and standardise approaches to human lactation studies

The goals of this work package will be to:

1. review the literature and evaluate the existing animal lactation models for comparison to human physiology and milk composition and/or develop animal lactation model (included but not limited the learnings from the FDA lactation workshop 2016);

2. conduct experiments to validate the selected or new animal lactation model – respecting the Reduce, Refine, Replace (3Rs) principle;

3. develop a well-characterised in silico and/or PBPK model(s) based on physicochemical properties of drugs and preclinical data to better predict human milk transfer of drugs and to derive concentrations of drugs in milk, permitting a more accurate prediction of Relative Infant Dose (RID); where justified, also using available human lactation data;

4. validate that the developed model(s) can predict the known human lactation data;

5. define factors that should be considered when calculating neonatal exposure e.g. gastro-intestinal maturation;

6. develop and publish standards and best practices in peer reviewed journals;

7. develop a guidance document when generating human data might still be justified;

8. propose consensus on minimal amount of any breastfeeding data to meet regulatory requirements for inclusion in the label;

9. publish the guidance document in peer reviewed journal(s) on best practice for conducting human lactation studies;

10. prepare aligned recommendations on medication use during breastfeeding for HCPs, patients and general public.

Industry contribution

Expertise in animal lactation studies; general and reproductive toxicology; physiologically based modelling and simulation expertise; expertise in bioanalytical methods; capabilities to develop animal lactation models and conduct animal lactation studies. The industry will also share relevant preclinical and/or clinical lactation data under the Honest broker concept.

Expected applicant consortium contribution

Expertise in animal and human lactation physiology and physiologically based modelling and simulation; capabilities of conducting animal lactation studies and/or developing animal lactation models; expertise in bioanalytical methods; expertise in gynaecology and neonatology; patients advocacy groups; representatives of professional medical associations; breastfeeding advocacy groups and experts in legal, ethics and privacy laws.

Work package 4 – Establish a non-commercial, Europe-wide breast milk biobank building on an already existing biobank setup with existing governmental support and an analytical centre for analysis of drug concertation in milk

The goals of this work package will be to:

1. investigate the legal basis of establishing a Europe-wide human milk biobank from healthy breastfeeding women and women taking medicines;
2. utilise and expand on existing tissue biobank structure/collaboration;
3. identify the population and stakeholders for breast milk collection;
4. develop human milk sample collection and handling methodology guidance (sampling, storage shipment, health data needed from breastfeeding women) and model informed consent form (ICF);
5. suggest a biobank Scientific Board structure to review and approve requests for milk samples for research purposes;
6. develop analytical methodology for human breast milk adaptable for drug product analysis;
7. propose the potential financing structure to ensure sustainability, in addition to the existing governmental support;
8. generate charters for collaboration between industry and academia based on the Good Pharmacovigilance Practice (GVP) Module 8 and Council for International Organizations of Medical Sciences (CIOMS).

Industry contribution

Expertise in bioanalytical methods and assay development; analytical capabilities, sample collection handling and transportation expertise; biological material sampling protocol development; legal, ethical, financial expertise.

Expected applicant consortium contribution

Ability to host a non-commercial human milk biobank, building on existing biobank structure with already existing and sustainable governmental support; milk samples analytical capabilities preferably in the same country, able to set up and analyse medications in human milk and capable of complying with all the necessary analytical quality standards. Expertise in assay development and adaptation of medication assays to milk; experts in regulatory environment related to collection and transport of biological material; experts in ethics; experts for advising on sustainable financial support.

Work Package 5 – Dissemination and education for HCPs, pregnant and breastfeeding patients and general public

The goals of this work package will be:

1. inventory of possible communication means to HCPs and patients using different professional and patient associations and selection of the most appropriate ones for the project purpose;

2. inventory of existing social media communication channels, including electronic tools to HCPs, pregnant and breastfeeding women and general public;

3. analysis of information searched and feedback on the quantity, utility and clarity by HCPs, pregnant lactating women, breastfeeding women and general public;

4. partnering to provide online information packages on points to consider when preparing for pregnancy and medication use during pregnancy and breastfeeding to HCPs, patients and general public, including generation of communication guidelines and customising information packages for different target audiences;

5. engage HCPs, pregnant and breastfeeding women and general public to set expectations and stimulate pregnancy reporting through PV system and participation in research;

6. communication tools for internal and external communication.

Industry contribution

Expertise in medical communications, patient affairs, drug labelling; experience in monitoring social media; experience of translating highly technical information into usable information for HCPs and patients.

Expected applicant consortium contribution

Experience in use of different communication channels to reach different interest groups and professional associations; ability to communicate and translate complex medical information into lay language; expertise in handling and dissemination of information through social media; expertise in training and continuous medical education; expertise in the area of legal and ethical questions across regions; expertise in psychology and sociocultural aspects; expertise in qualitative and quantitative analysis of social media feedback and machine learning; hosting and webmaster capacities; patient organisations; regulatory expertise; scientific societies working with malformations; and experts for advising on sustainable financial support.

Work Package 6 – Engagement with health and regulatory authorities

The goals of this work package will be:

1. interact with work package leaders on the need for health authorities (HA) input;

2. assist work package leaders in using correct regulatory language;

3. organise HA interaction webinars, teleconferences and/or meetings;

4. share the regulatory interaction knowledge gained through the process with other work packages;

5. regulatory support to milk biobank establishment.

Industry contribution

Expertise in drug labelling and interaction with the regulatory authorities as well as experience in use of real world evidence generated data.

Expected applicant consortium contribution

Experience in regulatory communication; experience in using real world data for scientific purposes as well as labelling expertise.

Work package 7 – Project management

The goals of this work package will be:

1. participate in joint governance structure;
2. implementation and management of the project, setting-up regular meetings and interaction between sub-groups and teams, coordination of the work efforts, preparing meeting minutes;
3. manage collaboration with external stakeholders and synergies with other related projects;
4. communication and information dissemination within the project;
5. coordinate activities across all work packages, track deliverables, ensure deliverables are achieved according to plan, on time and budget;
6. ensure meetings and interactions between work packages and consortium governance bodies to coordinate and follow-up on work effort.

Industry contribution

Support in work package project management within the company leading this work package.

Expected applicant consortium contribution

The applicant consortium should bring proven record of professional project management capabilities; expertise and experience in managing complex and long lasting projects, such as this one.

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Topic 10 : Improving the preclinical prediction of adverse effects of pharmaceuticals on the nervous system

Topic details

Topic code	IMI2-2017-13-10
Action type	Research and Innovation Action (RIA)
Submission and evaluation process	2 stages

Specific challenges to be addressed

Neurotoxicity (used in the context of this document as “any adverse effect on the central nervous system (CNS) or peripheral nervous system (PNS)”) is poorly predicted by preclinical studies performed on pharmaceuticals during research and development (R&D) process. As a consequence, adverse effects on nervous system are not uncommon during clinical development and post-marketing. This lack of predictability might have two types of consequences:

- for human volunteers/patients, this can lead to a risk of adverse effects during clinical trials or even after marketing;
- for the pharmaceutical industry, this can lead to substantial neurotoxicity-related attrition rates, generally at late stages (clinical phase 2 or 3); according to sources, the figures for this type of attrition are variable, but typically in the range of 5-25%.

Therefore, a better preclinical prediction of adverse effects on nervous system would benefit to human volunteers/patients (by safer drugs) and pharmaceutical industry (by increased productivity).

There are various reasons for poor prediction/detection of adverse effects on the nervous system at preclinical stages. The challenges relate to the following considerations:

- the brain is the most complex organ in the body, comprising numerous cell types and functions;
- full knowledge is lacking about the chain of events (molecular, subcellular, cellular, tissue, organ-level) and their timing leading to neurotoxicity;
- no robust *in silico* tool is available to establish (quantitative) structure-toxicity relationship;
- no *in vitro* cellular/tissue system is widely accepted/validated for screening;
- there is a lack of predictive *in silico* simulation or *in vitro* test system to predict blood-brain-barrier penetration or exposure of target tissues;
- traditional neurotoxicity testing in animal models is generally limited to symptoms (with lack of specificity), electroencephalography (EEG) (with inconsistent interpretation) and histopathological investigations (with lack of sensitivity) that are late endpoints, detecting rather severe effects;
- sensitivity and translatability to the human condition of each animal species are not clearly established;
- no soluble biomarkers of neurotoxicity are formally validated nor identified yet.

Under the wide umbrella of “neurotoxicity”, at least three types of effects are even more challenging in terms of preclinical prediction and translation to human situation:

- seizures/convulsions, thus further epileptogenic events/epilepsy;
- psychological/psychiatric changes: memory impairment, mood disorders, suicidality;
- peripheral sensory neuropathies (this may include optic/auditory nerve).

Recent scientific and technical developments in neurosciences have been made that raise hope for the future, especially in the field of *in vitro* [1] and *in vivo* [2] models, translational biomarkers [3]and risk assessment [4] e.g. : *in silico* modelling of the blood-brain-barrier, use of (embryonic or human induced pluripotent) stem cells,

single-cell analysis, 3D models and organs-on-chips, measurement of micro RNAs or post-transcriptional (e.g. RNA editing) biomarkers.

Consequently, there is a clear need for a project to deliver on: (i) increased knowledge on mechanisms of neurotoxicity (e.g. establish adverse outcome pathway for each type of neurotoxicity); (ii) better understanding of factors that favour neurotoxicity (pharmacological targets and pathways, physico-chemical properties, pharmacokinetics); (iii) implementing new-found knowledge to improve the current preclinical toolbox, through a combination of high throughput, predictive *in silico*, *in vitro* and *in vivo* models, including safety biomarkers, where appropriate (iiii) combine these tools in an integrated risk assessment approach for better decision-points throughout R&D process, and better protection of human volunteers and patients.

Need and opportunity for public-private collaborative research

Research for improved predictive preclinical tools necessitates (i) expansion of knowledge regarding physiopathology of neurotoxicity: individual genetic/epigenetic susceptibility, role of blood-brain-barrier (under normal and pathological situations), non-neuronal and neuronal interplay, protection factors, receptors and neurotransmitters involved, novel safety biomarkers, functional changes as precursor of lesions, thresholds for effects (ii) establishing, testing and validating new/improved *in silico*, *in vitro* and *in vivo* models.

It is clear that such a wide range of complex questions can only be addressed via a public-private multi-stakeholder consortium, bringing their diverse expertise in the following fields:

- *in silico* modelling;
- cellular culture (especially stem cells and organs-on-chips);
- 'omics, systems biology/toxicology;
- imaging;
- single-cell analysis;
- electrophysiology;
- animal models (especially behavioural investigations);
- predictive biomarkers.

These areas of expertise could be addressed by the following type of public-private stakeholders:

- research organizations and universities would better contribute in the field of fundamental research, biomarkers identification, data management (especially when data in the precompetitive field will be shared) and project management/logistical/administrative support;
- small- and medium-sized enterprises (SMEs) would better contribute in the field of *in silico* and *in vitro* tools;
- pharmaceutical industry would better contribute in the field of *in vivo* studies, drug testing, historical data, reference and test compound supply;
- patient associations could join as partners, especially in the field of therapeutics indications where adverse effects on nervous system could be viewed as more frequent (psychiatry, oncology, neurology, immunology) as well as providing access to disease-specific donor material for *in-vitro* (primarily induced pluripotent stem cells ((iPSC)-related) work.

Lastly, a joint public-private project engaging key stakeholders' expertise could provide clinicians and regulatory bodies with robust data for possible evolutions in the regulatory field. As appropriate, these potential partners will be asked to contribute, e.g. through participation to the advisory board.

Scope

The objective of the project is to improve the preclinical predictivity of adverse effects of pharmaceuticals on the central and peripheral nervous systems through increasing our knowledge on mechanisms of neurotoxicity and improving the experimental toolbox. The results would be an integrated prediction/evaluation approach that would include a combination of *in silico*, *in vitro* and *in vivo* models, including safety biomarkers (for peripheral neuropathies). This toolbox would increase the preclinical prediction of adverse effects of drugs throughout all aspects: identification of hazards, characterisation of mechanisms of toxicity, prediction of clinical consequences and possible follow-up in trials with safety biomarkers, and integrated risk-assessment approach for proper decision-making process.

The adverse effects in the following areas of test articles should be considered by the applicants.

- Any pharmaceuticals under research and development stages. Not only small molecules are in the scope of the present topic, since biotherapeutics can lead to adverse effects on nervous system, directly or indirectly:
    - in a recent search performed by Abbvie on Food and Drug Administration (FDA)/ European Medicines Agency (EMA) labels in 2015, about 40% of biological products (vaccines, recombinant proteins, monoclonal antibodies) had mention of two or more neuropsychiatric adverse events in approval documentation/label. In the field of oncology, antibody drug conjugates can also lead to similar safety risks than small molecules.
- Drugs that pass blood-brain-barrier (BBB) but also drugs that do not overtly pass the BBB, since (i) passage can be very low but still have consequences, especially if accumulation or microglia-based responses occurs in the brain (ii) passage can be increased under various pathological conditions (infection, inflammation, neurodegenerative diseases).
- Whether the indication is CNS or PNS or not: off-target pharmacology can often be responsible for adverse effects on nervous effect independently of the desired on-target action, as shown in a recent publication: out of 70 targets that have established linked with adverse effects, 50 (71%) relate to nervous system [5]. As an example, modulation of inflammation can lead to mood disorders, as illustrated by interferon effects.
- Biomarkers of peripheral neuropathies.

Should not be considered by the applicants:

- vaccines, because of specific development plans and regulatory requirements;
- recreational drugs;
- drug abuse liability assessment (DALA), since it is already addressed by international guidelines;
- biomarkers of central neurotoxicity, which might be covered in another IMI2 JU project and in an Health and Environmental Sciences Institute (ILSI-HESI) initiative on translational biomarkers of neurotoxicity (NeuTox).

Expected key deliverables

With the aim of improving the predictivity of the preclinical toolbox for assessment of neurotoxicity, the following deliverables are expected.

- **Deliverable 1:** new/improved *in silico* tools that allow establishing (quantitative) structure-activity relationship ((Q)SAR), “activity” meaning here neurotoxic effects.

  These tools would permit identifying “neurotoxicophores” and, thus, help companies to build chemical structures devoid of neurotoxic liabilities, as early stages of research (selection of best (pre-)candidates or chemical series).
  In silico models of cell networks will also be considered, to allow studying the effects of a target activation on the total network of a cell leading to an increased understanding and prediction of the regulation of other targets or pathways that might be involved in the adverse effects.
- **Deliverable 2:** better understanding, modelling and simulation of the blood-brain barrier passage (e.g. using human induced pluripotent stem (hiPS)-cell based models) or exposure of target organs (brain, nerves), including for biologics and novel drugs used for focal disease interception.

- **Deliverable 3a:** at least one new/improved *in vitro* tool for screening (pre-)candidate drugs for each type of toxicity tackled in this topic, especially using stem cell systems and organs-on-chips.
- **Deliverable 3b:** an improved blood-brain barrier model (e.g. using hiPS combined with microelectrode assay applied to neurons from the same clone, in order to provide correlation between permeation and neurotoxicity).
- **Deliverable 4:** at least one tool for elucidating mechanism of toxicity (target, pathway), especially using stem cell systems and organs-on-chips.
- **Deliverable 5:** new improved *in vivo* animal models, with more specific investigational endpoints, allowing focused, non-invasive detection and longitudinal follow-up of the central and peripheral nervous toxicities during drug development.

  Ultimately, this might help change regulatory requirement for entry into phase 1 (safety pharmacology assessment of central nervous system, as described in International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (ICH)-Safety guideline)
- **Deliverable 6:** better characterisation of the most relevant animal species for each type of toxicity.
- **Deliverable 7:** Identification and validation of safety biomarkers predictive of peripheral nervous system toxicity, translatable from pre-clinical testing (*in vitro* and animal) to humans. Non-invasive biomarkers that do not necessitate cerebrospinal fluid sampling will be preferred (e.g. from saliva).
- **Deliverable 8:** integration of the deliverables in a pharmacokinetic/pharmacodynamic/toxicodynamic (PK/PD/TD) platform with appropriate quantitative and qualitative decision points for risk assessment.
- **Deliverable 9:** Improved toolbox, especially for early, non-animal testing which would fulfil the 3Rs objective (reduction/refinement/replacement). In particular, automation strategies for high-throughput testing will be considered.

Expected impact

At the level of R&D, regulatory, clinical and healthcare practice the impact would be (i) safer drugs for human volunteers/patients (ii) shortened development timelines, through reduced attrition, reduced testing, and shortened development plans:

- improved subjects/patients safety during clinical trials and after marketing authorisation;
- reduced attrition, especially at late stages of R&D (during clinical trials), for safety reasons related to neurotoxic effects;
- reduced post-marketing events necessitating labelling changes;
- reduced post-marketing events resulting in drug withdrawal;
- greater R&D productivity/shorter timelines;
- lower development costs.

In terms of ethics/animal welfare/3Rs, innovation and integration of new knowledge the impact would be:

- replacement: whenever possible animal models would be replaced by *in silico/in vitro* models, provided they have at least the same level of prediction;
- refinement and reduction: relevant biomarkers or any other appropriate endpoints would enrich current *in vivo* animal experiment and help (i) earlier detection and longitudinal follow-up of toxicities before inappropriate animal suffering (ii) decision-making process.

In terms of improving European citizens' health and wellbeing (volunteers and patients), the impact would be:

- lower risk of neurotoxic events during clinical trials, whatever the clinical indication (relating to nervous system or not);
- improved monitoring and risk minimisation procedures during clinical trials;
- drugs with a better risk/benefit ratio.

In terms of industrial competitiveness the applicants should indicate how they will strengthen the competitiveness and industrial leadership of Europe by, for example, engaging suitable SMEs.

Potential synergies with existing consortia

Applicants should take into consideration, while preparing their short proposal, relevant national, European (both research projects as well as research infrastructure initiatives), and non-European initiatives. Synergies and complementarities should be considered in order to incorporate past achievements, available data and lessons learnt where possible, thus avoiding unnecessary overlap and duplication of efforts and funding.

The following completed, ongoing or forthcoming initiatives (the list is not exhaustive) have been identified and could be considered by the applicants.

- **FP7-HEALTH project PREDICT-IV** (http://cordis.europa.eu/result/rcn/148238_en.html)

  The objective was profiling the toxicity of new drugs: a non-animal-based approach integrating toxicodynamics and biokinetics. Two neuronal primary models were analysed and the work package on convulsions/seizures could be relevant.
- **FP7-HEALTH project NEUROBID** (neuroscience on barrier in development) (http://cordis.europa.eu/result/rcn/57029_en.html)

  One axis of research is to understand the involvement of normal and disturbed BBB function in normal and abnormal brain development therefore the entire project could be relevant.
- **FP7-HEALTH project ERA-NET NEURON** (http://www.neuron-eranet.eu/)

  The project supports basic, clinical and translational research in the diverse fields of disease-related neuroscience, in order to pave the way for new or improved routes for diagnosis and therapy and therefore could be of relevance.
- **HESI Committee on Translational Biomarkers of Neurotoxicity** (NeuTox) http://hesiglobal.org/committee-on-translational-biomarkers-of-neurotoxicity/

  The objective is to identify biomarkers for improving the prediction of neurotoxicity therefore the work packages 1 (*in vitro* prediction of electrical abnormalities) and 2 (peripheral neuropathies) could be relevant.
- **NC3Rs CrackIt challenge 17 Neuratect** (https://www.crackit.org.uk/challenge-17-neuratect)

  The objective is to generate physiologically relevant human stem cell-based model(s) to identify neurotoxicity and seizure liability (neuronal viability/functional impairment) *in vitro* and the work package on convulsions/seizures could be relevant.
- **IQ consortium on Preclinical Suicidality** (https://iqconsortium.org/initiatives/working-groups/preclinical-suicidality/):

  The goal is to provide an expert assessment of the science of preclinical evaluation of treatment-emergent suicidality therefore the work package on psychological changes could be relevant.
- **IQ consortium on MicroPhysiological Systems** (co-initiative with National Institute of Health (NIH)) https://iqconsortium.org/initiatives/working-groups/microphysiological-systems-iq-nih-collaboration/

  The work packages on convulsions/seizures and peripheral neuropathies could be relevant.

Please note that during the project implementation phase the applicants should also consider other potential knowledge generated by the forthcoming projects under IMI2 JU in the area of blood brain barrier, biomarkers of central nervous system toxicology, integrative knowledge management approaches, as well as the ongoing IMI/IMI2 JU initiatives:

- **TransQST** – for the use of quantitative systems toxicology(http://www.imi.europa.eu/projects-results/project-factsheets/transqst);
- **EBiSC** (European Bank for induced pluripotent Stem Cells) (http://www.imi.europa.eu/projects-results/project-factsheets/ebisc).

Industry consortium

The industry consortium is composed of the following EFPIA partners:

- Sanofi (lead)
- Novartis
- MSD
- AstraZeneca

- Fujifilm (CDI)
- Pfizer
- UCB

The industrial participants will contribute through their expertise, data and resources, and materials especially (i) direct full-time employees (FTE), (ii) data and data valorisation (iii) financial contribution (iv) material/reagent/consumable contribution.

Expected contribution from industry consortium:

- perform retrospective search into preclinical and pharmacovigilance databases to assess the incidence and nature of effects, and evaluate the predictability of current preclinical toolbox;
- provide necessary number and diversity of drugs for validation of models;
- provide retrospective data on reference or proprietary drugs that have showed neurotoxicity issues, preclinically or clinically;
- run prospective assays/studies with drugs under development;
- data and samples management:
    - expertise in samples and data management (including e.g. automated analysis of EEG),
    - database information and assessment,
    - biostatistics/programming,
    - provide data and samples from pre-clinical and clinical fields,
    - it is worth noting that competitive data would be shared to processes that will ensure protection of confidentiality/anonymity;
- coordination and communication:
    - project management support with project design and day-to-day operation,
    - legal expertise scientific background to support regular review of deliverables regarding quality and operational ability.

Applicants should also note the detailed description of the industry contribution under “Suggested architecture of the full proposal”.

Indicative duration of the action

The indicative duration of the action is 36 months.

Indicative budget

The indicative EFPIA in-kind contribution is EUR 4 331 000.

Due to the nature of the participating industry partners it is anticipated that some elements of the contributions will be non-EU/H2020 Associated Countries in-kind contributions.

The financial contribution from IMI2 JU is a maximum of EUR 5 331 000.

Applicant consortium

The applicant consortium will be selected on the basis of the submitted short proposals.

The applicant consortium is expected to address all the research objectives and make key contributions to the defined deliverables in synergy with the industry consortium which will join the selected applicant consortium in preparation of the full proposal for stage 2. This may require mobilising, as appropriate, the following expertise:

- systems toxicology/biology for the identification of mechanism of peripheral and central neurotoxicities;

- conception of *in silico* tools for the identification of neurotoxicophores and (quantitative) structure-toxicity relationship;
- building of dedicated modelling and simulation models of blood-brain-barrier passage supported by appropriate tools and databases;
- *in vitro* screening of neurotoxicity using human stem cell-derived systems;
- organ-on-chip: brain, nerve;
- animal neurotoxicity and neurobehavioral testing (including EEG, connection between cardiovascular function and convulsions…);
- safety biomarkers identification and bioanalysis; process for qualification;
- data management, data mining, biostatistics; integration of tools, applications and data in a single platform;
- project management.

Expected contribution from applicant consortium

The academic partners, research organisations and universities could potentially bring:

- scientific input to better understand parameters that lower the seizure threshold, and the transformation of seizure into convulsions;
- identify pharmacological targets and biological pathways involved in the neurotoxic effects (on-target and off-target);
- identify physicochemical parameters or any other feature that correlate (and allow prediction) of blood-brain-barrier passage; it was found that only 40% of the blood-brain barrier permeation kinetics was explainable by physicochemical parameters. Other parameters such as protein binding, lysosomal storage in CNS cells etc. contribute to the clinical relevance and free fraction of the compound, and thus, should be considered;
- propose biomarkers of peripheral neuropathies.

The contribution from SMEs can be of great benefit to IMI2 JU projects and, *inter alia* strengthen the competitiveness and industrial leadership of Europe. Their involvement might offer a complementary perspective to industry and the academia, and help deliver the long-term impact of the project. For these reasons, applicants should consider engaging SMEs throughout the proposal, if relevant. Under this topic, the contribution of SMEs could be beneficial for the following activities:

- propose innovative assays/techniques for detection of neurotoxic effects: stem cells, organs-on-chip, subcellular systems (synaptosomes, mitochondria), micro-electrode array (MEA) technology, blood-brain barrier assay (optionally: combined with MEA, in order to correlate brain passage and neurotoxicity), continuous video monitoring in rodents and non-rodents, live-brain imaging of neuronal activity;
- run prospective assays/studies with reference drugs;
- data and samples management:
    - data management: data access and data cleaning expertise,
    - biostatistics/programming: data analysis and programming expertise;
- coordination and communication:
    - ensuring the implementation of the coordinating tasks and running the day-to-day operation, such as project tracking and reporting, meetings, internal communication, budget management, etc.
    - ensuring the communication and dissemination with and/or media expertise and in developing tools.

The patient organisations and clinicians could potentially:

- identify indications, pathologies, treatments for which neurotoxicity is a more critical issue.

The regulatory bodies could:

- give feedback on tools, strategies, biomarkers that are proposed and their possible implementation in official guidelines (e.g. through qualification advice for biomarkers).

Suggested architecture of the full proposal

The applicant consortium should submit a short proposal which includes their suggestions for creating full proposal architecture, taking into consideration the industry contributions and expertise provided below.

In the spirit of the partnership, and to reflect how IMI2 JU call topics are built on identified scientific priorities agreed together with EFPIA beneficiaries/large industrial beneficiaries, these beneficiaries intend to significantly contribute to the programme and project leadership as well as project financial management.

The final architecture of the full proposal will be defined by the participants in compliance with the IMI2 JU rules and with a view to the achievement of the project objectives. The allocation of a leading role within the consortium will be discussed in the course of the drafting of the full proposal to be submitted at stage 2. To facilitate the formation of the final consortium, until the roles are formally appointed through the consortium agreement, the proposed project leader from among EFPIA beneficiaries/large industrial beneficiaries shall facilitate an efficient negotiation of project content and required agreements. All beneficiaries are encouraged to discuss the project architecture and governance and the weighting of responsibilities and priorities therein.

A plan for aspects related to sustainability, facilitating continuation beyond the duration of the project should also be proposed.

The architecture outlined below for the full proposal is a suggestion. Different innovative project designs are welcome, if properly justified.

Work package 1 – Convulsions and seizures

The goal of the work package “Novel methods and assays to predict seizures, convulsions and epileptogenesis” is to better detect pro-convulsant and convulsant compounds, using a combination of in silico (modelling, QSAR), *in vitro* and *in vivo* methods, including:

- ***in silico*** **models**

To develop and evaluate suitable *in silico* models to detect the potential for convulsions/seizures in drug development candidates. Such models may include systems biology/toxicology tools based on analysis of targets and pathways involved in such changes, as well as (Q)SAR systems that could help identifying toxicophores, based on physicochemical properties or peculiar exposure patterns in brain structures.

- ***in vitro* / *ex vivo*** **models**

To build on existing models and define their context of use for early *in vitro / ex vivo* detection of pro-convulsant/convulsant compounds. The aims of this work package are (1) to improve the performance of *in vitro* models, while moving away from and minimising the use of animal models with alternatives such as human iPSC-based neuronal tissue cells, and (2) to define the context of use for various models; 3D models (spheroids, hydrogel models, hollow-fiber models, models based on BioVascs) employing multiple cell types may be more physiological relevant, but this comes at a cost with material, time, resources, etc. Models will be specifically challenged to define their relative utility over each other and to provide guidance on when they should be employed. Effort will be directed toward creating robust, reproducible, and translatable models with clear benefits in these areas over existing current, commonplace models. Efforts can include 2D and 3D models using multiple relevant cell types, i.e. gamma-aminobutyric acid (GABA)ergic and glutamatergic neurons, astrocytes, microglia, etc. Blood-brain barrier models using hiPS cells from epileptic patients should also be considered, in order to increase the relevance to the human-disease situation.

- Applicant consortium: will contribute expertise in *in vitro* neuronal network (2D and 3D), electrophysiology, and systems analytical skills and expertise, which may contribute to the development of seizurogenic and pro-convulsant assays for detecting CNS-based electrical perturbations. Collaborators will develop appropriate assays and then evaluate their performance using a variety of drugs with known pre-clinical and clinical effects to assess sensitivity, specificity, and utility of the *in vitro* assay(s).

- Industry consortium: will contribute expertise in *in vitro* assay development, cellular material, and retrospective data on reference or proprietary drugs that have shown convulsant / electrical neurotoxicities in preclinical and clinical settings.

- ***in vivo* models**

The aims of this work package are to improve the performance and the specificity of *in vivo* models, especially through the refinement of endpoints in safety pharmacology and toxicology studies.

- Applicant consortium: will contribute expertise in animal models of seizure and/or EEG signal processing which may contribute to the development of relevant tools for detecting convulsions/seizures (e.g. automated home cage detection of convulsive behaviours in rodents using continuous video monitoring, EEG signal processing, live-brain imaging of neuronal activity, etc.). This could be extended to non-rodents. Collaborators will develop appropriate tools/assays/endpoints and then evaluate their fit-for-purpose performance using a variety of drugs to assess sensitivity and specificity. “Non-classical” animal species could be considered (e.g. zebrafish).

- Industry consortium: will contribute expertise in the conduct and analyses of *in vivo* animal studies, and retrospective data on reference or proprietary drugs that have shown seizurogenic/convulsant issues, both preclinically and clinically. Classical animal species for toxicology (rodent/non-rodent) will be considered as part of safety pharmacology/toxicology study packages as well as biological samples and/or raw data to partners for analysis.

Work package 2 – Psychological/psychiatric changes

The goal of this work package is to establish *in silico* (modelling, QSAR) and *in vitro* techniques and animal *in vivo* models for a better detection/prediction of psychological/psychiatric changes that may occur in clinical trials, including memory and cognition disorders, mood disorders (including suicide ideation and behaviour).

- ***In silico* and *in vitro* models**

To develop and evaluate suitable *in silico* models and *in vitro* assays to detect the potential for psychological/psychiatric changes in drug development candidates. *In silico* approaches may include systems biology/toxicology tools to identify targets and pathways that are involved in psychiatric/psychological changes. *In vitro* assays may include iPSC-derived neurons to identify early molecular signals that may predict development of such adverse effects. Blood-brain barrier models using hiPS cells from psychiatric (e.g. schizophrenic) patients should also be considered, in order to increase the relevance to the human-disease situation.

- Applicant consortium: will contribute expertise in *in silico* neurotoxicity expertise or *in vitro* neuronal cell assay development expertise which may contribute to the development of relevant tools for detecting psychological/psychiatric disorders. Collaborators will develop appropriate tools/assays and then evaluate their performance using a variety of drug to assess sensitivity and specificity.

- Industry consortium: will contribute expertise in *in vitro* assay development, and retrospective data on reference or proprietary drugs that have shown psychological/psychiatric issues, both preclinically and clinically.

- ***In vivo* models**

To develop and evaluate preclinical models that model features and traits of memory, cognition or mood disorders (including suicidal ideation and behaviour). Perform proof of concept in nonclinical models with known drugs. Evaluate their ability to translate across nonclinical species with potential to predict psychological/psychiatric changes in humans.

- Applicant consortium: will contribute expertise in animal models of memory, cognition and mood (i.e. rat, dog, and non-human primates). Studies or endpoints will need to be established, if not commercially available, and have some level of fit for purpose validation conducted.

- Industry consortium: will contribute expertise in animal studies, especially neurobehavioral endpoints, in rats, dogs and non-human primates.

Work package 3 – Peripheral neuropathies

The goal of this work package is establish *in vitro* methods to detect peripheral neuropathy risk in drug development candidates, and to identify and evaluate safety biomarkers to monitor peripheral neuropathy *in vivo* for nonclinical use and translation to the clinical.

- ***In vitro* models**

To develop and evaluate suitable *in vitro* assays to detect the potential for peripheral neuropathy in drug development candidates. Such models may include iPSC-derived sensory neurons with peripheral neuron character that can be used to screen drugs and detect toxicity or identify early molecular signals that may predict development of peripheral neuropathy.

  - Applicant consortium: will contribute expertise in *in vitro* neuronal cell assay development expertise which may contribute to the development of relevant assays for detecting peripheral neuropathies. Collaborators will develop appropriate assays and then evaluate their performance using a variety of drug to assess sensitivity and specificity of the *in vitro* assay.

  - Industry consortium: will contribute expertise in *in vitro* assay development, and retrospective data on reference or proprietary drugs that have shown peripheral neurotoxicity issues, both preclinically or clinically.

- ***In vivo* models and safety biomarkers**

Candidate biomarkers should have some level of evaluation in preclinical models that demonstrates their association with peripheral neuronal cell degeneration/necrosis. Depending on the nature of that evaluation, promising biomarkers may need additional proof of concept in nonclinical models with known induced peripheral neuronal injury. In addition, candidate biomarkers should be selected for their ability to translate across preclinical species with potential to monitor peripheral neuropathy in humans. Lastly, preparatory work for qualification advice will be sought through interaction with regulatory bodies.

  - Applicant consortium: will contribute expertise in (preferably non-invasive) biomarker candidate evaluation, or experience with particular biomarkers for peripheral neuropathy which may contribute to the assessment of sample sets. Biomarker candidates will be evaluated in rat, dog, and non-human primates. Assays will need to be established, if not commercially available, and have some level of fit-for-purpose validation conducted. In addition to the assessment of sensitivity, specificity will also be determined for biomarker candidates.

  - Industry consortium: will contribute expertise in assay development and analytical fit-for-purpose validation for clinical and/or non-clinical use. Industry participants will also provide samples (e.g. plasma, serum, cerebral spinal fluid) from rat, dog, and non-human primate studies with toxicants known to induce peripheral neuropathy. These study samples will be anchored with histopathological assessment, and should include nerve morphometry on semi-thin sections, neuro muscular junction (NMJ) imaging on whole mount and lumbrical muscle sections, functional endpoints (e.g. nerve conduction), as well as surrogate markers of small fiber damage such as intra-epidermal fiber density (IEFD) and conreal nerve fiber density (CNFD).

Work package 4 – Data and samples management

The goal of this work package is to ensure and develop appropriate processes for data and samples management with respect to guidelines and laws, including:

- identification and standardisation of diverse data sources: preclinical and clinical data coming from industry and public;
- develop plans for data (Data Management Plan, Data Sharing Plan) as well as for samples (Samples Management Plan and Samples sharing plan);
- integration of data into an appropriate support (ideally and integrated platform connected to database with appropriate granularity, so that it is usable by experts from various fields: biologists, toxicologists, chemists, modellers…).

Work package 5 – Consortium coordination and communication

The goal of this work package is the overall project coordination and communication, including:

- define work expectations of different work streams, deliverables, dates and activities and review progress regarding adherence to budget, timelines and quality;
- ensure legal and contractual management;
- ensure the set-up of joint governance structure;
- ensure appropriate communication/dissemination within the consortium and with the external scientific community and the public;
- ensure interaction with regulatory bodies, as necessary (e.g. for qualification process/advice of biomarkers);
- develop and manage communication via web portal and other social media tools with a repository of key document;
- quality assessment of documents;
- ensure that key cross-functional partners are engaged;
- define project interdependencies, stakeholders and risks;
- ensure ethics management.

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Topic 11 : Translational Safety Biomarker Pipeline (TransBioLine): Enabling development and implementation of novel safety biomarkers in clinical trials and diagnosis of disease

Topic details

Topic code	IMI2-2017-13-11
Action type	Research and Innovation Action (RIA)
Submission and evaluation process	2 stages

Specific challenges to be addressed

Early and reliable detection and monitoring of adverse events is essential for improving of patient safety, reducing late attrition of drug candidates, and enhancing understanding of toxic mechanisms. In particular, biomarkers that provide insights into mechanisms of tissue injury have the potential to revolutionise drug development as well as diagnosis of diseases. Therefore, the development of innovative, non-invasive biomarkers of tissue injury is of great interest to drug developers, regulators and the broader scientific community. Recent progress in biomarker development including the previous **SAFE-T** (http://www.imi-safe-t.eu/) that identified several promising biomarker approaches as well as the latest scientific advances in analysis of circulating microRNA provide excellent opportunities for biomarker research. Furthermore, the recent progress in regulatory science of biomarker qualification achieved by the Critical Path Institute and the Foundation for the National Institutes of Health (FNIH) provides a blueprint for conduct of formal qualification of emerging biomarkers via an innovative translational paradigm that relies on tissue injury caused by diseases and only limited clinical and non-clinical studies for assessment of biomarker performance. This approach optimises resource use and accelerates biomarker development.

Need and opportunity for public-private collaborative research

New biomarker approaches are needed to enable development of new therapeutic modalities and improve diagnosis of diseases. The development and qualification of biomarkers is a costly and time-consuming process. It requires developing new innovative scientific approaches and analytical technologies as well access to appropriate human populations for biomarker qualification and assay validation, and other large-scale cross-institutional efforts. Therefore only large international scientific collaborative projects that include industry, academic researchers and regulators can be successful. For instance, the previous IMI project SAFE-T in the EU and the Critical Path Institute's Predictive Safety Testing Consortium (PSTC) yielded several promising biomarker candidates that are under review by the regulatory agencies in Europe and USA. The PSTC approach that relies on human disease as approximation of chemical injury for evaluation of biomarker performance significantly reduced need for conduct of costly clinical trials. Furthermore, recent progress in circulating microRNA analysis and next generation sequencing has opened new avenues for development of mechanistic biomarkers and precision medicine. However, more research and robust datasets are necessary to qualify new biomarker approaches by regulatory agencies and to enable their implementation in clinical trials and diagnosis of disease. The proposed TransBioLine topic with funding from the Innovative Medicine Initiative 2 Joint Undertaking (IMI2) provides a unique platform for leading experts from industry, academia and regulators to design and execute the research needed for development and implementation of novel safety biomarkers in clinical trials and clinical practice. Furthermore, the topic provides an opportunity for partnering with Small- and Medium-sized Enterprises (SMEs), including diagnostic companies to enable the development of robust assays that are compliant with regulatory requirements for use in clinical laboratories thereby decreasing the time needed for transferring biomarker discoveries from bench to bedside.

Scope

The TransBioLine project will focus on development of biomarkers of injury for liver, kidney, pancreas, vasculature, central nervous system (CNS) and the development of non-invasive liquid biopsies. The project will have four strategic goals:

1. **Develop data sets enabling the implementation of emerging safety biomarkers in clinical trials and/or diagnosis of disease:**

   The consortium will be expected to develop robust learning and confirmatory datasets that will support appropriate “contexts of use” for the emerging biomarkers. The resulting datasets will form the foundation for formal biomarker qualification by the European Medicine Agency (EMA), Food and Drug Administration (FDA) and Pharmaceutical and Medical Devices Agency (PMDA).

2. **Develop non-invasive mechanistic biomarkers of tissue damage called “liquid biopsy” that will have a potential to revolutionise drug development and diagnosis of disease:**

   The consortium will be expected to exploit the circulating cell free serum microRNAs for development of non-invasive tissue- and mechanism- specific diagnostic signatures/biomarkers. This effort will exploit state of the art technologies such as next generation sequencing in conjunction with systems biology approaches to gain insights into mechanisms of toxicity and disease, and risk assessment.

3. **Develop standardised assays and technologies for detection of biomarkers and data interpretation:**

   For biomarkers pursued by the TransBioLine project, the consortium is expected to develop robust assays compliant with regulatory requirements for implementation in clinical laboratories for clinical trials and clinical practice including appropriate level of validation as well bioinformatics, sample and data management tools. This will provide opportunities for partnership with diagnostic companies and SMEs.

4. **Achieve regulatory acceptance for biomarkers:**

   The consortium is expected to submit regulatory documentation that supports formal biomarker qualification with EMA, FDA and PMDA, and manage biomarker qualification process. Furthermore, the consortium will establish and maintain collaborative relationship with regulatory agencies (EMA, FDA, PMDA) organise workshops and meetings.

Research approach: The biomarker development for each target organ will concentrate on a specific context of use with limited number of already identified emerging biomarker candidates. The main focus of each individual target organ work package will be on the development of learning and confirmatory datasets that are essential for supporting regulatory qualification and implementation of emerging biomarkers in clinical trials and diagnosis of disease. To enable application of biomarkers developed under TransBioLine project to routine clinical laboratories, assay development, statistics and an expertise in regulatory science will be essential for achieving regulatory acceptance by EMA, FDA and PMDA. It is expected that these functions will be fully integrated with target organ work packages (WPs) to achieve maximum flexibility and impact. The appropriate resources for these activities in addition to project management will be allocated from individual target organ WPs budgets.

Since disease approximates chemical injury, TransBioLine project will rely mainly on samples from subjects with tissue injury caused by appropriately selected diseases. Only targeted clinical and non-clinical studies with drug/chemical induced organ injury will be used as supportive evidence for assessment of biomarker performance. The clinical sample set for analysis of biomarker performance will predominantly consist of remaining samples from clinical studies and remaining samples from subjects with appropriate disease phenotypes collected during medically indicated examinations. This approach limits effects of storage on biomarker stability, optimises resource use and accelerates biomarker development. It requires close collaboration with clinics and clinical researchers, especially to enable accurate diagnosis and anchoring endpoint evaluations, adherence to inclusion/exclusion criteria, ensuring correct patient consent, and correct sample collection. The state of the art next generation sequencing and system biology with a proven track record in identifying miR signatures in human subjects and normalization approach to enable consistent quantification will be necessary for development of miR-based liquid biopsies. A partnership with SMEs and diagnostic companies will be required for development of robust assays that will enable application of the studied biomarkers in routine clinical laboratories. Since the qualification of biomarkers by regulatory agencies

is essential for implementation of biomarkers in clinical trials and diagnosis of disease, strong expertise in regulatory science and established relations with Health Authorities by the applicant consortium will be required. To achieve the TransBioLine goals appropriate sample and data management systems, statistical and bioinformatics tools and strategy will need to be integrated throughout TransBioLine WPs.

Expected key deliverables

The TransBioLine primary objective is the development of datasets enabling formal biomarker qualification and biomarker implementation in clinical trials and/or diagnosis of disease. The key deliverables will consist of:

- Biomarker qualification submissions to EMA, FDA and PMDA for specific high priority context of uses defined by TransBioLine for liver, kidney, vascular, pancreas and Central Nervous system (CNS);
- Datasets that will enable the acceptance of emerging safety biomarkers by regulatory agencies for specific drug development programs under individual Investigational New Drug (INDs) even before the biomarkers are qualified as drug development tools;
- A new paradigm-changing non-invasive biomarker approach for interrogating mechanisms of toxicity and disease via miR-based “liquid biopsies”. This will include (a) detailed characterization of cell free serum miR-nome in healthy subjects and in subjects with diseases and (b) system biology platform applicable for addressing safety in clinical trials that will enable investigators to de-convolute observed miRs signatures to biological pathways in specific tissues;
- Robust biomarker assays compliant with regulatory requirements defined as “Research Use Only” (RUO), “Laboratory Developed Tests” (LDT) and/or “In Vitro Diagnostics” (IVD) as appropriate. The long term goal is to have assays broadly available in clinical laboratories world-wide;
- To facilitate the biomarker qualification by regulatory agencies, the TransBioLine will organise an annual biomarker qualification workshop with EMA, FDA and PMDA. It is expected that the workshop will have a significant impact on harmonization of biomarker qualification across regions, maintain organisational timelines, and facilitate global collaboration and global reach;
- To promote application of new biomarkers in clinical practice, publications in high quality peer-reviewed journals as well as presentations at various national and international meetings is expected.

Expected impact

The biomarkers developed during TransBioLine are expected to accelerate drug development by providing innovative drug development tools and also significantly improve diagnosis of disease by enabling non-invasive interrogation of disease mechanisms. The availability of qualified biomarkers as drug development tools will have a broad positive impact on patient safety in clinical trials as well. The TransBioLine will open new markets by introducing new commercially available diagnostic products and services by diagnostic companies and SMEs. This will strengthen the competiveness and industrial leadership of Europe. TransBioLine will enable the development of new innovative biomarker approaches derived from genomics applicable as non-invasive “liquid biopsies” providing tools for precision diagnosis of mechanisms of toxicity or disease at the molecular level. Although the formal qualification of biomarkers as drug development tools by regulatory agencies is the ultimate deliverable, the biomarker data produced by TransBioLine will enable the acceptance of biomarkers by regulatory agencies under individual INDs even before the biomarkers are fully qualified.

Applicants should indicate how they will strengthen the competitiveness and industrial leadership of Europe by, for example, engaging suitable SMEs.

Potential synergies with existing Consortia

Applicants should take into consideration, while preparing their short proposal, relevant national, European (both research projects as well as research infrastructure initiatives), and non-European initiatives and consortia. Synergies should be considered in order to incorporate past achievements, available data and lessons learned where possible, thus avoiding unnecessary pitfalls, overlap and duplication of efforts.

Biomarker development and biomarker qualification by regulatory agencies is a recognised unmet medical need. In fact, IMI JU funded its first translational biomarker project **SAFE-T** (http://www.imi-safe-t.eu/) that yielded several biomarker candidates. Among current and future IMI consortia, **TransQST** (http://transqst.org) and TransBioLine WP liquid biopsies have an excellent opportunity to bridge in non-clinical and clinical systems toxicological approaches and realise synergies in the development of systems toxicology tools. Furthermore, several international organizations and consortia in the EU and US are actively working in this space. Most notable are the Predictive Safety Testing Consortium of Critical Path Institute in Tucson, AZ, and Biomarker Consortium of FNIH in Washington, DC, that have made significant progress in biomarker qualification for selected liver and kidney biomarkers and are collaborating with the FDA on developing a regulatory framework for biomarker qualification and more recently, biomarker assay validation. In addition, several technical committees at the Health and Environmental Science Institute in Washington, DC, are working on evaluating analytical technologies and developing best practices. Recently, Japan's NIHS initiated a large collaborative project in liver biomarkers. Therefore, developing collaborative partnerships with these organizations when applicable throughout duration of TransBioLine project will be important. In contrast to the previous and current biomarker development efforts, the proposed TransBioLine will focus on enabling implementation of emerging biomarkers in clinical trials via qualification by EMA, FDA and PMDA and integrating the progress in regulatory science with the development of unique state-of-the-art mechanism-based biomarkers and clinical assays.

Industry consortium

The industry consortium is composed of the following EFPIA companies:

- Pfizer (lead)
- Novartis
- Sanofi
- J&J
- MSD
- Roche (Genentech)
- Eli Lily

The industry consortium will provide expertise and assets in developing large data sets derived from subjects in clinical trials, access to healthy volunteer populations, and data generation for full characterization of biomarker performance. The use of samples from prospective clinical trials run by the member companies will bring significant savings to the project notwithstanding limiting the need for unnecessary clinical investigations. Because of the global nature of clinical studies run by the industry consortium, the TransBioLine project will be able to evaluate performance of biomarkers in a variety of populations. Furthermore, the member companies will contribute targeted non-clinical studies, targeted clinical studies, and clinical and non-clinical datasets. Additionally, the industry consortium will contribute expertise in assay validation and a regulatory perspective, expertise in conduct of clinical investigations, experience with biomarker use in preclinical and clinical studies, study data that will support development of novel imaging agents, and managing processes and samples among various laboratories participating in the project. The expected industry consortium contributions will also include biomarker assays when applicable, and expertise and scientific leadership.

Indicative duration of the action

The indicative duration of the action is 60 months.

Indicative budget

The indicative EFPIA in-kind contribution is EUR 14 000 000.

Due to the global nature of the participating industry partners, it is anticipated that some elements of the contributions will be non-EU/H2020 Associated Countries in-kind contributions.

The financial contribution from IMI2 JU is a maximum of EUR 14 000 000.

Applicant consortium

The applicant consortium will be selected on the basis of the submitted short proposals.

The applicant consortium is expected to address all the objectives and make key contributions to the defined deliverables in synergy with the industry consortium, which will join the selected applicant consortium in preparation of the full proposal for stage 2. This may require mobilising, as appropriate the following expertise:

- Expertise with a demonstrated track record via publications in peer-reviewed journals in pertinent biomarker assay technologies needed to conduct TransBioLine research;
- Demonstrated analytical capabilities such as immunoassays, Liquid Chromatography-Mass Spectrometry (LC-MS), next generation sequencing etc;
- Expertise and capabilities in sample management systems, patient compliance statements, data management including database systems that comply with managing clinical data, state-of-the-art statistical and bioinformatics tools including tools for next generation sequencing data;
- For the liquid biopsy approach, extensive expertise and proven track record in peer-reviewed literature in analysis and normalisation of circulating miRs in human subjects using next generation sequencing and state-of-the-art bioinformatics with demonstrated expertise in generating signatures of circulating miRs for specific disease phenotypes and/or toxicities in human subjects;
- To achieve regulatory acceptance of biomarkers by regulatory agencies, extensive expertise in regulatory science with a proven track record in biomarker qualifications including preparation of regulatory submissions to regulatory agencies (EMA and/or FDA), and interactions with regulatory agencies world-wide;
- Ability to prospectively enrol the remaining samples from subjects with disease phenotypes defined by individual WPs to assess the biomarker performance pertinent to the TransBioLine research;
- Capability to identify, retain and manage remaining serum, Cerebrospinal fluid (CSF) and urine samples from healthy subjects and subjects with relevant disease phenotypes, including a broad range of aetiologies and/or treated with a variety of therapeutic modalities as specified by individual WPs;
- Capability to obtain appropriate patient consent forms, access detailed medical records data for all subjects/samples, and adjudicate the data;
- Ability to potentially recruit subjects treated with appropriate drugs for conduct of limited prospective studies;
- Proven expertise in efficiently managing and maintaining time lines for large, multi-institutional scientific projects and proven expertise in project management.

In addition to academic groups, relevant Small- and Medium-sized Enterprises (SMEs) with relevant proved expertise are encouraged to participate in the applicant consortium. SMEs can be of great benefit to IMI projects and, inter-alia strengthen the competitiveness and industrial leadership of Europe. Their involvement might offer a complementary perspective to industry and the academia, and strengthen the long-term impact of the project. For these reasons, applicants should consider engaging SMEs throughout the proposal. Under this topic, the contribution of SMEs would be considered especially beneficial in areas that include bioanalytical expertise for diagnostic assay development, bioinformatic analysis, data mining, and data and sample management.

The size of the consortium should be proportionate to the objectives of the project.

Suggested architecture of the full proposal

In the spirit of the partnership, and to reflect how IMI2 JU call topics are built on identified scientific priorities agreed together with EFPIA beneficiaries/large industrial beneficiaries, these beneficiaries intend to significantly contribute to the programme and project leadership as well as project financial management.

The final architecture of the full proposal will be defined by the participants in compliance with the IMI2 JU rules and with a view to the achievement of the project objectives. The allocation of a leading role within the consortium will be discussed in the course of the drafting of the full proposal to be submitted at stage 2. To facilitate the formation of the final consortium, until the roles are formally appointed through the consortium agreement, the proposed project leader from among EFPIA beneficiaries/large industrial beneficiaries shall

facilitate an efficient negotiation of project content and required agreements. All beneficiaries are encouraged to discuss the project architecture and governance and the weighting of responsibilities and priorities therein. The architecture outlined below for the full proposal is a suggestion. Different innovative project designs are welcome, if properly justified.

The consortium is expected to have a strategy on the translation of the relevant project outputs into regulatory practices, regulatory, clinical and healthcare practice. A plan for interactions with Regulatory Agencies/health technology assessment bodies with relevant milestones, resources allocated should be proposed to ensure this e.g. qualification advice on the proposed methods for novel methodologies for drug development, qualification opinion.

A plan for aspects related to sustainability, facilitating continuation beyond the duration of the project should also be proposed.

Work package 1 – Biomarkers of Kidney injury

Context of Use:

A panel of qualified urinary kidney safety biomarkers may be used together with sCr and BUN in subjects with normal kidney function or in patients with some pre-existing kidney disease (and not just normal healthy volunteers**)** as a more sensitive and/or earlier biomarker to monitor for both glomerular as well as renal tubular safety in clinical trials. These biomarkers will be used when such injury has been demonstrated to be monitorable by the biomarkers in animal studies of similar duration with the same test agent. Applying the biomarkers in initial single and multiple ascending dose clinical studies, or in continuous dosing clinical studies could enable or restrict initial dose level selection and planned dose escalations, or drive decisions to interrupt or continue dosing.

Specific Goals:

1. **Progressive Qualification of Translational Tubular Injury Biomarkers in Patients with Mild Pre-existing Kidney Dysfunction:**

   Given that diabetes and hypertension are the two known top causes of chronic kidney disease (CKD) most worthy of being considered for advancing confidence in the use of tubular injury biomarkers in patients (and not just normal healthy volunteers (NHVs)), cohorts of such hypertensive and diabetic patients could be targeted for testing, such that comparable thresholds and significant fold-change from baseline performance results are seen as comparative data to reference against data on translational kidney safety biomarkers that have already been collected for NHVs and patients with normal renal function [1]. There is also anticipated value in comparing these tubular injury urine protein biomarkers that are currently being clinically qualified by IMI and FNIH/PSTC with the FDA and EMA. A goal is to complete and expand the context of use for protein urine biomarkers undergoing qualification presently and also to open the door for potentially exploring additional promising new biomarkers that may appear in blood and to derive an optimal panel for detection of drug-induced tubular injury in humans and that may not therefore also require urine collections.

   Expected Applicant consortium contribution:

   This is an example of contributions that will be required to support the proposed project. Since cisplatin has been used to benchmark thresholds and biomarker performance results in subjects with normal renal function (IMI-SAFE-T, FNIH Kidney Team) the proposal is made to assess cisplatin next in patients with hypertension and diabetes. Lung cancer patients often have a long history of smoking preceded by chronic obstructive pulmonary disease requiring corticosteroid treatment. Such patients frequently have concomitant hypertension and/or steroid induced diabetes. Lung cancer patients presenting with CKD1 or CKD2, who are eligible for cisplatin therapy could provide urine and plasma samples following treatment with cisplatin. Assessment of biomarker baseline values, variability, and responses associated with standard of care cisplatin treatment would be compared to the data generated from similarly treated subjects with normal renal function that have already been assessed [1]. Primary hypotheses should focus on statistical power for subgroups of patients based upon hypertension and diabetes and

that secondary hypotheses could include investigation as to whether higher BMI (> 30 kg/1.73 m^2) and eGFR < 60 ml/min may pose challenges to interpretation of biomarker responsiveness and utility.

Industry contribution:

(a) Pre-diabetic/diabetic, (b) hypertensive, (c) obese, (d) metabolic syndrome patients familiar to clinical research units already well benchmarked for their CKD1/ 2 status would be a valuable source for benchmarking baseline variability for this kidney safety biomarker research, (e) Additionally, monitoring of these injury biomarkers following initiation of therapy with new oral hypoglycemic Sodium Glucose Co-Transporter (SGLT2) inhibitors [2], which appear to be potential intervention agents against CKD progression, is also proposed for consideration to generate data to investigate a hypothesised baseline-elevated set of biomarkers, and post-intervention return of these biomarkers toward normal to support expanding the evidence for such biomarkers for qualification in a weight-of-evidence strategy.

2. **Advancing the Qualification of Translational Glomerular Injury Biomarkers:**

There is also value in advancing the qualification of novel early biomarkers of drug-induced glomerular injury to support drug development. Translational urinary protein biomarkers of drug induced glomerular injury have shown promising results (e.g., albumin, cystatin C, clusterin) in rodent studies [3][4], and it is hypothesised that small RNAs that may be measured in blood for the liquid biopsy project to strengthen the urinary protein biomarker data.

Expected Applicant consortium contribution:

Several types of studies are suggested for consideration within a proposal from academia to generate the appropriate clinical samples to support drug-induced glomerular injury biomarker qualification [5]. At least two of the following studies or other more appropriate suggestions are welcomed: (a) Renal adverse effects following mechanistic target of rapamycin (mTOR) inhibitor therapy of breast cancer are often preceded by hyperlipidemia, and may present with asymptomatic proteinuria increase to full nephrotic syndrome (15%), elevated serum creatinine (44%), or acute renal failure. (b) Renal adverse effects following anti-VEGF therapies may present as hypertension, asymptomatic proteinuria (23%), and, rarely, nephrotic syndrome or acute renal failure, suggesting a rich source of patient urine samples for detecting biomarkers of the earliest signals of glomerular change. (c) Elevation of serum creatinine is not uncommon in patients with hypercalcemia of malignancy or osteolytic bone metastases (breast cancer, multiple myeloma) receiving I.V. bisphosphonate therapy [6]. (d) Pre-eclampsia manifesting as proteinuria and hypertension can be observed in 5-10% of pregnancies. Such patients considered as high risk for such, would be expected to be readily detected by standard of care pre-natal blood pressure monitoring and urinalyses.

Industry contribution:

Industry member conduct of Non-human primate studies using the same agents as for those selected clinical glomerular injury studies, and using the same biomarker assays as for the human biomarkers to generate translational biomarker performance data supported by histopathologic analyses, would be highly supportive of a favorable regulatory qualification decision and to inform the optimised scheduling of clinical sampling.

Work package 2 – Biomarkers of liver injury

Context of Use:

1. **Risk of progression:**

Biomarker X or a panel of liver safety biomarkers anticipate a risk of progression from hepatocellular injury to severe Drug-Induced Liver Injury (DILI) in patients in whom an initial DILI diagnosis has been established based on elevations of the standard marker Alanine transaminase (ALT) alone or in combination with Total Bilirubin (TBIL). Applying the biomarkers to compounds with an identified hepatotoxic risk may allow prospective monitoring and identification of a DILI signal. Biomarker levels will be correlated with subsequent clinical outcome to allow prognostic assessment of patients with idiosyncratic DILI. This may drive decisions to interrupt or continue dosing or to implement intensified monitoring according to risk stratification (progression – recovery – adaptation).

Specific goal: As evidenced by the EMA and FDA Letters of Support [7], biomarkers suitable for this context of use include macrophage colony stimulating factor receptor 1 (MCSFR1), total and hyperacetylated high mobility group box 1 (HMGB1), osteopontin, and total and caspase cleaved keratin 18 (K18 and ccK18).

2. **Mechanism of DILI:**

Biomarker X may be incorporated into clinical trials to assess the mechanism of hepatotoxicity induced by (i) compounds, which cause DILI in patients, and (ii) compounds that have shown hepatotoxicity in preclinical species or in in vitro investigations. The focus will be placed on any of the following mechanisms of intrinsic DILI: (a) mitochondrial toxicity, (b) reactive metabolite generation/ oxidative and endoplasmic reticulum (ER) stress, (c) inhibition of transporters such as the bile salt export pump (BSEP). For inhibition of BSEP, serum bile acid profiles should be measured and correlated with parameters such as drug dosage, clinical outcome, pattern of DILI and preclinical findings.

3. **Causality assessment:**

Biomarker X or an *in vitro* assay will assess causality of a suspected DILI causing drug in patients in whom a diagnosis of DILI has been established. There is no test available which allows causality assignment of a suspect drug to the onset of DILI in patients.

Specific goal:

To carry out a proof-of-concept study with a test system that assesses the causality of a suspected drug in the context of acute DILI. In patients in whom a diagnosis of DILI has been established based on elevations of the standard markers ALT, AST, ALP and bilirubin, potentially hepatotoxic medications administered to the patient should be assessed individually in a personalised medicine approach in material derived from the patient. With this *in vitro* assay, causality of DILI with a suspected drug can be confirmed; conversely, a drug that is falsely suspected to cause or contribute to DILI, can be de-risked if the result is negative.

Expected Applicant consortium contribution:

- Applicant consortium will provide samples from patients with acute severe DILI identified in clinical routine, and – if available – disease controls (e.g. non-alcoholic steatohepatitis (NASH), fibrosis, autoimmune hepatitis). In addition, the academic consortium will prospectively enrol samples from subjects with disease phenotypes that resemble chemical injury for evaluation of biomarker performance. Academic involvement includes protocol design and writing and close collaboration with the work package lead. This will allow the generation of a sufficiently large clinical sample set;
- Academic labs and/or SMEs should provide biomarker assays according to the context of use statements above. Assay providers should aim to achieve GLP/GCP standard validation during the course of the consortium. Academic partners are expected to have a track record in DILI research, and extensive experience with DILI samples is mandatory for any biomarker or assay provider.

Industry contribution:

Clinical samples from patients who developed hepatotoxicity in phase I-III, clinical samples from placebo-treated patients and – if available – disease controls (ongoing trials for liver disease, e.g. NASH, fibrosis, autoimmune hepatitis); additional clinical or preclinical data (including biomarker data) for compounds for which biomarker measurements are performed in human samples, FTE support (e.g. for work package leads, statistical support, medical writing and data management support).

Work package 3 – Biomarkers of pancreas injury

Context of use:

A panel of serological pancreas safety biomarkers may be used together with enzymatic Amylase and Lipase in normal healthy volunteers in early phase clinical trials as a more sensitive and specific biomarker to monitor pancreas acinar cell degeneration/necrosis. These biomarkers will be used when such injury has been demonstrated to be monitorable in animal studies of similar duration with the same test agent.

Specific goals:

1. **Delivery of robust validated assays suitable for use in human plasma or serum:**

Prioritised pancreatic safety biomarkers shall consist of candidate proteins showing at least preliminary evidence of an association with acinar damage and pancreas-specific microRNAs (e.g. 216a-5p/216b-5p) [8][9]. It will be critical that reliable and sustainable assays are available to support clinical testing. Non-clinical versions of these assays are also desired.

Expected Applicant consortium contribution:

Academic collaborators with assay development expertise may contribute to the development and/or validation of relevant assays. Specific expertise with miRNA quantification is desired to help address important platform-related issues (e.g. qPCR) and supply suitable clinical assays.

Industry contribution:

Industry members will be expected to contribute platform expertise in assay development and analytical fit-for-purpose validation for clinical and/or non-clinical use. Industry participants will also provide important experience that will guide the transfer of assays to reliable commercial vendors or contract research organisations including SMEs to provide sample analysis to the consortium.

2. **Biomarker baseline determination:**

Characterization of biomarker variability, and effects of potential confounding variables (e.g. gender, age, body mass, etc.) present in populations representative of volunteers in early phase clinical trials. In order to confidently interpret significant changes in the biomarkers, relevant reference ranges in cohorts representative of these volunteers must be generated.

Expected Applicant consortium contribution:

Academic collaborators with access to unique cohorts of volunteers (e.g. various ethnicity, gender, age) may contribute to the assessment of sample sets, as well as and analytical support for the generation of these baseline assessments.

Industry contribution:

It is envisioned that industry members will provide a majority of the samples required from normal healthy volunteers with relevant metadata for sample analysis.

3. **Provide proof of concept that the biomarkers can detect pancreatic acinar cell degeneration/necrosis:**

Provide determination of biomarker variability in diseases known to be associated with such injury (e.g. pancreatitis, pancreas transplant, pancreatic cancer, alcoholism). Establishing a greater understanding of candidate biomarkers with respect to disease onset, progression, or resolution is an important component of the work package that would support extending the context of use to later phase clinical trials.

Expected Applicant consortium contribution:

Disease samples from medical centers/institutions. In cases of patients presenting diseases such as pancreatitis, longitudinal sampling and the recording of disease outcomes are essential. In addition, it is expected that standard of care tests (e.g. amylase, lipase, c-reactive protein (CRP)) will be collected. Academic partners are encouraged to investigate the candidate markers using clinical samples to probe the influence of co-morbidities and factors that affect biomarker clearance from circulation.

Industry contribution:

Analytical and experimental support using non-clinical species to support reverse translation of qualified clinical markers of pancreatic acinar injury.

Work package 4 – Biomarkers of vascular injury

Context of Use:

The panel of vascular injury safety biomarkers used in conjunction with the totality of preclinical and clinical information in healthy volunteers to monitor for vascular safety in early clinical trials to help inform dose level selection, dose escalation, or decision on continuation of dosing.

Approaches and biomarkers of interest:

1. A panel of biomarkers will be selected from candidate biomarkers identified by SAFE-T and PSTC [10]. The panel includes endothelial, smooth muscle and inflammation markers. The performance of the panel will be assessed in subjects with existing vascular diseases to evaluate the ability of a biomarker panel to detect vascular injury specifically and the role of the presence of co-morbidities. Although immunoassay technology may be supplementary, the applicant consortium should explore LC-MS analytical technology for biomarker assay development. LC-MS technology is important for smooth muscle biomarker assay development, cross-species translation and low sample volume requirements. The applicant consortium should build on progress of LC-MS assay development and validation made by the PSTC consortium. Sufficient level of assay validation should be completed prior to generating biomarker results beyond the learning phase.
2. The second objective is to explore a more accurate means to measure active vascular injury against which to qualify the emerging biomarker panel in humans, as currently we lack a standard, non-invasive, specific biomarker for vascular injury [11]. This may include optical coherence tomography (OCT), fluorescein angiography (FA), ultra-widefield FA, and fundus photographic evaluations in the ophthalmic vascular disease manifestations or imaging with contrast or bio labelled agents, such as PET tracers, in systemic vascular disease manifestations.

Specific goals:

1. **Select subset of vascular injury biomarkers in learning phase and use to advance the clinical qualification in patients with systemic vascular conditions to detect acute vascular injury:**

   The patient populations should include systemic vasculitides especially focused on active and untreated patients with non-infectious cutaneous leukocytoclastic vasculitis, anti-neutrophil cytoplasmic antibody-associated (ANCA+) vasculitis (PR3-ANCA+ and MPO-ANCA+ subtypes of granulomatosis with polyangitis [GPA] and microscopic polyangitis [MPA], giant cell arteritis and Takayasu's Disease, as well as balloon angioplasty (acute mechanical injury) as previously evaluated [9][10][12]. For those patients with ocular vascular injury manifestations of these vasculitides, this presents the opportunity to also measure the biomarkers against ocular vascular injury endpoints (see goal 4). The learning phase should be focused on a subset of these patients to provide a robust data set by which to select a subset of the panel of biomarkers to be used in the confirmatory phase, as well as the subsequent goals.

   Industry contribution:

   Expertise in data analysis and analytical support.

   Expected Applicant consortium contribution:

   Expertise in clinical vasculitides and/or dermatology research and access to unique cohorts of patients with the clinical vasculitides of interest, conducting observational cohort studies, clinical outcomes research, or pilot clinical projects that may contribute to the confirmatory data set. The clinical vasculitides academic collaborators should also have expertise or ready access to expertise in ophthalmology, as outlined in goal 4. Additionally, collaborators can provide analytical support.

2. **Augment healthy volunteer reference range data:**

   The panel of biomarkers selected in the learning phase of goal 1 will be assessed in subjects without detectable disease across age, gender and ethnic cohorts and with lower body mass index.

   Industry contribution:

   Industry members will provide samples from normal healthy volunteers with relevant metadata for sample analysis.

   Expected Applicant consortium contribution:

   Academic collaborators with access to unique cohorts of normal healthy volunteers (e.g. ethnic background, pediatric, or elderly samples) may contribute to the assessment of sample sets, as well as provide analytical support for the generation of these baseline assessments.

3. **Complement the clinical qualification of vascular injury biomarkers with imaging tools:**

Generate an exploratory data set to provide foundation for future confirmatory studies to enable clinical qualification of non-invasive imaging tools to support diagnosis and monitoring of clinical vasculitis, preferably PR3-ANCA+ vasculitis in combination with a panel of circulating vascular injury biomarkers (from goal 1). Imaging tools will include biomarkers already with compelling performance, such as MMP3, or that provide increased specificity to the vascular bed, such as an endothelial-specific tracer.

Expected Applicant consortium contribution:

Expertise in clinical vasculitides research and access to unique cohorts of patients with clinical vasculitis, preferably PR3-ANCA+ vasculitis, conducting observational cohort studies, clinical outcomes research, or clinical projects that may contribute to the exploratory data set. Academic collaborators would provide analytical support and clinical imaging capabilities to support a small scale exploratory clinical study to assess the diagnostic performance/value of a novel imaging agent of PR3-ANCA-associated vasculitis in combination with circulating vascular injury biomarkers. Additionally, academic collaborators with radiochemistry or medicinal/synthetic organic chemistry resources could also support the development and evaluation of potential radionuclides for vascular imaging.

Industry contribution:

Industry members will provide the exploratory MMP3-based imaging tools or support academic imaging candidates with a foundational preclinical qualification package demonstrating proof of concept in animal models and preclinical studies required to enable the clinical use of the imaging tool.

4. **Augment the clinical qualification of vascular injury biomarkers in patients with acute non-infectious ocular diseases with vascular injury** [13]**:**

This exploratory data set may enable an easier, more sensitive monitoring scheme and a patient population without underlying chronic vascular injury to support the clinical regulatory qualification outlined in goal #1. The biomarker levels in circulation may be compared to those in the ocular fluid. Diseases of interest include those with pathophysiology of vasculitis and microangiopathy with vascular leak that are not of infectious origin, including wet acute macular degeneration (AMD) diabetic retinopathy (DR) and various forms of acute uveitis (iritis, iridocyclitis, choroiditis, retinal vasculitis, chorioretinitis, anterior/intermediate/posterior uveitis, and drug-induced/idiopathic/immune-mediated uveitis). Clinical evaluation can be augmented by preclinical evaluation especially for drug-induced uveitis.

Expected Applicant consortium contribution:

Expertise in ophthalmology diagnostics (to include ultra-widefield FA, FA, OCT and fundus photographic evaluations), research, and access to unique cohorts of patients with the clinical ocular diseases of interest, conducting observational cohort studies, clinical outcomes research, or clinical projects that may contribute to the exploratory data set. Additionally, collaborators can provide analytical support.

Industry contribution:

Expertise in data analysis and analytical support and samples from ophthalmology programs.

Work package 5 – Biomarkers of CNS injury

Context of use:

The recent tragedy associated with the BIAL clinical trials in France underscores the critical need for more sensitive preclinical biomarkers predictive of neurotoxicity that can be readily translated to clinical trials. Thus, the goal of the current proposal is to evaluate the potential of non-invasive, fluid-based biomarkers (in human blood, urine, and/or CSF) to predict clinical neurotoxicity risk.

Approach and biomarkers of interest:

Several fluid-based biomarkers have been studied in attempts to improve diagnosis and prognosis of CNS injury and disease. Some of these biomarkers have also been studied in preclinical models of neurotoxicity.

However, none have been qualified for a specific clinical use. One of the reasons for this is that these candidate biomarkers have not been thoroughly evaluated in large enough numbers of human samples in order to fully characterise background variation or the influence of age, sex, body weight, ethnicity, comorbidities, drug treatments, etc. The successful applicant consortium will have: 1) demonstrated clinical experience with CNS injury/disease biomarkers and associated assays, 2) past experience with bioanalytical method validation of assays per Industry guidance; 3) the capacity to obtain relevant clinical samples for analysis.

Specific goals:

1. **Select and validate a panel of biomarker assays consisting of 4-5 proteins (e.g. GFAP, UCH-L1, tau) and 4-5 cytokines (e.g. IL1-β, TNF, IL10, TGF-β2) for use with human blood (serum or plasma), CSF or urine samples.**

   Other classes of biomarkers (e.g. isoprostanes) may also be proposed. The focus should be on achieving GLP/GCP standard validation (full or partial as needed) of up to 10 assays.

   Industry contribution:

   Expertise in development of biomarkers of CNS injury, analytical expertise, samples from clinical studies (healthy volunteers), data from preclinical studies.

   Expected Applicant consortium contribution:

   Expertise in CNS biomarkers, development and validation of biomarker assays, access to relevant samples.

2. **Fully characterise the baseline variation of biomarkers in samples from "healthy" volunteers using assays validated in Goal 1 to establish reference ranges including assessing the influence of age, sex, body weight, ethnicity, etc.**

   Depending on sample availability this objective will require up to 500 samples for each assay from volunteers with no known CNS disease or injury. In collaboration with the Liquid Biopsies work package, specific miRNA biomarkers (4-5 miRNAs) will also be identified for further evaluation.

   Industry contribution:

   Expertise in the development of biomarkers of CNS injury, samples from clinical trials (healthy volunteers).

   Expected Applicant consortium contribution:

   Clinical expertise in development of biomarkers of the CNS and access to samples from healthy subjects across various populations.

3. **Evaluate the influence of 2-3 injury/disease states and 1 neurotoxic chemical treatment on biomarkers identified in stages 1 and 2: this will include samples from patients with brain injury (e.g. stroke, TBI), neurodegenerative disease (e.g. AD, MS, etc.) and chemical-induced neurotoxicity.**

   Depending on sample availability, this objective will utilise ~100 samples from each type of patient.

   Industry contribution:

   Expertise in the development of biomarkers of CNS injury.

   Expected Applicant consortium contribution:

   Clinical expertise in appropriate disease phenotypes, ability to identify and access relevant samples from subjects with appropriate disease phenotypes, conduct biomarker studies.

Work package 6 – Liquid biopsies

Availability of non-invasive methods capable of differentiating underlying mechanisms of toxicity and/or disease is an unmet medical need. Micro RNAs (miRNAs) are regarded as a promising source of tissue-specific biomarkers that are released to circulation as a result of tissue damage and/or active secretion. Although some miRs showed promise as tissue specific leakage biomarkers [14] the recent progress in multiplexing technologies and next generation sequencing uncovered a paradigm changing potential of miRs to provide insights into pathogenesis of disease and/or mechanism of toxicity. Thus measuring miR profiles or signatures has been proposed as liquid biopsies capable of detecting injury in distal tissues including their mechanistic context [15]. It has been shown that , panels of miRs were able to differentiate APAP overdose from ischemic liver injury [16], diagnose types of diabetes [17], chronic heart failure [18], and Parkinson and Alzheimer disease [19][20]. Recently, next generation sequencing enabled unbiased interrogation of the whole miRNome including structural modifications of miRNAs, also called isomiRs. Interestingly, changes in the relative isomiR distribution have been associated with specific developmental stages and disease progression [21], APAP-induced liver injury [22] and hepatocellular carcinoma tissues [23] and a variety of liver impairments [15]. Therefore the proposed project will focus on evaluation of miR profiles as liquid biopsies that would be applicable for interrogation of mechanisms of toxicity and etiology and pathogenesis of diseases. Since liquid biopsies WP will require the development of new innovative approaches that include sequencing of a large number of serum samples and development of bioinformatic tools, it is expected that significant resources up (to 40%) will be committed to this WP.

Specific goals:

1. **Characterization of NextGen platform:**

   There are at least three categories of concern with miRNA sequencing which need to be addressed by the consortium such as (a) ligase bias, (b) effect of potential inhibitors of cDNA synthesis and qPCR present in serum and/or plasma samples and (c) characterisation of NextGen sequencing method performance. It is expected that the applicants will justify the selected sequencing platform with available published data and when not available outline studies that will sufficiently characterise selected sequencing technology.

   Industry contribution:

   Expertise in method development and validation.

   Expected Applicant consortium contribution:

   Nextgen sequencing methodology and data analysis expertise.

2. **Characterise circulating miRnome in healthy subjects:**

   The interpretation of the miR-based liquid biopsy approach is dependent on detailed characterization of the circulating miRNome in healthy subjects including evaluating the potential influence of age, sex, ethnicity, longitudinal variability, inter and intra-individual variability, effect of food etc. Since the characterization of circulating miR-nome will provide a foundation for the development of tissue damage-specific signatures, a large cohorts of subjects (500-2000) will need to be interrogated.

   Industry contribution:

   Serum samples from healthy volunteers of various specifications, expertise in design of studies, data interpretation, bioinformatics.

   Expected Applicant consortium contribution:

   Serum samples from healthy subjects (ages, sex, ethnic groups), Next gen sequencing methodology and data analysis.

3. **Develop specific target organ injury miR signatures:**

   This will require obtaining a sufficient number of samples from subjects with characterised impairments of various aetiologies. The focus of this specific goal is expected to be in line with target organ WP. If tissue

biopsies are available, tissue and liquid biopsy miRNA profiles will be compared. To be successful large numbers of subjects will need to be included in this project.

Industry contribution:

Serum samples from healthy volunteers of various specifications, expertise in design of studies, data interpretation, bioinformatics.

Expected Applicant consortium contribution:

Serum samples from subjects with specific diseases, Next gen sequencing methodology and data analysis.

4. **Develop an informatics platform that allows the deconvolution of miR based signatures to pathways and mechanisms:**

The goal is to develop a user-friendly system that will enable researchers to interrogate miR profiles for meaningful mechanistic information. This objective will need to utilise available databases of miR tissue distribution across human and non-clinical species that are available publicly or from member companies.

Industry contribution:

Data from existing databases (miR atlas), expertise in design of studies, data interpretation, bioinformatics.

Expected Applicant consortium contribution:

Bioinformatic expertise, development of databases and search engine approaches for data mining.

Work package 7 – Assay development, sample and data management, and statistical support

This WP will be integrated with individual WPs and provide backbone support for other WP activities. This might be an opportunity for including SMEs with appropriate expertise. Availability of robust assays that are transferable to research and ultimately to clinical laboratories for commercial use is essential for implementation of safety biomarkers in clinical trials and diagnosis of diseases. It is important to note that the level of validation will need to reflect the stage of the biomarker candidate [24]. For example, a kidney marker intended for regulatory review differs from the qualification of an emerging vascular or CNS biomarker candidate. These issues will be addressed through assay validation plans co-authored by consortia partners and the SME or laboratory performing a particular validation. This WP will provide opportunity to engage SMEs to standardise assay methodologies for particular stages of development and potentially develop commercially available diagnostics. Furthermore, appropriate sample and data management tools that are compliant with data management and patient privacy standards and statistical support will be essential for TransBioLine success. This WP will provide necessary support across individual target organ- and liquid biopsies-based WPs.

Specific goals:

1. **Coordinate the development of standardised validation procedures and SOPs for all biomarker assays and sample management**;

2. **Prioritise most impactful biomarker assays for development of diagnostics as laboratory developed tests (LDTs) or potentially as in vitro diagnostics (IVDs);**

Industry contribution:

Assay validation, SOP and quality control.

Expected Applicant consortium contribution:

Assay development, validation, LDT and potentially IVD development capabilities.

3. **Provide sample and data management support for TransBioLine project;**

Industry contribution:

Expertise in compliance.

Expected Applicant consortium contribution:

Sample management and distribution across laboratories. Data warehousing in compliant databases.

4. **Statistical support for individual WPs.**

Industry contribution:

Expertise and conduct of statistical analysis**.**

Expected Applicant consortium contribution:

Expertise and conduct of statistical analysis.

Work package 8 – Regulatory acceptance of biomarkers

Achieving regulatory acceptance of emerging safety biomarkers by EMA, FDA and PMDA is essential for their application in clinical trials and diagnosis of disease. Although the biomarker qualification process utilises evidentiary standards that were recently formalised [1][24], it is necessary to develop and maintain a dialog and collaborative relationship with regulatory agencies via consultations, meetings and workshops. In addition, establishing connections and relationships with stakeholders from wider scientific and health care communities will be essential for dissemination of and implementation of novel biomarkers in clinical practice.

Specific goals:

1. **Develop biomarker qualification strategy for all safety biomarkers in the TransBioLine project;**
2. **Develop individual biomarker qualification packages and manage submissions to regulatory agencies as part of the routine regulatory interactions;**
3. **Organise annual workshops with regulatory agencies to discuss biomarker qualification**.

Industry contribution:

Support writing regulatory documents, expertise in regulatory interactions.

Expected Applicant consortium contribution:

Expertise in regulatory science, managing submissions to regulatory agencies, organizing workshops and meetings with regulatory agencies.

Work package 9 – Project management

The goal of this work package is the overall project coordination, integration and dissemination.

Specific goals:

1. **Financial management, maintain timelines, and execute on deliverables and milestones;**
2. **Legal and contractual management;**
3. **Communication to the scientific community and the public.**

Industry contribution:

Programme co-leadership, WP co-leadership of all aspects of the project; contribution to application and valorisation aspects, project and financial management, contribution to communication and dissemination.

Expected Applicant consortium contribution:

Programme co-leadership, WP co-leadership; proven record of professional project management capabilities; expertise and experience in managing complex and long lasting projects including financial management; previous experience with management of IMI projects including scientific and technical programme coordination and reporting to the commission; contribution to communication and dissemination.

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Pilot programme on a Clinical Compound Bank for Repurposing

Topic 12: Cardiovascular diseases and diabetes

Topic 13: Respiratory diseases

Topic 14: Neurodegenerative diseases

Topic 15: Rare/orphan diseases

Topic details

Topic code	IMI2-2017-13-12 IMI2-2017-13-13 IMI2-2017-13-14 IMI2-2017-13-15
Action type	Research and Innovation Action (RIA)
Submission and evaluation process	2 stages

Specific challenges to be addressed

On average it takes about 14 years for a new drug to travel from the research lab to market approval at an average cost of ≥€2 billion. Only 10% of compounds that enter preclinical testing ever make it into clinical trials, with only 20% of these achieving marketing approval [1][2].

A number of innovative programmes have been established over the last few years between research funding agencies and industry to provide academic researchers with access to high-quality pharmaceutical industry compounds that have stalled at some stage during research or development. Many of these compounds have already undergone preliminary testing in humans, but have not been progressed further because they were not found to be sufficiently effective in the indication for which they were originally developed.

These compounds represent valuable tools that researchers can use to test their novel hypotheses for alternative therapeutic indications, with the ultimate aim of identifying alternative uses for these compounds in other indications ('repurposing', 'repositioning'). Since partial preclinical and clinical documentation packages have been developed for these assets, any positive findings hold the opportunity to progress towards the market more quickly and cost-effectively, with the ultimate goal of benefiting patients in diseases of high unmet need. Examples of ongoing open innovation schemes include the National Institute of Health/National Center for Advancing Translational Sciences (NIH/NCATS), the New Therapeutic Uses program in the US[158], the Medical Research Council (MRC) industry asset sharing initiative in the UK[159] and the ERA-Net E-Rare

[158] https://ncats.nih.gov/ntu/about?_sm_au_=iDVNkL6Rk8jPqH55
[159] https://www.mrc.ac.uk/news/browse/world-s-largest-collection-of-deprioritised-pharma-compounds-opens-to-researchers/

2016 call[160] in which many EFPIA members already provide previously unprecedented access to a subset of their assets. Expanding this asset-sharing repurposing programme through IMI2 JU aims to provide researchers across the EU with the same opportunity to form hypothesis, to engage in collaborative research with industry and to access discontinued compounds that have already passed through several stages of the drug development process.

In this call, a number of compounds are made available for exploration in specific therapy areas: cardiovascular diseases and diabetes, respiratory diseases, neurodegenerative diseases and rare/orphan diseases.

The pharmaceutical small molecule compounds made available are listed in the Appendix, together with key information on mechanism of action, pharmacology, safety, tolerability and exclusions relating to these compounds. The applicants will submit proposals to utilise these assets to test their hypotheses for alternative indications within the above-mentioned therapeutic areas, to generate clinical data and, if needed, prerequisite preclinical data, with the ultimate aim of taking these assets to the market in alternative indications to those that they were originally developed for.

If these pilot topics on drug repurposing are successful, the programme will be expanded in future calls.

Need and opportunity for public-private collaborative research

The European research organisations, including universities, hospitals and small and medium-sized enterprises (SMEs) are renowned for their cutting-edge science and innovative spirit, yet often do not have the tools nor the expertise to develop their discoveries towards the clinic and regulatory approval. The pharmaceutical industry has built up significant experience, knowledge and research and development (R&D) information for a large number of deprioritised or disused compounds arising from terminated programmes. Public-private collaboration enables the investigation of scientific advances within research organisations using drugs and drug candidates from industry. Academic organisations benefit from access to clinic-ready assets and prior R&D information. This includes predefined preclinical and clinical dosing regimens, toxicological and pharmakokinetic/pharacodynamic data packages which help to ensure their studies are designed with the best possible chance of success, alongside the industrial guidance on the data package needed to support development and transition towards the market.

By collaborating and bringing the strengths of European research communities and pharmaceutical companies together, it may be possible to accelerate the research in drug repurposing and potentially speed up the development of new treatments and giving patients access to these new therapies.

Parallel grant-funding schemes with the NIH/NCATS, MRC and selected institutions around the world, contain many examples of preclinical and clinical proof-of-concept studies in which the academic and industry collaboration has provided the opportunity for a rapid transition towards clinical development. This model has also previously provided the opportunity to spin out new SMEs based on positive repositioning data, enabling funds to be raised to progress to later stages of clinical development. All of these advantages have the long-term effect of getting drugs to the market quicker and more cost effectively for the benefit of patients.

A private-public partnership like IMI2 JU provides the opportunity to test interesting compounds in new indications that may not be otherwise tested. In addition, IMI2 JU provides an exciting possibility for translational research funding accessible to researchers across the EU and H2020 Associated Countries.

[160] http://www.erare.eu/previous-calls

Scope

The overall objective of this pilot programme is to take one of the nine previously deprioritised clinical compounds listed in the Appendix – and investigate their therapeutic potential in new clinical indications in areas of high unmet need.

Under the Clinical Compound Bank for Repurposing pilot programme, there will be four separate topics, one for each disease area listed below:

- **TOPIC 12 : Cardiovascular diseases and diabetes**
- **TOPIC 13 : Respiratory diseases**
- **TOPIC 14 : Neurodegenerative diseases**
- **TOPIC 15 : Rare/orphan diseases**

Potential applicants must be aware that only the compounds identified in the Appendix are within the scope of these four topics. These compounds are listed therein together with key information including mechanism of action, original indication, route of administration pharmacology, safety, tolerability and links to previous clinical studies and publications, to facilitate idea generation by investigators with hypotheses for novel uses. The listed compounds have all been through clinical phase 1 studies.

All proposals submitted under one topic will be evaluated by a panel of independent experts and ranked together. For each topic, only one proposal will be eventually retained and a grant agreement will be signed.

- Proposals should cover clinical Phase 2A proof of concept studies, though larger Phase 2 studies are also in scope if these are within the budget. Clinical submissions should aim at moving towards the next stage of development and positive data should be a starting point for further investment into developing a drug towards clinic and regulatory approval.
- If preclinical work is deemed necessary to provide additional support and confidence before moving into a clinical study in an alternative indication, proof-of-concept/feasibility preclinical studies of up to a year in duration can be included in the proposal. These studies should have clear go/no-go criteria for progressing in to the clinical phase of the project.

Important note: This programme intends to support only innovative clinical development for the compounds listed in the Appendix. This means that proposals for clinical development should not be considered in an indication which has been already tested (i.e. original primary indication or additional studies) or if there are already ongoing or planned clinical studies on identical or related disease indications with the compound or with a compound with overlapping mechanism of action that impacts the novelty of a given proposal.

Information on original primary indications, already tested indications, ongoing and/or planned clinical studies for each of these nine compounds can be found in the Appendix.

Therefore, applicants must demonstrate in their stage 1 application (short proposal) that the proposed study is innovative for the chosen compound.

Expected key deliverables

Proposals should have the potential to identify a new indication for the compound chosen among those made available within this pilot programme. Each selected project must aim at making clear scientific advances within a given disease area.

Key deliverables for each selected project include:

- initiation and completion of new Phase 2A clinical proof-of-concept study in the chosen indication which was not previously investigated with the specific compound;
- preclinical data to support a go/no-go decision for initiation of the clinical study in the new indication, if this is deemed necessary for the selected project;
- dissemination of the results in high-impact publications.

Expected impact

The expected impact is as follows:

- achieving early proof-of-concept for new mechanisms with the potential to rapidly bring novel drugs to patients in areas of high unmet need and/or those with greatest disease burden;
- generation of ideas and/or data licensed from the research organisation, leading to further development of the compound in the new indication;
- added value by repurposing pharmaceutical assets which have already passed through several stages of the R&D process. This can offer significant time, cost and risk savings over embarking on discovery programmes with novel targets;
- supporting EU academic institutions to conduct well-designed and high-standard translational and drug development research with quality compounds under GCP conditions, resulting in high impact publications and patents when possible;
- pooling of resources and greater collaboration between the public and private sectors, with the potential for pharmaceutical involvement or establishment of SMEs following in/out-licencing;
- boosting the discovery and development of therapeutics in the areas of cardiovascular diseases and diabetes, respiratory diseases, neurodegenerative diseases and rare/orphan diseases using a more cost-effective approach to drug development;
- advancing science and knowledge of disease (patho)physiology through testing of new hypothesis;
- boosting European competiveness by contributing to the establishment of closer links between industry and academia across the EU, and ensuring Europe is competitive in line with initiatives already in place in other leading scientific regions around the world.

Potential synergies with existing consortia

Applicants should take into consideration, while preparing their short proposal, relevant national, European (both research projects as well as research infrastructure initiatives), and non-European initiatives. Synergies and complementarities should be considered in order to incorporate past achievements, available data and tools/models and lessons learned where possible, thus avoiding unnecessary overlap and duplication of effort.

The projects generated from this topic will be complementary to other ongoing similar initiatives in other parts of the world.

Industry consortium

The industry consortium is composed of the following EFPIA companies:

- AstraZeneca (lead)
- Servier

The industry consortium will contribute the following expertise and assets:

AstraZeneca and Servier will supply compounds for these pilot topics. The EFPIA companies will cover the costs associated with manufacturing, supply and delivery of active pharmaceutical ingredient (API) required for a given study. Clinical studies costs associated with supply, packaging and distribution of drug product will also be covered by the EFPIA companies. The EFPIA companies will provide expert support for e.g. study design, protocol writing, study oversight, pharmacovigilance, as well as expert support throughout the duration of the funded studies with the aim of working with the consortium to move positive data towards the next stage of development. Under each topic, only one of the two contributing companies listed above will be involved in the full proposal and selected project. This will depend on the clinical compound which will be developed under a new indication.

Indicative duration of the action

The indicative duration of the action is 48 months.

Clinical studies are anticipated to have a maximum duration of 36 months per action. If preceded by a preclinical study, this study should have a maximum duration of 12 months, giving a maximum of total 48 months per action.

Indicative budget

The indicative EFPIA in-kind contribution is EUR 4 160 000.

Due to the global nature of the participating industry partners, it is anticipated that some elements of the contributions will be non-EU/H2020 Associated Countries in-kind contributions.

The financial contribution from IMI2 JU is a maximum of EUR 4 160 000.

Under each topic, the maximum IMI2 JU contribution is EUR 1 000 000 per clinical study and an additional EUR 40 000 if a preceding preclinical study is proposed.

Applicant consortium

The applicant consortium will be selected on the basis of the submitted short proposals. Applicants are expected to form consortia with other investigators to bring in relevant expertise and ensure study recruitment targets are met in the clinical studies. All experimentation should be undertaken within the investigators' research institutions and/or their linked third parties.

The proposals should be based on a strong scientific rationale from prior preclinical and/or clinical data. The planned studies should have the potential for improvement of currently available treatments and it is also important that the proposed clinical studies in the projects have a clear feasibility for further clinical development and commercialisation of the compounds in the suggested indications, beyond the project duration.

The applicant consortium is expected to address all the research objectives and make key contributions to the defined deliverables in synergy with the relevant contributing company from the industry consortium which will join the selected applicant consortium for preparation of the full proposal in stage 2.

This may require mobilising, as appropriate, the following expertise and resources:

- experience and capability to conduct all aspects of a clinical trial using an investigational medicinal product (including data analysis and reporting) under good clinical practice (GCP) in the proposed indication;
- clinical and preclinical expertise as necessary for the scope of a given study;
- expertise in the science of drug development including aspects of clinical pharmacology, study design and conduct;
- experience and capability to submit an application for clinical trial authorisation with the European Medicines Agency (EMA)/ national regulatory authorities in all member countries of a given consortium;
- capacity to recruit sufficient number of patients within a few clinical study centers;
- strong project management and communication expertise.

Suggested architecture of the full proposal

The applicant consortium should submit a short proposal which includes their suggestions for creating a full proposal architecture, taking into consideration the contributing company participation including its contributions and expertise.

In the spirit of the partnership, and to reflect how IMI2 JU call topics are built on identified scientific priorities agreed together with EFPIA beneficiaries/large industrial beneficiaries, these beneficiaries intend to significantly contribute to the programme and project leadership as well as project financial management.

The final architecture of the full proposal will be defined by the participants in compliance with the IMI2 JU rules and with a view to the achievement of the project objectives. The allocation of a leading role within the consortium will be discussed in the course of the drafting of the full proposal to be submitted at stage 2. To facilitate the formation of the final consortium, until the roles are formally appointed through the consortium agreement, the proposed project leader from among EFPIA beneficiaries/large industrial beneficiaries shall facilitate an efficient negotiation of project content and required agreements. All beneficiaries are encouraged to discuss the project architecture and governance and the weighting of responsibilities and priorities therein.

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Appendix – Compound information sheets

	Compound name: AZD0328
Mechanism of action	Nicotinic acetylcholine receptor alpha 7 (α7 nAChR) agonist
Overview	AZD0328 is a stereo-selective, potent, full agonist of the human α7 nAChR (binding IC50 of 3 nM; activation of whole cell current (half maximal inhibitory concentration) IC50 of 2.9 μM; intrinsic activity = 101% compared with acetylcholine). It is ~20-fold selective to the α1β1γδ nAChR, 1000-fold selective to other nicotinic receptors and a panel of other targets (inhibition of radioligand binding), and is equipotent with the structurally related serotonin 5HT3 receptor (2 μM). Oral administration of AZD0328 significantly improves operant conditioning and long-term potentiation in rats. In rhesus monkeys, spatial working memory is enhanced at doses above 0.001 mg/kg (plasma compound levels of ~0.2 x whole cell current IC50).
Additional information	In a 14 day phase 2A clinical study in patients with schizophrenia, concurrently taking an additional anti-psychotic drug, AZD0328 (0.00093 to 0.675mg; plasma levels ~5 x IC50 at 0.675mg dose), did not show a statistically significant improvement in cognition nor other secondary endpoints.
Safety/Tolerability	In single and multiple ascending dose clinical studies, where AZD0328 was studied at up to 2 mg and 1.35 mg (for 13 days), respectively, the most common adverse events reported were nausea, facial flushing and gastrointestinal disturbances; nausea limited clinical tolerability at doses ≥1.35 mg. In a phase 2A study, AZD0328 at concentrations of up to 0.675 mg once daily for 14 days, did not show any major safety or tolerability concerns in subjects with schizophrenia other than a dose-related incidence of nausea. The (maximum tolerated dose) MTD for multiple dose administration in the context of the original indication was determined to be 1 mg. Preclinical studies of up to 6-month duration have been performed.
Suitable for and Exclusions	The reproductive toxicology package indicates a risk of fetal toxicity. The inclusion of women of child-bearing potential would need to be assessed for any proposal based on the risk-benefit and the use of appropriate highly effective contraception. AZD0328 is renally cleared and, therefore, future studies will require an assessment of the risk-benefit for subjects with renal impairment.
▪ **Clinical trials** ▪ **Previous, ongoing and planned**	Link to clinicaltrials.gov Original indication: schizophrenia
Additional characteristics: ▪ Central nervous system (CNS) penetrance ▪ Pediatric diseases	 Yes Not studied
Publications	Pubmed AZD0328

	Compound name: AZD0530 (saracatinib)
Mechanism of action	Src tyrosine kinase family inhibitor
Overview	Saracatinib (AZD0530) is a potent inhibitor of the Src family of tyrosine kinases (IC50 of 2.7 – 5 nM) with >250-fold selectivity over other tyrosine kinase families. AZD0530 has sub-micromolar activity in a variety of cellular assays of human tumour cell proliferation and inhibits tumour growth in murine and rat allografts and xenografts at compound levels of ~2 x IC50 in plasma when dosed orally.
Safety/Tolerability	In healthy human volunteers, AZD0530 was tolerated in single dose studies up to 1000 mg and in 14 day multiple dose studies at up to 250 mg. A maximum tolerated dose in oncology patients of 175mg per day has been determined. Adverse events across various patient groups include: anemia, nausea, anorexia, asthenia, pyrexia, vomiting, diarrhea, and pneumonitis. Preclinical safety studies to support clinical dosing up to 12 months in duration have been performed. These reveal haematological changes and proliferative, hypertrophic and degenerative changes in multiple organs which were mild in severity and showed evidence of reversal. All changes were considered generally to be consistent with SRC inhibition.
Additional information	Target coverage has been demonstrated in patients by decreased phosphorylation of focal adhesion kinase and paxilin in tumour biopsies. In healthy volunteers and patients, reduction in serum βCTX, a marker of bone resorption, was evident at doses of 125 & 175 mg (125 mg achieves plasma levels of ~5 x IC50 at Cmin steady state). To date no effect on survival has been observed in a number of oncology trials with AZD0530 as monotherapy (at doses of up to 175 mg).
Suitable for and Exclusions	The reproductive toxicology package indicates a risk of fetal toxicity. AZD0530 is a moderately potent CYP3A4 inhibitor; concomitant administration of compounds / medicines that are metabolised by this route should be avoided. Unsuitable for further oncology research. Use in respiratory indications is also excluded.
▪ **Clinical trials** ▪ **Previous, ongoing and planned**	European Clinical Trials Register Clinicaltrials.gov Oncology, Alzheimer's disease, metastatic bone pain, alcohol abuse, Parkinson's disease
Additional characteristics: ▪ CNS penetrance ▪ Pediatric disease	 Yes Not suitable
Publications	Pubmed AZD0530

	Compound name: AZD1981
Mechanism of action	Chemoattractant receptor-homologous molecule expressed on Th2 cells (CRTh2) antagonist [prostaglandin D2 (DP2) receptor antagonist]
Overview	AZD1981 is a potent (binding IC50 of 4 nM), fully reversible, functionally non-competitive antagonist of human CRTh2. It blocks agonist-induced human eosinophil CD11b expression, shape change (including in whole blood), and chemotaxis as well as basophil shape change and Th2-cell chemotaxis at IC_{50}'s of 8.5 – 50 nM. Potency is similar across species as is plasma protein binding (~97%). AZD1981 is a weak (10's of µM) inhibitor *in vitro* of CYP2C9, OATP1B1 and UGT1A1 as well as inducer of CYP3A4. These potential DDI effects appear to translate to in vivo at super pharmacologic doses/exposures (see below).
Safety/Tolerability	AZD1981 has been found to be generally well tolerated in healthy volunteers (single oral dose up to 4000 mg; multiple doses up to 2000 mg (twice a day) BID for 2 wks), asthma or COPD patients (up to 100 mg, BID for 4 wks), and asthmatics (up to 400 mg BID for 12 wks). A small percentage of patients treated with AZD1981 had notable elevations of (alanine aminotransferase) ALT and (aspartate aminotransferase) AST without notable increase in total bilirubin. Results suggest a dose-response relationship with the highest percentage of subjects having identified LFT abnormalities in the AZD1981 400 mg BID group (~2 – 3% above placebo). In all cases, transaminases returned to baseline after AZD1981 was stopped. However, the possibility that AZD1981 may be associated with an increased risk of liver injury cannot be excluded. In completed DDI studies, AZD1981 at 400 or 500 mg BID, but not at 100 mg BID (where tested), increased the plasma exposure of ethinyl estradiol in female volunteers receiving a combined oral contraceptive (COC), warfarin (CYP2C9 substrate), and pravastatin (OATP1B1 substrate), while decreasing midazolam (CYP3A4 substrate). Preclinical safety studies of up to 12-month duration have been performed.
Additional information	Target engagement was demonstrated in the (single ascending dose) SAD and (multiple ascending dose) MAD phase 1 studies using an *ex vivo* whole blood PGD_2-induced eosinophil shape change assay (A_2 = 35nM). Data from these as well as asthma efficacy studies indicate effective target coverage at doses of 40 – 80 mg BID or (three times a day) TID.
Suitable for and Exclusions	Preclinical reprotoxicology data are available and have not identified any specific risks. Women of child-bearing potential using highly effective contraception can be included. Given the potential for DDI and LFT effects (see above), dosing regimen (level and duration) as well as inclusion/exclusion criteria should be selected carefully to support a favourable risk-benefit.
▪ **Clinical trials** ▪ **Previous, ongoing and planned**	clinicaltrials.gov Asthma, chronic sinusitis with nasal polyps, chronic idiopathic urticaria, diabetes
Additional characteristics: ▪ CNS penetrance ▪ Pediatric diseases	Low CNS penetrance. There are currently no clinical data to support use in pediatric populations below 12 years of age, although existing preclinical data would support clinical studies in a pediatric population of >5 years.
Publications	pubmed azd1981

	Compound name: AZD4017
Mechanism of action	11-beta-hydroxysteroid dehydrogenase type 1 (11β-HSD1) inhibitor
Overview	AZD4017 is a competitive, fully reversible inhibitor of human recombinant 11β-HSD1 (IC_{50} of 2 nM) and of 11β-HSD1 activity in isolated human adipocytes (1.8 nM) with cortisone as substrate. It is selective (>2000x) over human recombinant 11β-HSD2 and other closely homologous enzymes *in vitro*. AZD4017 has limited activity in pre-clinical species other than cynomolgus monkey. However, related tool compounds with activity in all species are available; e.g., in diet-induced obese mice, a rodent-active AZ 11β-HSD1 inhibitor induced significant, and approximately half-maximal, reduction in adipose mass and weight gain when compound exposure was ~1 x IC_{50}.
Safety/Tolerability	In single ascending dose studies, Caucasian and Japanese volunteers were exposed to AZD4017 dosed up to 750 mg BID. In a MAD study, volunteers received single doses of AZD4017 followed by repeated doses ranging from 75 mg QD up to 900 mg BID for 9 days. A few subjects on treatment had transient increased liver enzyme levels above ULN (>3 x ULN in one subject) with no concurrent increase in bilirubin. An activation of the HPA axis was demonstrated by an increase in ACTH and DHEAs levels and by an increase of total urinary glucocorticoid metabolites. However, s-cortisol and testosterone levels were not changed. In a phase 2a glaucoma study, a number of subjects had incidences of raised liver enzymes at 1 x ULN, but with no associated adverse events. Preclinical toxicity studies of up to 3 month duration have been performed in rat and non human primate. Changes in adrenal glands were noted in both preclinical species but were considered an adaptive response of this organ to altered function. Findings in the liver and the thyroid gland of rat were also considered adaptive and not degenerative in nature.
Additional information	In a 9-day proof of mechanism study, AZD4017 (1200 mg QD) significantly inhibited hepatic 11β-HSD1 activity as measured by an oral prednisone challenge. Measurements of urine glucocorticoid metabolites further indicate an inhibitory effect on the whole body 11β-HSD1 activity. Regarding the 11β-HSD1 inhibitory effect in adipose tissue, a MAD and PoM study in abdominally obese subjects demonstrated inhibition of 11β-HSD1 after single dosing, yet no sustained inhibitory effect after repeated doses at the tested dose levels. However, *ex vivo* investigations suggest the possibility to obtain an inhibition after repeated dosing at high AZD4017 concentrations. In a 28 day phase 2a study in patients with raised intraocular pressure, AZD4017 dosed at 400mg BID, produced no change in IOP when compared to placebo (plasma concentrations of ~10 x IC_{50}).
Suitable for and Exclusions	Preclinical reprotoxicology data are not available for this compound. The inclusion of women of child-bearing potential using highly effective contraception in trials of modest size and duration could be considered based on the risk benefit and in accordance with territory specific requirements. Preclinical safety studies support future clinical studies of up to 3-month duration with the need for monitoring liver enzymes, thyroid, and adrenal function.
▪ **Clinical trials** ▪ **Previous, ongoing and planned**	clinicaltrials.gov Post-menopausal osteopenia, idiopathic intracranial hypertension, glaucoma, iatrogenic Cushing's syndrome, diabetic wound healing, metabolic disorders.
Additional characteristics: ▪ CNS penetrance ▪ Pediatric diseases	 Low CNS penetrance Not studied
Publications	pubmed AZD4017

	Compound name: AZD7325
Mechanism of action	Gamma-aminobutyric acid receptor A alpha 2 & 3 ($GABA_{Aα2,3}$) positive modulator
Overview	AZD7325 is a high affinity, selective modulator of the $GABA_A$ receptor system, with differential binding and modulatory properties dependent on the particular GABAA subtype. Binding affinity is high at $GABAA_{α1}$, $_{α2}$ and $_{α3}$ (Ki of 0.5, 0.3 and 1.3 nM, respectively), but not $GABA_{Aα5}$ (230 nM). Using whole cell electrophysiology after specific expression of a $GABA_A$ subunit in Xenopus oocytes, AZD7325 did not display intrinsic agonist activity at any subtype, but potentiated the response of diazepam at Aα2 and Aα3 (43 and 45%, respectively at 100 nM), but not Aα1 or Aα5. In contrast, AZD7325 acted as a full antagonist of zolpidem at Aα1 consistent with a lack of sedative liabilities in vivo. Selectivity was >100-fold in a panel of 160 other receptors, ion channels and enzymes, with the closest secondary pharmacology target being melatonin MT1 receptor antagonism (IC_{50} of 126nM). AZD7325 also potentiated native GABA responses in neurones prepared from the rat prefrontal cortex, occupied brain binding sites in non human primates as assessed by PET (approximately 50% receptor occupancy at plasma levels of ~1 x Ki), and demonstrated efficacy in a number of rat anxiety models.
Safety/Tolerability	AZD7325 has been administered to healthy volunteers at single doses of up to 100 mg and repeated doses up to 50 mg for 7 days. Adverse events were CNS in nature, and included dizziness, feeling of relaxation, euphoric mood, somnolence, and headache. These were transient, mild, and related to peak plasma concentrations. In patients dosed for up to 28 days, AZD7325 was generally well tolerated with the most frequent adverse events being dizziness, headache, and somnolence although one grand mal convulsion was also reported and considered to be treatment related. Preclinical toxicity studies of up to 3-month duration have been performed. These have identified pharmacologically mediated changes in behavior and, additionally, changes to heart rate, increases in cholesterol, AST and ALT, and also changes in hematology parameters. No compound related histopathogical changes were found.
Additional information	Receptor occupancy was measured by PET imaging in healthy volunteers; maximal occupancy was achieved at doses of 10mg, 20mg and 30 mg. Two phase 2a GAD studies have been conducted. In the first, AZD7325 was dosed at either 2 or 5 mg BID or 10mg QD for 28 days, achieving compound plasma exposures of ~4 x K_i. In the second, it was dosed at either 5 or 15mg BID and compared with lorazepam. While the primary objective of greater efficacy vs. placebo and/or lorazepam, as assessed by the Hamilton Anxiety scale, was not met at any of the doses tested, the placebo response rate was considered to be high and reduction in other anxiety endpoints at 10 mg and depression (Montgomery-Asberg depression scale) MADRS score were noted.
Suitable for and Exclusions	Preclinical reprotoxicology data are available and have not identified any specific risks. Women of child-bearing potential using highly effective contraception can be included. Subjects with past or present symptoms of alcohol or drug abuse/dependence and/or subjects suspected of abusing alcohol or illicit or prescription medications should be excluded. Subjects with past or present history of seizures or convulsions should be excluded.
▪ **Clinical trials** ▪ **Previous, ongoing and planned**	clinicaltrials.gov Generalised Anxiety Disorder, fragile X syndrome, peripheral sensory neuropathy, dystonia, autistic spectrum disorder

Additional characteristics: ▪ CNS penetrance ▪ Pediatric diseases	 Yes Not studied
Publications	pubmed AZD7325

	Compound name: AZD1656
Mechanism of action	Glucokinase (GK; hexokinase 4) activator
Overview	AZD1656 is a potent, selective (>100-fold versus hexokinase 1 and 2 and a pharmacology screening panel), activator of human and rat glucokinase *in vitro*; EC_{50}'s = 0.057 and 0.072 µM, respectively, for the recombinant enzymes, which translates into cellular systems (EC_{50}'s = 1.39 and 0.47 µM in human and rat hepatocytes, respectively). AZD1656 reduces plasma glucose levels in a dose-dependent fashion, with a rapid onset of action, in normo-glycaemic insulin resistant rats and diabetic mice, when dosed acutely and when dosed once daily for up to 28 days.
Safety/Tolerability	AZD1656 has been studied in single doses of up to 180mg and multiple doses to 150mg BID for 8 days in healthy volunteers as well as alone and in combination with other blood glucose control agents in diabetic patients at 200 mg daily for up to 6 months duration. In both healthy volunteers and diabetic patients no significant clinical effects other than glucose lowering were noted. Preclinical studies of up to 12-month duration have been performed. These revealed a potent glucose lowering effect, and thereby, the results of chronic toxicology studies in healthy animals were confounded by severe hypoglycaemia at higher doses and sequelae such as Wallerian type nerve degeneration and skeletal muscle fibre degeneration. Additional changes, also considered secondary to hypoglycaemia, were seen in the liver (loss of hepatocellular glycogen).
Additional information	In a phase 2 study in Japanese type 2 diabetic subjects, AZD1656, given BID at high (40 – 200 mg/day), medium (20 – 140 mg/day) and low (10 – 80 mg/day) doses over a 4-month period, has been found to lower HbA1c and fasting plasma blood (FPG) glucose levels with a 50 mg dose producing compound levels of ~2 x EC_{50} in plasma. However, this effect was transient trending towards pre-dose levels between weeks 8 and 16 and there was no statistically significant change in either HbA1c or FPG from baseline at 4 months.
Suitable for and Exclusions	Preclinical reprotoxicology data are available and have not identified any specific risks. Women of child-bearing potential using highly effective contraception can be included. Proposed indications should be evaluated against the risk of hypoglycaemia in non-diabetic subjects.
▪ **Clinical trials** ▪ **Previous, ongoing and planned**	clinicaltrials.gov European Clinical Trials Register Diabetes / metabolic disease
Additional characteristics: ▪ CNS penetrance ▪ Pediatric diseases	 Low CNS penetrance Not studied
Publications	pubmed AZD1656

	Compound name: AZD5904
Mechanism of action	Myeloperoxidase (MPO) inhibitor
Overview	AZD5904 is a potent (IC_{50} of 140 nM), irreversible inhibitor of human MPO with similar potency in mouse and rat. It is 10 to 19-fold selective compared to the closely related lactoperoxidase and thyroid peroxidase; >70-fold to a broad panel of other enzymes, ion channels, and receptors. In isolated human neutrophils, 1 µM inhibited PMA stimulated HOCl by >90%. In rats, a plasma concentration of ~5 µM decreased the *in vivo* formation of glutathione sulphonamide (a product of the reaction of HOCl with glutathione) from *in situ* zymosan activated peritoneum neutrophils.
Safety/Tolerability	AZD5904 has been administered orally to healthy volunteers in single doses of up to 1200 mg (1400 mg with extended release (ER) formulation) and multiple doses of up to 325 mg TID (600 mg BID for 10 days with ER formulation). In total, 181 subjects have been dosed in five phase 1 studies. No overtly drug-related adverse event has yet been identified, although a minimal effect on free P-Thyroxin (T4) and free P-Triiodothyronine (T3) could not be ruled out in the first multiple ascending dose study. Preclinical studies of up 12 month duration have been performed.
Additional information	Via both standard (TID) and extended release (BID) oral formulations, 300 mg yielded blood concentrations of ~30 µM peak, ~4 µM trough, and 12 -16 µM C_{avg}. The main route of clearance is renal, possibly via active transport. Plasma protein binding is 44%. *In vitro* studies indicate CYP2C19 inhibition and P-gp substrate as well as low (blood–brain barrier) BBB penetration.
Suitable for and Exclusions	The reproductive toxicology package indicates a risk of fetal toxicity. The inclusion of women of child-bearing potential would need to be assessed for any proposal based on the risk-benefit and the use of appropriate highly effective contraception. AZD5904 is renally cleared, thus, requiring caution and (pharmacokinetics) PK monitoring if dosed to subjects with impaired renal function. As AZD5904 has only previously been dosed for up to 10 days, clinical studies with dosing duration of no longer than 4 months are advised. Proposals for HFpEF will not be considered.
▪ **Clinical trials** ▪ **Previous, ongoing and planned**	No ongoing studies. Original indication: inflammation
Additional characteristics: ▪ CNS penetrance ▪ Pediatric diseases	 Low CNS penetrance Not studied
Publications	Pubmed MPO inhibitors

	Compound name: S 38093
Mechanism of action	Moderate antagonist/inverse agonist at histaminergic H_3 receptors Moderate antagonist at adrenergic α_{1A} and Sigma 1 receptors
Overview	In adult or aged rodents and monkeys, S 38093 (0.3 mg/kg p.o. or i.p.) demonstrates memory-enhancing properties in several models of working memory and episodic memory with an activity comparable to that of donepezil. S 38093 also displays positive effects on attention and cognitive flexibility as evidenced in monkeys. In addition, combination studies with S 38093 and AChEI (donepezil, rivastigmine or galantamine) or memantine in a mouse model of age-related episodic memory deficit have shown a synergistic beneficial effect of the combination compared to each drug given alone. Moreover, S 38093 (0.3 to 3 mg/kg p.o.) possesses beneficial effects on 3 pain symptoms (mechanical hyperalgesia, mechanical and thermal allodynia) in different neuropathic pain models in rat. On the whole, the kinetics and size of effect of S 38093 are comparable to those of positive controls gabapentin and/or pregabalin. In healthy young subjects submitted to a sleep deprivation procedure, S 38093 demonstrated a transitory effect on alertness at the highest tested dose of 100 mg and attentional properties at lower doses of 20 and 50 mg In healthy elderly volunteers, S 38093 showed a statistical significant activation in fMRI in several areas involved in working memory at 5 mg and in several areas involved in declarative/episodic memory at 5 and 20 mg. No beneficial effect of S 38093 alone or in combination with donepezil was observed on cognitive performance in patients with mild or moderate Alzheimer's disease.
Safety/Tolerability	▪ In animals: no cardiovascular or respiratory warning, no addictive potential. CNS and endocrine effects may occur, but only at higher doses / plasmatic concentrations than in pharmacological studies: potentiation of PTZ- or ECS-induced seizures in rat, increase in prolactin release. S 38093 was clinically well tolerated in rats and in monkeys in long-term toxicity studies; targets organs in rats at the high dose being female genital system, mammary glands and prostate. In repro toxicity study, no effect was observed on male fertility but S 38093 decreased global fecundity of females and increased post–implantation loss rate. ▪ During phase I studies, S 38093 (up to 100 mg/d) was administered as a single or repeated administration to young (males) and elderly (males and females) volunteers (n>300). Clinical overall acceptability was good. Main observed adverse events were mild or moderate sleep disorders (nightmares and insomnia), asthenia, diarrhoea and orthostatic hypotension. Two phases IIa and two phases IIb studies were performed with S 38093 (5 to 50 mg/d) in patients with mild or moderate Alzheimer's disease (n > 1000). These studies confirmed a global good tolerance of S 38093 alone or in add on to donepezil in patients. Main adverse events were falls, headaches, dizziness and depression. The review of overall safety data since the beginning of the development program for S38093 lead to consider seizure, orthostatic hypotension, fall and prolactin increase as expected for the S 38093.
Additional information	Favourable PK (almost complete absorption, high absolute bioavailability, linear pharmacokinetics, elimination terminal half-life in humans: 20h to 40h). Main enzymes involved in metabolism: CYP2C19 for 80-85%, CYP2C8 for 5-10% and amidases for 5-10%.

Suitable for and Exclusions	S 38093 should be avoided in pregnant and breast-feeding women and in subjects with history of epilepsy or history of a solitary seizure. Poor metabolisers and treatments known to inhibit CYP 2C19 activity are authorised due to low impact on PK. Suitable for indications in which there is a cognitive deficit (Alzheimer's disease excluded) and pain, in particular neuropathic. Not optimal for treatment of arousal disturbance (narcolepsy for instance).
▪ **Clinical trials** ▪ **Previous, ongoing and planned**	Link to EU Clinical Trial register
Additional characteristics: ▪ CNS penetrance ▪ Pediatric diseases	 In rat and mouse, the brain distribution of S 38093 is rapid and high. Waiver asked for children (Alzheimer's disease indication)
Publications	▪ Mechanistic characterization of S 38093, a novel inverse agonist at histamine H3 receptors. Sors A, Panayi F, Bert L, Favale D, Nosjean O, Audinot V, Arrang JM, Buisson B, Steidl E, Delbos JM, Huhtala T, Kontkanen O, Chollet AM, Casara P, Lestage P. Eur J Pharmacol. 2017 May 15;803:11-23. ▪ *In vivo* pharmacological profile of S 38093, a novel histamine H3 receptor inverse agonist. Panayi F, Sors A, Bert L, Martin B, Rollin-Jego G, Billiras R, Carrié I, Albinet K, Danober L, Rogez N, Thomas JY, Pira L, Bertaina-Anglade V, Lestage P. Eur J Pharmacol. 2017 May 15;803:1-10. ▪ The Synergistic Enhancing-Memory Effect of Donepezil and S 38093 (a Histamine H3 Antagonist) Is Mediated by Increased Neural Activity in the Septo-hippocampal Circuitry in Middle-Aged Mice. Sors A, Krazem A, Kehr J, Yoshitake T, Dominguez G, Henkous N, Letondor C, Mocaer E, Béracochéa DJ. Front Pharmacol. 2016 Dec 22;7:492. ▪ S 38093, a histamine H₃ antagonist/inverse agonist, promotes hippocampal neurogenesis and improves context discrimination task in aged mice. Guilloux JP, Samuels BA, Mendez-David I, Hu A, Levinstein M, Faye C, Mekiri M, Mocaer E, Gardier AM, Hen R, Sors A, David DJ. Sci Rep. 2017 Feb 20;7:42946. ▪ Effects of S 38093, an antagonist/inverse agonist of histamine H3 receptors, in models of neuropathic pain in rats. Chaumette T, Chapuy E, Berrocoso E, Llorca-Torralba M, Bravo L, Mico JA, Chalus M, Eschalier A, Ardid D, Marchand F, Sors A. Eur J Pain. 2017 Sep 6.

	Compound name: S 47445
Mechanism of action	S 47445 is a positive allosteric modulator of alpha-amino-3-hydroxy-5-methyl-4-isoxazole-propionic acid (AMPA) receptors (AMPA-PAM). It has no effect alone, no effect on NMDA nor kainate receptors. S 47445 (10µM) showed no interaction up to 10^{-5}M on about a hundred of receptors, enzymes and ion-channels tested. No difference of potentiation among the different AMPA receptors subtypes (GluA1/2/4 flip and flop variants) (EC_{50} between 2.5-5.4 µM), except a higher EC_{50} value for GluA4 flop (0.7 µM) and a greater amount of potentiation on GluA1 flop. S 47445 did not increase the release of monoamines in the frontal cortex after 5 days of oral administration of 40 mg/kg in mice in a microdialysis experiment. S 47445 at 10 mg/kg p.o. in awake mice in anesthetised rats enhanced the long-term potentiation (LTP) and reversed the deficit of LTP observed in middle-aged mice at 10mg/kg, p.o. It presented neurotrophic properties *in vitro* (on BDNF) and *in vivo* in hippocampus and cortex of adult rats in basal conditions and submitted to a mild stress and also in aged rats of 18 months old (from 1 to 10mg/kg p.o.).
Overview	Pharmacological data from animal models: *In vivo*, S 47445 has shown memory-enhancing properties in adult rats, adult, middle-aged and aged mice in 5 models of episodic memory tests after acute and chronic administration, and 3 rodent models of working memory, at pharmacologically-active doses between 0.3 and 3 mg/kg p.o. S 47445 presented antidepressant-like activity after repeated administration in 4 depression-like behaviour models, the chronic mild stress and the prenatal stress in rats, the corticosterone model and the olfactory bulbectomy in mice. In two of these models (the corticosterone model in mice and the prenatal stress in rats), it also presented anxiolytic-like activity. At 30 mg/kg i.p., S 47445 showed a neuroprotective effect on delayed hippocampal neuronal death induced by a global transient ischemia in rats and in an excitotoxic brain model in neonates at 0.1 and 0.3 mg/kg i.p. S 47445 significantly increased neurogenesis of neural progenitors in the dentate gyrus of the hippocampus of adult mice treated with corticosterone at antidepressant-active doses. This effect was associated with an increase of dendritic length and number of intersections of neural progenitors of dentate gyrus. Pharmacodynamics data in healthy volunteers: S 47445 at 5 mg facilitates interactions between task-positive networks during a cognitive task compared to placebo. In the posterior cingulate cortex, S 47445 at 5mg and 20mg induced a significant increase of glutamate (excitatory neurotransmission) in elderly women. S 47445 showed a statistically significant increase in plasma BDNF protein at pooled doses 20 and 50 mg after a 10-day treatment in young. Two parallel developments were considered for this drug: 1/“symptomatic treatment of mild to moderate Alzheimer’s disease (AD) in patients with depressive symptoms” and 2/-“adjunctive treatment of (major depressive disorder) MDD patients with inadequate response to an initial antidepressant treatment”.
Safety/Tolerability	Safety pharmacology: No cause of concern up to 1000 mg/kg p.o. on behaviour, body temperature, locomotion, coordination, autonomic function and respiratory function in rats. A possible proconvulsant potential noted at 200 and 1000 mg/kg p.o. in the rat PTZ-induced seizure model: induction of a slight but statistically significant decreases of the time required for initiation of PTZ-induced seizures. Up to 30mg/kg p.o., single dose did not show addictive potential in rats trained on cocaine in a drug discrimination procedure. No difference in clinical observations in combination with donepezil or SSRI or SNRI. Concerning the integrated cardiac risk assessment: no *in vitro* effects were observed on hERG assay and no *in vivo* cardiovascular effects (haemodynamic and ECG parameters) were observed in telemetered primates, up to 150 mg/kg p.o. Toxicology: Administered orally during 26 weeks in rats and 39 weeks in monkeys, no toxicological findings were observed up to 1000 mg/kg/day inclusive of S 47445-11. No target organ for toxicity was observed in both species. S 47445-11 was devoid of genotoxic potential in 3 tests, phototoxic potential in an *in vitro* test and immunotoxic potential in a 4-week rat study. In reproduction

	toxicity studies, S 47445-11 did not show any effect on male and female fertility in the rat and on embryo-foetal development including teratogenicity in the rat and the rabbit. Clinical studies: Phase I studies: In the single dose studies, S 47445 was administered at doses from 5 to 800 mg. Clinical and biological tolerance was good up to the dose of 800 mg. In the repeated 21-day administration studies, S 47445 was administered at 5 mg (elderly volunteers), 20 and 50 mg (young and elderly volunteers) and at 100 mg (young volunteers). Clinical and biological tolerance was good up to the dose of 100 mg. The Maximal Tolerated Dose was not reached either after single or repeated administration in these studies. Phase II studies: No specific and/or unexpected safety signal was observed in any of the S47445 arms compared to placebo in AD patients or in any of the S47445 arms compared to placebo (SSRI) in MDD patients.
Additional information	Pharmacokinetics and metabolism in human: Moderate bioavailability, high protein binding; mean apparent terminal elimination half-life value ranges between 30h to 40h after single and repeated oral administrations. The steady-state is reached after about 8-10 days after repeated oral administration in young and elderly volunteers with an accumulation ratio of about 2.5. Mainly eliminated through metabolism and the renal clearance is very low. *In vivo*, CYP1A2 is the major enzyme involved in S 47445 metabolism. According to pharmacokinetics data, concomitant use of S 47445 with potent CYP1A2 inhibitors (e.g. fluvoxamine, ciprofloxacin) and BCRP substrates are not recommended. S 47445 C_{max} and AUC increase less than proportionally with the dose.
Suitable for and Exclusions	
▪ **Clinical trials** ▪ **Previous, ongoing and planned**	Link to Clinical Trial.gov NCT02805439: Efficacy and Safety of **S 47445** Versus Placebo as Adjunctive Treatment in Depressed Patients Not Fully Recovered From Depressive Symptoms With a Current Antidepressant Treatment NCT02626572: Efficacy and Safety of 3 Doses of **S 47445** Versus Placebo in Patients With Alzheimer's Disease at Mild to Moderate Stages With Depressive Symptoms.
Additional characteristics: ▪ CNS penetrance ▪ Pediatric diseases ▪ Other	 Yes. After repeated administration, Kp between brain and blood was high: in rat >7 and in mice ~ 4 to 5. Ratio $AUCT_{CSF/blood}$ is similar after 20 and 50 mg doses: around 4 %. No data in pediatric disease: biowaiver related to developed clinical indications (Alzheimer's disease and MDD in adjunctive therapy). In models predictive of antipsychotic activities such as prepulse inhibition in normal and PCP-treated rats, hyperactivity induced by amphetamine or amnesia induced by MK-801, S 47445 has shown no effect alone and no synergy of effect in presence of clozapine. S 47445 presented no impact on ventilatory response in neonate mice after single administration in normoxia and hypercapnia conditions (5% CO_2). Moreover, no modifications of the ventilatory response by S 47445 were observed after administration of the opiate fentanyl in pup mice.
Publications	▪ Calabrese F et al. Upregulation of neurotrophins by S 47445, a novel positive allosteric modulator of AMPA receptors in aged rats. Pharmacol Res. 2017 Apr 23;121:59-69. ▪ Guilloux JP et al. S 47445 produces antidepressant and anxiolytic-like effects through neurogenesis dependent and independent mechanisms Front Pharmacol. 2017; 8:462.

	▪ Giralt A et al. The AMPA receptor positive allosteric modulator S 47445 rescues in vivo CA3-CA1 long-term potentiation and structural synaptic changes in old mice. Neuropharmacology. 2017 Sep 1;123:395-409. ▪ Bretin S. et al. Pharmacological characterisation of S 47445, a novel positive allosteric modulator of AMPA receptors. PLoS One. 2017 Sep 8;12(9):e0184429.

Conditions for this Call for proposals

All proposals must conform to the conditions set out in the H2020 Rules for Participation (https://ec.europa.eu/research/participants/portal/doc/call/h2020/common/1595113-h2020-rules-participation_oj_en.pdf) and the Commission Delegated Regulation with regard to IMI2 JU http://eur-lex.europa.eu/legal-content/EN/TXT/PDF/?uri=CELEX:32014R0622&from=EN.

The following conditions shall apply to this IMI2 JU Call for Proposals:

Applicants intending to submit a Short proposal in response to the IMI2 Call 13 should read this topics text, the IMI2 JU Manual for submission, evaluation and grant award *[link to be updated after GB approval]* and other relevant documents (e.g. IMI2 model Grant Agreement).

Call Identifier	**H2020-JTI-IMI2-2017-13-two-stage**
Type of actions	**Research and Innovation Actions (RIA)** **Coordination and Support Actions (CSA)**
Publication Date	**30 November 2017**
Stage 1 Submission start date	**30 November 2017**
Stage 1 Submission deadline	**28 February 2018 (17:00:00 Brussels time)**
Stage 2 Submission deadline	**6 September 2018**
Indicative Budget From EFPIA companies and IMI2 JU Associated Partners	EUR 106 629 000
From the IMI2 JU	EUR 116 421 000

Call Topics

IMI2-2017-13-01	The indicative contribution from EFPIA companies will be EUR 6 000 000 The financial contribution from IMI2 JU will be a maximum of EUR 6 700 000	Research and Innovation Action (RIA) Two-stage submission and evaluation process. Only the applicant consortium whose proposal is ranked first at the first stage is invited for the second stage.
IMI2-2017-13-02	The indicative contribution from EFPIA companies will be EUR 8 300 000 The financial contribution from IMI2 JU will be a maximum of EUR 10 500 000	Research and Innovation Action (RIA) Two-stage submission and evaluation process. Only the applicant consortium whose proposal is ranked first at the first stage is invited for the second stage.
IMI2-2017-13-03	The indicative contribution from EFPIA companies will be EUR 1 945 000 The indicative IMI2 JU Associated Partners contribution will be EUR 4 855 000 The financial contribution from IMI2 JU will be a maximum of EUR 6 800 000	Research and Innovation Action (RIA) Two-stage submission and evaluation process. Only the applicant consortium whose proposal is ranked first at the first stage is invited for the second stage.

IMI2-2017-13-04	The indicative contribution from EFPIA companies will be EUR 3 120 000 The indicative IMI2 JU Associated Partners contribution will be EUR 168 000 The financial contribution from IMI2 JU will be a maximum of EUR 4 500 000	Research and Innovation Action (RIA) Two-stage submission and evaluation process. Only the applicant consortium whose proposal is ranked first at the first stage is invited for the second stage.
IMI2-2017-13-05	The indicative contribution from EFPIA companies will be EUR 1 056 000 The indicative IMI2 JU Associated Partners contribution will be EUR 144 000 The financial contribution from IMI2 JU will be a maximum of EUR 1 200 000	Coordination and Suppert Action (CSA) Two-stage submission and evaluation process. Only the applicant consortium whose proposal is ranked first at the first stage is invited for the second stage.
IMI2-2017-13-06	The indicative contribution from EFPIA companies will be EUR 4 000 000 The financial contribution from IMI2 JU will be a maximum of EUR 4 600 000	Research and Innovation Action (RIA) Two-stage submission and evaluation process. Only the applicant consortium whose proposal is ranked first at the first stage is invited for the second stage.
IMI2-2017-13-07	The indicative contribution from EFPIA companies will be EUR 24 700 000 The financial contribution from IMI2 JU will be a maximum of EUR 25 500 000	Research and Innovation Action (RIA) Two-stage submission and evaluation process. Only the applicant consortium whose proposal is ranked first at the first stage is invited for the second stage.
IMI2-2017-13-08	The indicative contribution from EFPIA companies will be EUR 16 350 000 The financial contribution from IMI2 JU will be a maximum of EUR 17 830 000	Research and Innovation Action (RIA) Two-stage submission and evaluation process. Only the applicant consortium whose proposal is ranked first at the first stage is invited for the second stage.
IMI2-2017-13-09	The indicative contribution from EFPIA companies will be EUR 13 500 000 The financial contribution from IMI2 JU will be a maximum of EUR 15 300 000	Research and Innovation Action (RIA) Two-stage submission and evaluation process. Only the applicant consortium whose proposal is ranked first at the first stage is invited for the second stage.
IMI2-2017-13-10	The indicative contribution from EFPIA companies will be EUR 4 331 000 The financial contribution from IMI2 JU will be a maximum of EUR 5 331 000	Research and Innovation Action (RIA) Two-stage submission and evaluation process. Only the applicant consortium whose proposal is ranked first at the first stage is invited for the second stage.

IMI2-2017-13-11	The indicative contribution from EFPIA companies will be EUR 14 000 000 The financial contribution from IMI2 JU will be a maximum of EUR 14 000 000	Research and Innovation Action (RIA) Two-stage submission and evaluation process. Only the applicant consortium whose proposal is ranked first at the first stage is invited for the second stage.
IMI2-2017-13-12 -> 15	The indicative contribution from EFPIA companies will be EUR 4 160 000 The financial contribution from IMI2 JU will be a maximum of EUR 4 160 000	Research and Innovation Action (RIA) Two-stage submission and evaluation process. Only the applicant consortium whose proposal is ranked first at the first stage is invited for the second stage.

LIST OF ACRONYMS

Acronym	Meaning
3Rs	Reduction/Refinement/Replacement
AAIC 2016	Alzheimer's Association International Conference
ABAC	Accrual Based Accounting System
ACE Program	Autism Centres of Excellence Program
AD	Alzheimer’s disease
AD (HR)	Administrator
ADAS-Cog	Alzheimer’s Disease Assessment Scale Cognitive Subscale
ADC	Apparent diffusion coefficient
ADL	Activities of Daily Living
AER	Average error rate
ALT	Alanine transaminase
ADMET	Absorption, Distribution, Metabolism, Excretion, Toxicity
AMR	Antimicrobial Resistance
API	Application Programming Interface
ASD	Autism spectrum disorder
ARTI	Acute Respiratory Tract Infection
ASP	Antibiotic stewardship programmes
AST	Assistant
AWP2016	Annual Work Plan 2016
BBB	Blood brain barrier
BD4BO	IMI2 Big Data for Better Outcomes Programme

Acronym	Meaning
BRIDG	Biomedical Research Integrated Domain Group
BIT	Booking of IT material application
BMI	Body Max Index
BSEP	Bile Salt Export Pump
BUN	Blood urea nitrogen
CA-ARTI	Community-Acquired Acute Respiratory Tract Infection)
CA (Budget)	Commitment Appropriation
CA (HR)	Contractual Agent
CDISC	Clinical Data Interchange Standards Consortium
CEDEFOP	European Centre for the Development of Vocational Training
CEOi	Global CEO Initiative
CFAST	Coalition for Accelerating Standards and Therapies
CFS	Certificates on Financial Statements
CKD	Chronic kidney disease
CMT	carrier-mediated transcytosis
CNFD	Conreal nerve fiber density
CNS	Central Nervous System
COPD	chronic obstructive pulmonary disease
C-Path	Critical Path Institute
CPD	Continuing professional development
CRC	Australian Cooperative Research Centres
CRISP/CAS	Clustered Regularly Interspaced Short Palindromic Repeats/associated

Acronym	Meaning
CRO	Contract research organisation
CRP	C-reactive Protein
CSA	Coordination and Support Action
CSC	Common Support Centre
CSF	Cerebrospinal fluid
ctDNA, ctRNA	Circulating Tumour DNA / RNA
CyTOF	Methodology for single cell mass cytometry
CTCAE	Common Terminology Criteria for Adverse Events
DALA	Drug Abuse Liability Assessment
DG AGRI	Directorate-General Agriculture and Rural Development (European Commission)
DG HR	Directorate-General Human Resources and Security (European Commission)
DG GROW	Directorate-General for Internal Market, Industry, Entrepreneurship and SMEs (European Commission).
DG RTD	Directorate-General for Research and Innovation (European Commission)
DG SANTE	Directorate-General for Health and Food Safety (European Commission)
DILI	Drug-induced liver injury
DIVI	Drug-induced vascular injury
DORA	Document Registry Application
DPO	Data protection officer
DPUK	Dementia Platform UK
E&T	Education & Training
EBiSC	European induced pluripotent stem cell

Acronym	Meaning
EC	European Commission
ECA	European Court of Auditors
eCDR	electronic Career Development Report application
EDPS	European Data Protection Supervisor
EEG	Electroencephalograph
EFPIA	European Federation of Pharmaceutical Industries and Associations
eGFR	Estimated Glomerular Flitration Rate
EHDN	European Health Data Network
EHR	electronic health record
EHR4CR	Electronic Health Records for Clinical Research
ELF	European Lead Factory
EMA	European Medicines Agency
eMA	Electronic Missions Application
EMCDDA	European Monitoring Centre for Drugs and Drug Addiction
EMIF	European Medical Information Framework
ENABLE	European Gram-negative Antibacterial Engine
ENSO	Exploring New Scientific Opportunities
EPAD	European prevention of Alzheimer’s dementia consortium
ER	Endoplasmic Reticulum
ESSDAI	EULAR Sjögren's syndrome disease activity index
ESSPRI	EULAR Sjogren's Syndrome Patient Reported Index
eTRIKS	European Translational Information & Knowledge Management Services

Acronym	Meaning
EU-ADR	Exploring and Understanding Adverse Drug Reactions
EULAR	European Leaguse against Rheumatism
EUPCTN	Sustainable pan-EU paediatric CT network
ESFRI	European Strategy Forum on Research Infrastructures
eTOXdb	eTOX rich preclinical database
eTOXsys	eTOX *in silico* toxicology prediction system
EU	European Union
FA	Fluorescein Angiography
FACS	Fluorescence-activated cell sorting
FAIR	Findable, Accessible, Interoperable, Reusable
FDA	Food and Drug Administration
FG	Function Group
FLT	Fluorothymidine
FTE	Full-Time Equivalent
FWC	Framework Contract
fNIH	Foundation for the National Institute of Health
FP	Full Proposal
FP7	Seventh Framework Programme
FWC	Framework Contract
GA	Grant Agreement
GAP	Global Alzheimer's Platform
GB	IMI2 JU Governing Board

Acronym	Meaning
GCP	Good Clinical Practice
GWAS	Genome-wide association study
H2020	Horizon 2020 is the financial instrument implementing the Innovation Union, a Europe 2020 flagship initiative aimed at securing Europe's global competitiveness. For more information, click here: http://ec.europa.eu/programmes/horizon2020/en/what-horizon-2020
HA	Heath Authorities
HCP	healthcare professionals
HCT	Human challenge trials
Helmsley Charitable Trust	Leona M. and Harry B. Helmsley Charitable Trust
HEOR	Health Economics and Outcomes Research
HFpEF	Heart Failure with preserved Ejection Fraction
HIV	Human Immunodeficiency Virus
HMGB1	high mobility group box 1
HNV	Healthy normal volunteer
HR	Human resources
HTA	Health Technology Assessment
hIPSC	Human induced pluripotent stem cells
IAC	Internal Audit Capability
IAPO	International Alliance of Patients' Organisations
IAS	Internal Audit Service of the European Commission
IBS	Irritable bowel disease
ICC	Internal Control Coordinator

Acronym	Meaning
ICD	International Classification of Diseases
I/O	Immunooncology
ICF	Informed Consent Forms
ICH	International Council for Harmonisation
ICHOM	International Consortium for Health Outcomes Measurement
ICH S 1	International Conference on Harmonisation's Safety (S) 1
ICI	Immune Checkpoint Inhibitor
ICS	Internal Control Standards
ICT	Information Communications Technology
IEFD	Intra-Epidermal Fiber Density
IF	Immunofluorescence
IHC	Immunohistochemistry
I-HD	European Institute for Innovation through Health Data
ILG	Industry Liaison Group
IMI 1 JU	Innovative Medicines Initiative 1Joint Undertaking
IMI 2 JU	Innovative Medicines Initiative 2Joint Undertaking
IMI JU	Innovative Medicines Initiative Joint Undertaking
IND	Investigational New Drug
IP	Intellectual Property
IPCF	Informed Patient Consent Form
iPS cells	Induced pluripotent stem cells
IVD	In Vitro Diagnostics

Acronym	Meaning
ISA	IMI Information System for Absences
ITF	EMA Innovation Task Force
ITI-PF&S	Innovative therapeutic interventions against physical frailty and sarcopenia
JDRF	Juvenile Diabetes Research Foundation
JUs	Joint Undertakings
KM	Knowledge Management
KPI	Key performance indicator
LC-MS	Liquid Chromatography-Mass Spectrometry
LDT	Laboratory Developed Test
LEAP	Longitudinal European Autism Project
MAH	Marketing Authorisation Holder
MAPPs	Medicines adaptive pathways to patients
MCI	Mild Cognitive Impairment
MCSFR1	Macrophage Colony Stimulating Factor Receptor 1
MEP	Member of the European Parliament
MIAME	A Minimum Information About a Microarray Experiment
MRC	Medical Research Council
MRI	Magnetic resonance imaging
MS	Multiple sclerosis
MSD	Merck Sharp & Dohme Corp
MS status	Microsatellite status
MTA	Material transfer agreement

Acronym	Meaning
mTOR	Mechanistic Target of Rapamycin
NAFLD	Non-alcoholic fatty liver disease
NASH	Non-alcoholic Steatohepatitis
ND4BB	New Drugs for Bad Bugs
NHVs	Normal Healthy Volunteers
NICE	The National Institute for Health and Care Excellence
NIH/NCATS	National Institute of Health/National Center for Advancing Translational Sciences
NIMH	National Institute of Mental Health
NMDA-Receptor	N-methyl-D-aspartate receptor
NMJ	Neuro Muscular Junction
OCT	Ooptical Coherence Tomography
OECD	Organisation for Economic Co-operation and Development
OHDSI	Observational Health Data Sciences and Informatics
OLAF	European Anti-Fraud Office
OMOP	Observational Medical Outcomes Partnership
PA	Payment Appropriation
PAGE	Population Approach Group in Europe
PBMC	Peripheral blood mononuclear cell
PBPK	Physiologically Based Pharmacokinetics
PD	Parkinson's disease
PD-1	Programmed cell death protein-1 (CD279)

Acronym	Meaning
PD-L1	Programmed death-ligand 1 (CD274)
PET	Positron emission tomography
PK/PD/TD	Pharmacokinetic/Pharmacodynamic/Toxicodynamic
PLLR	Pregnancy and Lactation Labelling Rule
PM	Person/month
PMDA	Pharmaceuticals and Medical Devices Agency
PNS	Peripheral Nervous System
PONDS	Province of Ontario Neurodevelopmental Disorders
PPP	Public-private partnership
PRO	Patient reported outcomes
pSS	primary Sjögren`s syndrome
Pso	Psoriasis
PSTC	Predictive Safety Testing Consortium
PV	Pharmacovigilance
QC	Quality Controlled
QOL	quality of life
QST	Quantitative sensory testing
R&D	Research and development
RA	Rheumatoid arthritis
RADAR	Remote Assessment of Disease and Relapse
RADAR-CNS	Remote Assessment of Disease and Relapse in Central Nervous System Disorders

Acronym	Meaning
RAE	Risk assessment exercise
RCSA	Risk and control self-assessment
RCT	Randomized controlled trial
RepER	Representative error rate
ResER	Residual error rate
RIA	Research and Innovation Action
RMT	receptor-mediated transcytosis
RNA	Ribonucleic acid
RNAseq	RNA sequencing
ROADMAP	Real World outcomes across the AD spectrum for better care: Multi-Modal data Access Platform
RUO	Research Use Only
RWE	Real World Evidence
RWD	Real World Data
RWS	Real-world walking speed, gait speed in a home environment
SAB	Scientific advisory board
SAR	Structure activity relationship
SC	IMI2 Scientific Committee
sCr	Serum creatinine
SDTM	Study Data Tabulation Model
SEND	CDISC SEND Controlled Terminology
SGGs	Strategic Governing Groups to the IMI2 JU Governing Board

Acronym	Meaning
SGLT	Sodium Glucose Co-Transporter
SMEs	Small and medium-sized enterprises
SLC	Solute carriers
SNP	Single-nucleotide polymorphism
SOP	Standard operating procedure
SP	Short Proposal
SRA	Strategic Research Agenda
SRG	IMI2 JU States Representatives Group
STE	Speckle Tracking Echo-cardiograph
SVM	Support Vector Machine
SW	Semantic Web
SWOT	Strengths-Weaknesses-Opportunities and Threats analysis
T1D	Type 1 diabetes
T2D	Type 2 diabetes
TA	Temporary Agent
TB	Tuberculosis
TBIL	Total Bilirubin
Tg	Transgenic
TME	Tumour microenvironment
TSD	Total sleep deprivation
TTG	Time to Grant
TTP	Time to Pay

Acronym	Meaning
UPSA	Ultrasound-based plaque structure analysis
US	United States
VC	Venture capital
WHO	World Health Organisation
WP(s)	Work Package(s)

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