

First amended Annual Work Plan and Budget for 2017

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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 first amended Annual Work Plan will be made publicly available after its adoption by the Governing Board.

**Annex to the Decision of the IMI2 JU Governing Board
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Chronology and list of reviews

Version	Date of Governing Board approval	Items
Version 1.0	23.12.2016	Annual Work Plan and Budget for 2017
Version 2.0		<p>IMI2 States Representatives Group and Scientific Committee consultation carried out from 22 February 2017 to 13 March 2017</p> <p>Update of the following sections:</p> <ul style="list-style-type: none"> ▪ 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 <p>Insertion of Annexes I and II</p>
Version 3.0		<p>IMI2 States Representatives Group and Scientific Committee consultation carried out from 12 May 2017 to 07 June 2017</p> <p>Update of the following sections:</p> <ul style="list-style-type: none"> ▪ 2.2.2 Scientific priorities for 2017 ▪ 2.3 Call management rules ▪ 2.4.2 Procurement and contracts <p>Insertion of new topics in Annex II</p>

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 a subsequent amendment of the Annual Work Plan 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			
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	<ul style="list-style-type: none"> Article 2(a) and 2(b) Article 1(c) in Statutes of IMI JU 	<ul style="list-style-type: none"> 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	<ul style="list-style-type: none"> Article 2(a) and 2(b) 	<ul style="list-style-type: none"> 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
				<ul style="list-style-type: none"> KPI 3: Target estimated average number of IMI publications³ 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 publications⁵ 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.	<ul style="list-style-type: none"> 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			
				<p>KPI 5: Target to measure extent to which the citation impact of IMI publications⁵ is higher than the EU average</p> <p>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 publications⁵ 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 bodies⁴ (KPI 6.2)</p>	The benchmarking analysis with other international funding bodies to be performed by external contractor, applying internationally recognised standards and criteria	<p>KPI 5: ≥20% higher than EU average</p> <p>KPI 6.1: ≥15% higher than the average of sampled institutions</p> <p>KPI 6.2 ≥5% higher than the average of sampled institutions</p>
Impact on regulatory framework and standardization	IMI projects translate key scientific discoveries into clinical practice and regulatory framework	<ul style="list-style-type: none"> ▪ Article 2 ▪ Article 1(e) in Statutes of IMI JU 	<ul style="list-style-type: none"> ▪ Article 2 ▪ Article 1(b) in Statutes of IMI2 JU 	<p>KPI 7: Target to measure the number of scientific advice and qualified opinions initiated by the IMI projects at the EMA and FDA</p> <p>KPI 8: Target to measure the number of regulatory guidelines derived from IMI projects</p> <p>KPI 9: Target to measure new standards and best practices derived from IMI projects</p>	<p>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</p> <p>Each Scientific Officer will report annually during the preparation of the Annual Activity Report</p> <p>If necessary, additional complementary information may also be collected as part of an annual survey of the consortia</p>	<p>KPI 7: ≥ 5</p> <p>KPI 8: Baseline data will be collected in 2017</p> <p>KPI 9: Baseline data will be collected in 2017</p>

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	<p>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 implementation⁵</p> <p>KPI 11: Target to measure impact on EU competitiveness</p> <p>KPI 12: Target to measure the number of spin-off companies or foundations created as a result of IMI projects</p> <p>KPI 13: Target to measure the estimated number of reported Full-Time Equivalent (FTEs) based in the EU that can be considered as directly related to the IMI programme</p>	<p>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</p> <p>If necessary additional complementary information may also be collected as part of an annual survey of the consortia</p> <p>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</p> <p>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</p>	<p>KPI 10: ≥2 patent applications per EUR 10 million of costs accepted and reimbursed by IMI JU.⁶</p> <p>KPI 11: Baseline data will be collected in 2017</p> <p>KPI 12: 25% of finalised projects</p> <p>KPI 13: ≥ 1500</p>

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	<ul style="list-style-type: none"> Article 2(e) 	<ul style="list-style-type: none"> Article 2(a) Article 1(c) in Statutes of IMI2 JU 	<p>KPI 14: Target percentage of participants in signed Grant Agreements that are SMEs</p> <p>KPI 15: Target percentage of overall budget for projects that has been allocated to SMEs</p>	<p>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</p> <p>All participations from the start of IMI up the end of the year under review are considered in this calculation</p>	<p>KPI 14: ≥20%</p> <p>KPI 15: ≥20%</p>
Patient participation	IMI2 JU projects promote the involvement of patient organisations	<ul style="list-style-type: none"> Article 2 	<ul style="list-style-type: none"> Article 2(a) Article 1(c) in Statutes of IMI2 JU 	<p>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</p> <p>KPI 17: Target to measure impact for patients</p>	<p>Calculation is based on the latest available data extracted from IMI IT applications for the project partners</p> <p>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</p> <p>If necessary, additional complementary information may also be collected as part of an annual survey of the consortia.</p> <p>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</p>	<p>KPI 16: 100%</p> <p>KPI 17: Baseline data will be collected in Q1 2017</p>
Impact on society	IMI2 JU projects address the unmet healthcare needs, e.g. chronic, emerging or diseases lacking effective treatment	<ul style="list-style-type: none"> Article 2 	<ul style="list-style-type: none"> Article 2 	<p>KPI 18: Target to measure additional impact on society</p>	<p>For KPI 18, the evaluation methodology development is in progress and the baseline data for establishing the target will be determined in 2017.</p>	<p>KPI 18: Baseline data will be collected in 2017</p>

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	<p>KPI 19: Target number of average monthly visitors to the IMI2 JU website</p> <p>KPI 20: Target to measure the performance of communication activities</p>	<p>Average number of monthly unique visitors as reported by Google Analytics for the year under review</p> <p>For KPI 20, the methodology for capturing the information and the baseline data for establishing the target will be determined in 2017</p>	<p>KPI 19: ≥10 000</p> <p>KPI 20: Baseline data will be collected in 2017 and used to determine the appropriate target</p>
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	<p>KPI 21: Target timeframe for TTG of 245 days</p>	<p>Comply with the timeframe set out in the Horizon 2020 Rules for Participation (Article 20.2 in Regulation (EU) No 1290/2013)</p> <p>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</p>	<p>KPI 21: ≤245 days</p>
	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	<p>KPI 22: Annual budget execution target for commitment appropriations of running costs</p> <p>KPI 23: Annual budget execution target for commitment appropriations of operational costs</p> <p>KPI 24: Annual budget execution target for payment appropriations of operational costs</p>	<p>Extracted from annual figures compiled for IMI JU report on the budgetary and financial management</p>	<p>KPI 22: ≥95%</p> <p>KPI 23: ≥95%</p> <p>KPI 24: ≥95%</p>

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	<p>KPI 25: Annual Average Time to Pay (TTP) target for pre-financing payments to beneficiaries</p> <p>KPI 26: Annual Average TTP target for interim payments to beneficiaries</p>	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	<p>KPI 25: ≤30 days</p> <p>KPI 26: ≤90 days</p>

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 far⁷. 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 2017⁸.

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:

Diabetic cardiomyopathy:

1. 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 disease, as the risk remains increased even after correcting for 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. As a consequence of this lacking correlation between tight glycaemic control and overall mortality, the regulatory guidelines today make for each novel antidiabetic drug candidate a CV outcome study mandatory to obtain approval. The aim of this topic is to unveil the underlying mechanisms of diabetic cardiomyopathy and its impact on CV mortality in diabetic patients.

A clinical reference baseline database in support of flexible clinical trial designs in the area of metabolic diseases:

2. Major problems to determine a clear and unequivocal assessment of the benefits and advantages of novel drug candidates to treat type 2 diabetes in clinical drug trials are caused among other factors by the heterogeneity of the type 2 diabetes population, the lack of understanding of the impact of the multidrug treatment of diabetic patients on clinical outcomes, the lack of understanding of the incidence of safety outcomes which are not treatment-related and potentially inherent to the disease. The aim of this topic is to create a pooled database of safety data collected from the placebo/standard of care arms of clinical drug trials performed in type 2 diabetes patients by industry and clinical institutions involving all relevant key study details such as: inclusion/exclusion criteria, standard of care, length of follow up, demographic data and patient medical history, safety data etc. The participating partners will provide full access to the respective databases to extract fully anonymized patient information to build a reference baseline database of individuals with diabetes and metabolic disorders to enable flexible and stratified clinical trial designs.

Involvement of the microbiome in the context of metabolic disorders: mechanistic understanding of the role of the microbiota-induced immunoregulation in the ethiopathogenesis of diabetes and metabolic disorders

3. The incidence of diabetes and obesity has reached epidemic dimensions. Increased food intake and sedentary lifestyles are two major contributing and driving factors behind the development and progression of these metabolic diseases. The underlying biochemical mechanisms with the involvement of a variety of genetic and environmental influences are only marginally understood. In the past years increasing evidence was found that the gut microbiota plays a major role in the development of obesity and diabetes. Gut microbiota can increase energy production from ingested food and contribute to low-grade inflammation and regulation of fatty acid tissue composition; changes in gut microbiota composition can impact key metabolic pathways like insulin secretion and incretin production. Therefore, the link between obesity and diabetes and the microbiome is well documented, but the underlying mechanisms, the individual contribution of the various factors, the diversity regarding ethnic and inter-individual differences are not known. This topic aims to elucidate the role of the microbiome in the development and progression of metabolic diseases. This could be a first step in a more and broader microbiome programme.

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).
- Facilitating the design and interpretation of rationally designed stratified clinical trials via the better understanding and scientific base of the diabetes and metabolic disorders population.
- A faster evaluation of the benefit and benefit/risk relationship of novel treatment options.
- Identification of key contributing pathways involving the microbiome with the potential to find efficacious and causative therapeutic options to treat and/or prevent diabetes and metabolic disorders.
- 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.

Furthermore there is still a high unmet need in the areas of understanding, treating and managing pain. The pain priorities address the following themes: 1) increase disease aetiology understanding for new drug target identification & validation; 2) translational models and biomarkers; 3) clinical trial methodologies.

More specifically activities in 2017 will address the following topics:

Neurodegeneration - Alzheimer's disease:

1. Coordination and Support Action for collaboration and alignment of the many initiatives (including but not limited to IMI-AD platform) devised in the aftermath of the G8 Dementia Summit Declaration⁹ 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.
2. Tau imaging. Accelerating development of tau radioligands to enhance exploitation of tau PET imaging that has the potential to serve as a target engagement biomarker for emerging tau therapies and to enable their use in AD clinical trials and clinical practice (e.g. for patient selection and outcome measures).
3. New genes as Alzheimer's disease modifiers. Identification of new genes as Alzheimer's disease modifiers: In order to identify novel, validated targets a platform should be developed that covers new biological and phenotypic approaches for improved disease understanding based on systems biology.
4. Immune system and Alzheimer's disease. Further explore the role of the innate immune system in neurodegeneration, complementing the TREM2/CD33 activities launched in 2016.
5. Early markers of progression in Alzheimer's disease. Identification of early markers of progression of AD to facilitate recruitment into - and read out of - clinical trials.

Neurodegeneration - Parkinson's disease:

6. Personalised treatment. Support the development of innovative personalised treatments for Parkinson's disease using a biomarker approach.
7. Mitochondrial deficiency. Explore mitochondrial deficiency as a potential key factor in the neurodegenerative process underlying Parkinson's disease.

Biomarkers in neurodegeneration:

8. Participate in- and build on- global biomarker development efforts, and validate translational biomarkers for decision making in clinical trials of disease-modifying agents in neurodegenerative diseases.

Discovery and characterization of blood-brain barrier (BBB) targets and transport mechanisms:

9. 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

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

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.

Pain:

10. Identification and validation of novel pain targets / pathways with disease-modifying potential: analysis of tissue samples from pain patients using omics-scale technologies to increase disease understanding; development of new platforms to facilitate future drug screening.
11. Validation and standardisation of methods to measure neuronal activity in pain: In patients, employ e.g. electrophysiological measurements, fMRI, QST, and test biomarkers to achieve a better understanding of which (sub)-groups of patients preferentially respond to which drugs, and back-translation of the measures into preclinical models to improve translational trajectories for chronic pain.
12. Clinical endpoints in headache medicine: Exploration and validation of clinical endpoints in abortive and preventive migraine trials in adult and paediatric populations. Abortive migraine trial endpoints: pain freedom, associated migraine symptoms, migraine-associated disability, quality of life, real-world evidence for functional outcome or treatment preference. Preventive migraine trial endpoints for chronic and episodic migraine: reduction of headache days, reduction in migraine-associated disability, quality of life and real-world evidence of functional outcome and treatment preference. Planning work for a framework for clinical biomarkers of disease, disease progression, and treatment response.

Expected impact of the topics:

- The fostering of a global dementia research agenda that most efficiently uses the investments of all stakeholders.
- Assignment of new functional roles to rare genetic variants implicated in disease causation.
- Validation of tools and platforms for discovery of new biological insights into Parkinson's and Alzheimer's disease understanding, and beyond the central nervous system compartment
- Accelerating tau tracers development and better integration of novel imaging techniques into pharma development
- 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
- Reducing attrition rates with more predictive translational models and stratification of patients responding to specific treatments to drive reinvestment into new treatment options for chronic pain.
- Modernise and optimise clinical development for CNS therapies.
- Improved understanding of pain mechanisms and increasing feasibility for drug development paving the way to new disease-modifying treatment options.
- Reducing attrition rates with optimised methods to assess pain phenotypes and innovative clinical trial paradigms to drive reinvestment into new treatment options for chronic pain.
- Increase predictive validity and translational value of animal models of chronic pain.
- Better definition of clinical endpoints in acute migraine episodes and in chronic migraine.

Type of actions:

Research and Innovation Actions; Coordination and Support Actions

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:

Inflammatory bowel disease:

1. Development of biologic therapies has greatly transformed the ability of physicians to treat inflammatory bowel disease (IBD), but current therapies, while effective at controlling established inflammation, tend to lose efficacy over time in many patients. It is currently unclear why patients lose response despite initially responding well to treatment. Therefore, this topic will specifically study the remission phase of disease to elucidate the mechanisms that cause loss of remission and to determine if there are systemic, endoscopic, and/or stool biomarker(s) that will predict IBD flares effectively. As such, this topic will address the unmet medical need for early indicators of IBD flares and for a mechanistic understanding of IBD flares and potentially guide towards the development of evidence based treatment sequences aimed at long term remission.

Fibrosis

2. Fibrotic diseases are diverse in nature but share common molecular and cellular drivers. At present, significant gaps exist in our understanding of this group of diseases, particularly relating to immune-fibrotic cross talk. Immune based approaches relating to treatment of fibrotic conditions have met with limited success. There is a lack of tools to assess disease progression, and limited acceptance of non-invasive markers to monitor disease progression. The topic will focus on common underlying mechanisms that offer the opportunity to explore cross disease approaches including but not limited to immune-fibrotic pathways and cross talk, biomarkers, patient stratification and in particular the identification of rapid progressors in addition to experimental medicine approaches across different disease settings.

Systemic lupus erythematosus

3. Systemic lupus erythematosus (SLE) is associated with multiple symptoms such as rash, arthritis and fatigue and affects multiple organ systems. The various symptoms and organ systems affected by SLE are often responsive to different therapies. Most disease activity measures in SLE are global measures, such as the SLE Disease Activity Index (SLEDAI) and British Isles Lupus Activity Group (BILAG), and are not sensitive indicators of changes in individual symptoms or disease manifestations. Drug approval in SLE has been slow, partly because most therapies under study have used global measures of disease activity or composite indices as primary study endpoints. The topic will focus on the implementation of activities that will enable the implementation of clinical trial endpoints and therefore better clinical trials ultimately improving the quality of therapies for patients.

Sjögren's syndrome

4. Sjögren's syndrome is one of the more prevalent autoimmune disorders that presents as primary Sjögren'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.

Epigenetics

5. The scope of this topic will be an improved understanding of the molecular pathways leading to the identification of new epigenetic and non-epigenetic therapeutic targets, biomarkers and diagnostics involved in immune mediated diseases. Approaches should be based on mapping the epigenomes in disease tissue samples in immune mediated diseases and comparing these with both normal tissues and tissues from other disease. Advances in epigenetic mapping technologies will now allow these to be applied to ever smaller quantities of samples such that we can start to realise the ambition of being able to study disease samples available from well characterised patients enrolled on clinical studies provided as industry in-kind contribution. The topic will allow an increase in understanding of disease pathways and provide insights into the importance of epigenetic dysfunction in disease along with the identification of new targets (epigenetic and other), disease biomarkers and epigenetic correlates of disease status.

Microbiome research

6. The topic will focus on understanding the impact of the microbiome on immune disease development and how learnings can be applied across therapeutic areas. This could be a first step towards the creation of a broader microbiome research programme.

Disease deconstruction and target identification

7. The topic will aim to deconstruct the pathways leading to manifestation of immune diseases via genomic or disease biomarker analysis that will ultimately lead to the identification of a series of key targets within the disease area. The topic will focus on the implementation of activities that will ultimately lead to the precompetitive identification of new drug targets within key disease areas including, but not limited to, type 1 diabetes (T1D), fibrosis, osteoarthritis (OA), rheumatoid arthritis (RA), systemic lupus erythematosus (SLE), respiratory diseases and Sjögren's disease. The topic will also develop ways to prosecute newly identified targets via the use of tool molecules, or drug repositioning with clinical trial cohorts.

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
- Advance the understanding of epigenetics of immune and inflammatory disease progression or during drug treatment, and potentially the identification of new drug targets.
- An understanding of the role of the microbiome in immune disease that can open to novel drug pathways and target discovery.

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:

Antimicrobial resistance – antibiotics and diagnostics:

1. One of the most challenging aspects of antibacterial drug development is the execution of late stage clinical trials. Therefore, the ND4BB programme is successfully building a clinical trial network under the IMI project Combacte-NET, and running several large scale clinical trials with new treatments against some of the most difficult to treat multi-drug resistant pathogens. For more standard trials with new antibiotics, trial sites are still established de novo and disassembled after the completion of the trial, incurring time delays and expense in the start-up and shut down of activities. Activities in 2017 will therefore aim at further progressing the idea of an ongoing network that can test more than a single, novel antibacterial agent in a “semi-contemporaneous time frame”. The key paradigm change will be a change in the way we run clinical trials. This is especially true for non-inferiority trials with clinically approved comparator drugs. The goal is to establish an ongoing network that can conduct trials with multiple drugs (comparators and novel agents). It is estimated that this could save up to 40% of the expense of these trials.
2. 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.

Innovation in vaccines:

3. Innovative solutions to understand and measure the maturation of the immune system and to tackle emerging/unmet medical needs are needed. Approaches will include the development of novel immunisation strategies and technologies, as well as measures to assess the effectiveness and safety of new vaccines. Research should also lead to a better understanding of the drivers underpinning inconsistent utilisation of available immunisation measures as well as to reduce the use of experimental animals.
4. 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.

5. Coordination and Support Action. The IPROVE (Innovation Partnership for a Roadmap on Vaccines in Europe) roadmap (<http://www.euvaccine.eu/news-events/news/iprove-roadmap-launched-16-march>) on vaccines in Europe has been developed through a collaborative effort of the leading vaccine experts in Europe. A coordination and support action (CSA) is planned to address the key challenges and gaps identified in relation to e.g. vaccines R&D, awareness, education and training, and regulatory pathways.

Emerging infectious diseases:

6. In light of the recent outbreaks of e.g. Ebola and Zika virus infections it is clear that there is a need for improved preparedness and faster response to emerging infections. The aim is to support the development of new platforms that facilitate rapid deliveries novel and improved diagnostics, vaccines and treatments for these infections.

Expected impact of the topics:

- A pipeline of promising new agents for tackling antibiotic-resistant bacterial infections.
- Improved antibiotic stewardship, decreased risk of antimicrobial resistance, and better preservation of the microbiome.
- An ongoing clinical trial network that has the prospect of faster trials with reduced expenses and better comparative data
- Novel and rapid diagnostics and new business models for improved access and use
- Delivery of better vaccines in response to target group-specific needs.
- Strengthened coordination across sectors and stakeholders resulting in improved structures and governance for joint action to tackle societal challenges.
- Improved preparedness and faster response to emerging infectious diseases
- Major impact on the improvement of public health.

Type of actions:

Research and Innovation Actions and Coordination and Support Action

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.

Reduce safety-related attrition during drug development

1. Reducing neurotoxicity. 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.
2. Translational microphysiological systems. Over 30% of candidate drugs are stopped in clinical trials due to toxicity. Frequently these toxicities were either undetected in preclinical models or the models underestimated clinical toxicity margins that ultimately prevented clinical progression. Therefore, there is the urgent need to identify and characterize alternative models with better predictive capacity. Microphysiological systems (MPS) using cells derived from different species capable of predicting drug-induced toxicities earlier in drug discovery process would be of tremendous benefit. However, although many MPS have been developed the performance of these systems, their appropriate context of use, and their translational potential have not been established particularly in organs such as kidney and the intestine. The aim of the topic launched under this priority will be to understand better the translational potential of novel MPS systems for both organs types with the aim of deriving predictive quantitative toxicological information from these models not possible in traditional cell culture models.
3. Biomarkers for toxicities. 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.

Better protect patients, launch safer medicines

4. Toxicities in women of childbearing age. 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.

5. Dosing in specific populations. The term specific population has been used to describe patient attributes that may require alterations in the course of therapy when compared to typical patients; examples include renal and hepatic impairment, children, elderly, and pregnancy. These populations are often excluded or under-represented in pivotal trials. 50% to 80% of new molecular entities do not have explicit dosing recommendations for severe renal and hepatic impairment, respectively. Thus, dosing recommendations for some specific populations may lag for years without assurance that they will ever be studied. Modelling and simulation (M&S) approaches offer the opportunity to bridge this gap. Therefore, topics will be brought forward to establish a framework for developing models, criteria for establishing adequacy of predictions, and a drug development-regulatory framework for incorporation of derived dosing recommendations into product labels.
6. Human metabolism, disposition and pharmacokinetics. Many compounds in drug development fail sooner or later because of undesirable pharmacokinetics (PK), insufficient efficacy, and/or safety concerns that were not foreseen even after having a plethora of data available from animal studies. Therefore, it would be highly desirable that information on **human metabolism, disposition and pharmacokinetics** (PK) could be evaluated early and directly in humans. However, this requires general acceptance of advanced analytical methodologies that bring new opportunities to the field. A topic is envisaged that will generate the necessary evidence to support the use of advanced analytical methodologies that would enable earlier testing of compounds in humans.

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
- Reduce dependence on animal models to investigate intestinal and renal toxicities
- 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
- Models and a drug development-regulatory framework for incorporation of derived dosing recommendations into product label

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 health 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:

Establishing a sustainable legacy of IMI data assets:

1. 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 IMI 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).

Access, standards and interoperability:

2. Biomedical metadata registry. Develop well-established, sustainable, industry-wide metadata standards to support tracking, moving, compiling, storing, harmonizing and reconciling biomarker data to accelerate the interoperability of all databases (including non-IMI project databases), and allow queries within individual and across different databases. Interoperability should be supported by developing tools and methods to confirm data provenance as well as exchange of data standards for all biomarker modalities.
3. Coordination and Support Action for building the basis for a common European biomedical 'language' across all stakeholders in the biomedical and health care space. This should be achieved by establishing a governance body and governance processes for all relevant metadata standards and by implementing a sustainable European biomedical metadata registry under a broadly agreed governance structure and standardized tools to lower the barrier to adoption of standards.

Development of enabling platforms to support new research paradigms:

4. Life science networks. Develop advanced network-based *in silico* approaches to get a better mechanistic understanding and hypothesis formulation in areas such as: disease mechanisms and new disease associated genes, disease subtyping and patient stratification, biomarkers, drug efficacy and drug induced side effects.
5. OpenPhacts Reasoning Engine. Tools and methods will be developed to facilitate the application of machine learning to predict biochemical activities of chemical structures making use of historical biological assay data.
6. Big Data for Better Outcomes (BD4BO): Use big data approaches for optimization of care pathways and improving outcomes for patients' multi-diseases/multi-morbidities; investigate how big data could support better outcomes for rare cancers, with the example of neuro-endocrine tumours; develop a real world big data registry for better respiratory disease outcomes. Projects under the BD4BO programme will be required to conclude collaboration agreements¹⁰ with each other.

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

7. 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 agreements¹¹ 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.
8. 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 agreements¹⁰ with each other.
9. Personal health data ecosystem. Build data management systems that can provide individuals with ownership of their own health care data. Such systems should allow the evaluation of the opportunities of using the personal health ecosystem to realize their true potential in human research and clinical practise.
10. Adaptive designs: Develop solutions to improve the adoption of adaptive methods in R&D process.

Digital solutions for better compliance and adherence:

11. Develop approaches to help monitor and improve medication compliance by creating a multi-stakeholder network which will establish common processes, standards and guidelines for a digital patient platform with approved medicines information and map trusted sources and needs for additional information.

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.
- Develop coherent and transparent framework to address data privacy and personal integrity issues inherent in the use of health records and personal genomic data.
- An improved transparency of data re-use and impact on R&D.
- Faster translation of insights from real world health data to biomedical research and development approaches.
- Improve compliance and adherence to prescribed medicine.
- Create structure and guidance for information on medicines and related topics.

¹¹ IMI2 Grant Agreement article 41.4: Relationship with complementary beneficiaries — Collaboration agreement.

Type of actions:

Research and Innovation Actions and Coordination and Support 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 topics:

Beyond patient stratification:

1. Gathering large amounts of longitudinal diagnostic and treatment information for a greater understanding of signalling networks, how the function of these networks is altered by treatment, and how cells adapt to pharmacological treatment, including resistance mechanisms vs. escape for checkpoint. The high quality, integrated datasets obtained should be used to profile tumours and deeply interrogate tumour microenvironment and the patient immune system over time.

Increasing context specificity:

2. Develop new ways to study clinically and preclinically the “contextual space” of a tumour. This will require complex studies to test different drugs in different context and different indications to systematically explore and predict contextual dependencies.

Immune oncology:

3. Develop patient selection tools to identify responder populations for immune oncology (IO), IO-IO treatment combinations and / or IO targeted therapy.

Cell free DNA – liquid biopsy:

4. Explore the potential of cell free tumour DNA (cfDNA) assessment, as an alternative to classic biopsies.

Big data in oncology:

5. Creation of a centralized repository of data from patient populations affected by solid tumours (sequencing, RNA expression, protein profiling, metabolite and methylation profiling) capable of storing and processing sample information in a consistent fashion. This should be accompanied by efforts in standardisation of laboratory testing and data. This will facilitate patient access to the most advanced and appropriate treatment; speed up the enrolment of patients with rare genetic variants in clinical trials; allow the development of new clinical and molecular endpoints, and the generation of new hypotheses, methodologies and exploratory algorithms. Other elements of the solution are the establishment of an appropriate data architecture and software tools. Analytic and visualization tools allowing deeper exploration of the data are also required, as are ways for inclusion of other sources of information, such as patient reported outcomes, health economic and real world evidence of treatment.

Expected impact

- 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.
- An outcomes-focused data platform to empower policy makers and clinicians to optimize care for patients with solid tumours

Type of actions:

Research and Innovation Actions

H. Other enablers of innovation

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.

Activities in 2017 will address the following topic:

1. 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.

Expected impact:

- 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.

Type of action:

Research and Innovation Action

Facilitating the translation of advanced therapies to patients in Europe

Recent advances in biomedicine are now opening the door to new treatment approaches for diseases with high unmet medical need. These approaches include advanced therapy medicinal products (ATMPs) such as products based on genetic engineering, innovative cell-based therapies and tissue-engineered products. However, numerous factors and challenges complicate the translation from research into patient access of ATMPs.

Activities in 2017 will address the following topics:

1. Improving preclinical studies of ATMPs. Develop solutions, including tools and methods to address the key challenges in the area of preclinical development of ATMPs. This could include demonstration of proof of concept in relevant animal models, the study of new and effective approaches for delivery of ATMPs, the assessment of established vector systems and development of new enhanced vectors, as well as development of new approaches based on targeted gene editing. For improving the reproducibility of preclinical studies an increased understanding of all impacting factors and a joint effort towards standardisation, including development of the relevant regulatory science should be aimed for.
2. Novel approaches for clinical study of ATMPs. Address the issues raised from clinical exploratory studies to demonstrate safety and proof of concept/initial efficacy of ATMPs, as well as from confirmatory studies. The approach used should allow the incorporation of aspects of evidence, and effectiveness and the interpretation of the data in the context of clinical meaningfulness. This will require an organic study of the clinical condition and patient populations with the perspective of a case-by-case basis and/or specific categories. Issues to be addressed include the development of primary and secondary endpoints, the interpretation of preclinical to clinical translatability using potential biomarkers and surrogate markers (of pathophysiology and of evidence of clinical

- effectiveness), and the mapping and inventory of the type of data available via clinical use programmes (registries, hospital exemption, compassionate use) in Europe.
3. ATMPs manufacturing. Address the challenges of manufacturing of ATMPs. This will require developing common best practices and 'automated' production platforms, highly sensitive analytical tools/methods and scaled down/micro assays. Manufacturing knowhow and education specific for the ATMP business, regulatory sciences and Current Good Manufacturing Practice (CGMP) related to ATMP usage should also be developed.
 4. Vector technology platform for ATMPs. Establish a common technology platform for the production of specific vectors with respect of all aspects of the current regulatory standards on safety, stability, robustness and validation. This should be based on innovative production, analytical tools and equipment and achieved by combining in-depth knowledge of cell biology, culture technology and innovative solutions in bioprocessing technology and bioreactor engineering.
 5. Immunogenicity of ATMPs. Explore how cells can be genetically re-engineered of to lower immunogenicity.
 6. European stem cells facility. Establish a single central processing facility for inducible pluripotent stem (iPS) cell technology, building on the foundational infrastructure created by the IMI EBiSC project. The solution should become operationally self-funding within 5-7 years, and should couple quality control with cell line expansion, in order to standardise production workflow from sample procurement to cell line qualification.
 7. Patient access to ATMPs. Build a knowledge base on health technology assessment (HTA) and hospital exemption (HE) implications of ATMPs. This should include the study of ways for development of health systems provisions for innovative reimbursement and payment mechanism, and the facilitation of the delivery of ATMPs through select centres of excellence to optimise cross-border health care delivery.

Expected impact of the topics

- To enhance research and development of advanced therapies in Europe as a fully-fledged industrial activity to make the EU more competitive and make advanced therapy products available to all patients in need.
- To facilitate translation from preclinical studies to the clinic and contributing to the 3Rs via development and validation of novel robust preclinical models and increased data reproducibility.
- A more consistent and reproducible manufacturing of ATMPs.
- A significant (not just incremental) acceleration in the progress of this field via development of standardised technological platforms, tools, biobanks (especially for iPS cells) and databases.
- A powerful public private innovation platform for addressing efficiently all challenges in the pathway from science to healthcare systems and patients, including price and reimbursement implications.

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 results¹² – 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.

Scope:

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 rules¹³.

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 Action

¹² 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.

¹³ Annex II of the IMI Model Grant Agreement 'Part C – Intellectual Property Rights, Use and Dissemination' and in particular 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 ¹⁴	Indicative IMI2 JU funding (in EUR), ¹⁵	Indicative in-kind contribution (in EUR) from EFPIA entities and Associated Partners	Call process
IMI2 Call 11¹⁶ (postponed from 2016) <i>Exploitation of IMI Project Results (RIA)</i>	19 July 2017	5,000,000	-	One-stage Call with predefined submission deadline: 24 October 2017 Research and Innovation Actions (RIA)
IMI2 Call 12¹⁷ <i>Neurodegeneration and other Neuroscience Priorities</i> <ul style="list-style-type: none"> ▪ Discovery and characterization of blood-brain barrier targets and transport mechanisms for brain delivery of therapeutics to treat neurodegenerative & metabolic diseases (RIA) <i>Immunology</i> <ul style="list-style-type: none"> ▪ Development of sensitive and validated clinical endpoints in primary Sjögren's Syndrome (pSS) (RIA) <i>Infection control including vaccines</i> <ul style="list-style-type: none"> ▪ Analysing the infectious disease burden and the use of vaccines to improve healthy years in aging populations¹⁸. <i>Data & Knowledge Management</i> <ul style="list-style-type: none"> ▪ FAIRification of IMI and EFPIA data (RIA) ▪ European Health Data Network (RIA)¹⁹. 	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)

¹⁴ 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.

¹⁵ The maximum possible rate of co-financing is 100 %.

¹⁶ The full indicative Call for proposals' text is set out in Annex I.

¹⁷ The full indicative Call for proposals' text is set out in Annex II.

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.

¹⁹ 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 ¹⁴	Indicative IMI2 JU funding (in EUR), ¹⁵	Indicative in-kind contribution (in EUR) from EFPIA entities and Associated Partners	Call process
<ul style="list-style-type: none"> ▪ Development and validation of technology enabled, quantitative and sensitive measures of functional decline in people with early stage Alzheimer's Disease (RADAR-AD)²⁰ (RIA) <p><i>Other Enablers of innovation</i></p> <ul style="list-style-type: none"> ▪ European Screening Centre: unique library for attractive biology (ESCulab) (RIA) 				
<p>IMI2 Call 13</p> <p><i>Diabetes/metabolic disorder</i></p> <ul style="list-style-type: none"> ▪ Diabetes cardiomyopathy (RIA) ▪ Database for clinical trials in metabolic disorders (RIA) ▪ Microbiome & metabolic disorders (RIA) <p><i>Neurodegeneration and other Neuroscience Priorities</i></p> <ul style="list-style-type: none"> ▪ Neurodegeneration - Alzheimer's disease: Coordination and Support Action (CSA) ▪ Neurodegeneration – Alzheimer's disease: immune system and Alzheimer's disease (RIA); Tau imaging (RIA); New genes as Alzheimer's disease modifiers (RIA); Early markers of progression in Alzheimer's disease (RIA). ▪ Neurodegeneration - Parkinson's disease: Personalised treatment (RIA); Mitochondrial deficiency (RIA) ▪ Biomarkers in neurodegeneration (RIA) ▪ Pain (RIA) <p><i>Immunology</i></p> <ul style="list-style-type: none"> ▪ Inflammatory bowel disease (RIA) ▪ Epigenetics (RIA) ▪ Disease deconstruction and target identification (RIA) ▪ Fibrosis (RIA) ▪ Systemic lupus erythematosus (RIA) ▪ Microbiome research (RIA) <p><i>Infection control including vaccines</i></p> <ul style="list-style-type: none"> ▪ Antimicrobial resistance – antibiotics and diagnostics (RIA) 	30 November 2017	124,526,844	131,241,844	<p>Two-stage Call with predefined submission deadline</p> <p>Research and Innovation Actions (RIA) & Coordination and Support Actions (CSA)</p> <p>Indicative Call deadline for Short proposals:</p> <p>28 February 2018</p> <p>Indicative Call deadline for Full Proposals:</p> <p>5 September 2018</p>

²⁰ 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 ¹⁴	Indicative IMI2 JU funding (in EUR), ¹⁵	Indicative in-kind contribution (in EUR) from EFPIA entities and Associated Partners	Call process
<ul style="list-style-type: none"> ▪ Innovation in vaccines (RIA) ▪ Innovation in vaccines (CSA) ▪ Emerging infectious diseases (RIA) <p><i>Translational safety</i></p> <ul style="list-style-type: none"> ▪ Reduce safety-related attrition during drug development: Reducing neurotoxicity. (RIA); Translational microphysiological systems (RIA); Biomarkers for toxicities (RIA) ▪ Better protect patients, launch safer medicines: Toxicities in women of childbearing age (RIA); Dosing in specific populations (RIA); Human metabolism, disposition and pharmacokinetics - early and direct evaluation (RIA) <p><i>Data & Knowledge Management</i></p> <ul style="list-style-type: none"> ▪ Development of enabling platforms to support new research paradigms: BD4BO multi-morbidities (RIA); Digital solutions for better compliance & adherence (RIA) ▪ Access, standards and interoperability: Biomedical metadata registry (RIA); Coordination and Support Action (CSA) ▪ Enabling platforms to support new research paradigms: Life science networks (RIA); OpenPhacts reasoning engine (RIA); BD4BO rare cancers (RIA); BD4BO respiratory diseases (RIA); Personal health data ecosystems (RIA); Adaptive designs (RIA) <p><i>Oncology</i></p> <ul style="list-style-type: none"> ▪ Beyond patient stratification (RIA) ▪ Increasing context specificity (RIA) ▪ Immune oncology (RIA) ▪ Cell free DNA-liquid biopsy (RIA) ▪ Big data in oncology (RIA) <p><i>Other Enablers of innovation</i></p> <ul style="list-style-type: none"> ▪ Facilitating the translation of advanced therapies (RIA); European stem cells facility (RIA) 				
OVERALL TOTAL		193,603,844	193,603,844	

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	Amended Budget 2017.1		
	Commitment Appropriation (CA)	Payment Appropriation (PA)	Payment Appropriation (PA)	Commitment Appropriation (CA)	Payment Appropriation (PA)	
Operational expenditure	178 038 671	196 782 634	-56 000 000	178 038 671	140 782 634	EC contribution to grant agreements - Payments
Appropriations carried over from 2016	467 173	134	77 282 369	134 467 173	77 282 369	The amount carried over from 2016.
Operational expenditure		2 831 000		0	2 831 000	EFPIA companies' and Associated Partners' contributions to grant agreements - Payments
Total	312 505 844	199 613 634	21 282 369	312 505 844	220 896 003	

The difference between the total budget available for Title 3 and the budget available for fresh Calls in 2017 is EUR 118 902 000. This amount represents the unused commitment appropriations carried over to the 2017 budget, to conclude Grant Agreements for IMI2 - Call 7 (EUR 46 802 000), Call 8 (EUR 70 000 000) and Call 3 (EUR 2 100 000).

A breakdown of the appropriations carried over is set out below.

	Commitment appropriation EUR	Payment appropriation EUR
2016 unused operational appropriations IMI2 (H2020)	133 951 888	77 282 369
2016 - 50 % unused running costs	515 285	
TOTAL	134 467 173	77 282 369

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

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.²¹

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).

²¹ 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"

IMI Calls	ongoing in 2017	Project periodic report due in 2017						Of which	
		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
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 (CAFAST).

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.

2.3 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 derogation²² 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 established²³.

STANDARD ADMISSIBILITY CONDITIONS AND RELATED REQUIREMENTS

Part B of the General Annexes²⁴ to the Horizon 2020 -Work Programme 2016– 2017 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 short proposals is 30 pages.

For a single stage call, as well as at stage 2 of a two-stage call, the limit for full proposals is 70 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:

²² 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

²³ In accordance with Article 10(2) of the Regulation (EU) No 1290/2013 and Article 1 of Commission Delegated Regulation (EU) No 622/2014

²⁴ 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.²⁵

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	<p>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:</p> <p>Clarity and pertinence of the proposal to meet all key objectives of the topic;</p> <p>Credibility of the proposed approach;</p> <p>Soundness of the concept, including trans-disciplinary considerations, where relevant;</p>	<p>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:</p> <p>The expected impacts of the proposed approach as mentioned in the call for proposals</p> <p>Added value from the public private partnership approach on R&D, regulatory, clinical and healthcare practice as relevant;</p> <p>Strengthening the competitiveness and industrial leadership and/or addressing specific societal challenges;</p>	<p>The following aspects will be taken into account:</p> <p>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;</p> <p>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;</p>

²⁵ 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*
	<p>Extent that proposed work is ambitious, has innovation potential, and is beyond the state of the art;</p> <p>Mobilisation of the necessary expertise to achieve the objectives of the topic, ensure engagement of all relevant key stakeholders</p>	<p>Improving European citizens' health and wellbeing and contribute to the IMI2 objectives²⁶.</p>	<p>Appropriateness of the proposed management structures and procedures, including manageability of the consortium.</p>
<p>RIA and IA</p> <p>Single stage, and 2nd stage evaluation</p>	<p>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:</p> <p>Clarity and pertinence of the proposal to meet all key objectives of the topic;</p> <p>Credibility of the proposed approach;</p> <p>Soundness of the concept, including trans-disciplinary considerations, where relevant;</p> <p>Extent that proposed work is ambitious, has innovation potential, and is beyond the state of the art;</p> <p>Mobilisation of the necessary expertise to achieve the objectives of the topic, ensure engagement of all relevant key stakeholders.</p>	<p>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:</p> <p>The expected impacts of the proposed approach as mentioned in the call for proposals;</p> <p>Added value from the public private partnership approach on R&D, regulatory, clinical and healthcare practice as relevant;</p> <p>Enhancing innovation capacity and integration of new knowledge;</p> <p>Strengthening the competitiveness and industrial leadership and/or addressing specific societal challenges; Improving European citizens' health and wellbeing and contribute to the IMI2 objectives;²⁶</p> <p>Any other environmental and socially important impacts;</p> <p>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.</p>	<p>The following aspects will be taken into account:</p> <p>Coherence and effectiveness of the project work plan, including appropriateness of the roles and allocation of tasks, resources, timelines and budget;</p> <p>Complementarity of the participants within the consortium (where relevant);</p> <p>Clearly defined contribution to the project plan of the industrial partners (where relevant);</p> <p>Appropriateness of the management structures and procedures, including manageability of the consortium, risk and innovation management and sustainability plan.</p>

²⁶ 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	<p>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:</p> <p>Clarity and pertinence of the proposal to meet all key objectives of the topic</p> <p>Credibility of the proposed approach;</p> <p>Soundness of the concept, including trans-disciplinary considerations, where relevant;</p> <p>Quality of the proposed coordination and/or support measures.</p> <p>Mobilisation of the necessary expertise to achieve the objectives of the topic, ensure engagement of all relevant key stakeholders.</p>	<p>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:</p> <p>The expected impacts of the proposed approach as mentioned in the Call for proposal;</p> <p>Added value from the public private partnership approach on R&D, regulatory, clinical and healthcare practice as relevant.</p> <p>Strengthening the competitiveness and industrial leadership and/or addressing specific societal challenges;</p> <p>Improving European citizens' health and wellbeing and contribute to the IMI2 objectives²⁷.</p>	<p>The following aspects will be taken into account:</p> <p>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;</p> <p>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.</p> <p>Appropriateness of the proposed management structures and procedures, including manageability of the consortium.</p>
CSA Single stage and 2nd stage evaluation	<p>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:</p> <p>Clarity and pertinence of the proposal to meet all key objectives of the topic;</p>	<p>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:</p> <p>The expected impacts of the proposed approach as mentioned in the Call for proposal;</p> <p>Added value from the public private partnership approach on R&D, regulatory, clinical and health care practice as relevant</p>	<p>The following aspects will be taken into account:</p> <p>Coherence and effectiveness of the project work plan, including appropriateness of the roles and allocation of tasks, resources, timelines and budget;</p> <p>Complementarity of the participants within the consortium (where relevant);</p>

²⁷ 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*
	<p>Credibility of the proposed approach;</p> <p>Soundness of the concept, including trans-disciplinary considerations, where relevant;</p> <p>Quality of the proposed coordination and/or support measures.</p> <p>Mobilisation of the necessary expertise to achieve the objectives of the topic and to ensure engagement of all relevant key stakeholders.</p>	<p>Strengthening the competitiveness and industrial leadership and/or addressing specific societal challenges;</p> <p>Improving European citizens' health and wellbeing and contribute to the IMI2 objectives²⁸.</p> <p>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.</p>	<p>Clearly defined contribution to the project plan of the industrial partners (where relevant);</p> <p>Appropriateness of the management structures and procedures, including manageability of the consortium, risk and innovation management and sustainability plan.</p>

* 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.²⁹

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

²⁸ 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)

²⁹ http://www.imi.europa.eu/sites/default/files/uploads/documents/IMI2_Call1/Manual_for_submission_evaluation_grant%20award_2014.06.26.pdf

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 proposal³⁰ (first stage) for each topic³¹ 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.

³⁰ 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.

³¹ 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

ACTIONS INVOLVING FINANCIAL SUPPORT TO THIRD PARTIES

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. A template for the Data Management Plan is available on the [IMI website](#).

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_v2_01602.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.³²

In order to ensure excellence in data and knowledge management consortia will be requested to Disseminate scientific publications on the basis of open access³³ (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 documents³⁴ (e.g. IMI2 JU model Grant Agreement).

CONSORTIUM AGREEMENTS

In line with the Rules for Participation and Dissemination applicable to IMI2 actions³⁵ and the IMI2 model grant agreement, participants in IMI2 actions are required to conclude a consortium agreement prior to grant agreement.

³² Article 19 of Horizon 2020 Framework Programme, and Articles 13 and 14 of the Horizon 2020 Rules for Participation.

³³ 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

³⁴ http://www.imi.europa.eu/content/documents#calls_for_proposals_-_imi_2_programme

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

³⁵ Regulation (EU) No 1290/2013 of 11 December 2013 and Commission Delegated Regulation (EU) No 622/2014 of 14 February 2014.

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
Regional events	Ongoing activity
Event with and for patients	tbc
IMI Stakeholder Forum 2017	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 Resources

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.

Chapter	Heading Title 1	Financial year 2017		
		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	<p>To prepare the implementation of the General Data Protection Regulation</p> <p>To promote a culture of data protection at IMI2 JU</p> <p>To support projects in establishing common minimum requirements for protecting and sharing personal data</p>
Planned Activities	<p>To prepare the implementation of the General Data Protection Regulation and in particular:</p> <ul style="list-style-type: none"> ▪ <u>increased accountability</u>: advise controller and data processors on their upcoming responsibility and liability for further processing ▪ <u>higher data handling standards</u>: 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); ▪ <u>data security</u>: establish internal procedures in relation to the use of technologies ▪ <u>transparency</u>: analyse the implications of changes in consent and the shifting of the burden of proof for compliance. <p>To promote a culture of data protection at IMI2 JU:</p> <ul style="list-style-type: none"> ▪ 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 <p>To support projects in establishing common minimum requirements for protecting and sharing data:</p> <ul style="list-style-type: none"> ▪ advising ▪ follow-up on recommendations addressed to IMI by the European Data Protection Supervisor
Expected results	<p>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.</p> <p>Actions:</p> <ul style="list-style-type: none"> ▪ 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 charter³⁶.

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.

³⁶

http://www.imi.europa.eu/sites/default/files/uploads/documents/IMI2_GB_DEC_2016_21_Decision_on_new_SGGs_Charter_SIGNED_30_SEP2016.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 continuous 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 assess 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) and 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	Amended Budget 2017.1		
Chapter		Commitment Appropriation (CA)	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	182 953 171	145 697 134	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 140,782,634.
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	317 420 344	224 396 213	
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	322 334 844	232 141 713	

STATEMENT OF EXPENDITURE

Heading Title 1		Financial year 2017					Comments
Chapter		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
Chapter		Commitment Appropriation (CA)	Payment Appropriation (PA)	<i>Payment Appropriation (PA)</i>	Commitment Appropriation (CA)	Payment Appropriation (PA)	
30	Implementing the research agenda of IMI JU	178 038 671	199 613 634	-56 000 000	178 038 671	143 613 634	Grant agreements - Payments: EU- EUR 140,782,634; 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	312 505 844	220 896 003	
	Total contributions	322 334 844	209 442 634	22 699 079	322 334 844	232 141 713	

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	
A02350	Other operating expenditure	13 000	13 000	2 000
A02351	Petty expenses	0	0	

Expense budget line	Description	Commitment appropriations	Payment appropriations	C2 - Payment Appropriation (PA)
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	120 000 000	
B03020	Implementing the research agenda of IMI2 JU	178 038 671	23 613 634	
B03020 - C2	Implementing the research agenda of IMI2 JU	134 467 173		77 282 369
30	Implementing the research agenda of IMI JU	312 505 844	143 613 634	77 282 369
	Total expenditures	322 334 844	153 442 634	78 699 079

3.1 Staff Establishment Plan

Grade	Establishment Plan 2016			Year 2017											
				Posts evolution						Organisational evolution			Establishment Plan 2017		
	PERM			Promotion / Career advancement			Turn-over (departures/arrivals)			New posts (per grade)			Requested (Budget)		
				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															
AST10															
AST9															
AST8		1	1											1	1
AST7															

Grade	Establishment Plan 2016			Year 2017														
				Posts evolution						Organisational evolution			Establishment Plan 2017					
	PERM			TEMP			Promotion / Career advancement			Turn-over (departures/arrivals)			New posts (per grade)			Requested (Budget)		
							Officials	TA - LT	TA - ST	Officials	TA - LT	TA - ST	Perm	TA - LT	TA - ST	Perm	TA	Total
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 created³⁷ 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 World³⁸.

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 companies³⁹, 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)⁴⁰ 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 protection⁴¹.

Before submitting a proposal, applicant consortia should familiarise themselves with all Call documents such as the IMI2 Manual for evaluation, submission and grant award⁴², and the IMI2 evaluation criteria. Applicants should refer to the specific templates and evaluation procedures associated with the topic type: Research and Innovation Actions (RIA), Coordination and Support Action (CSA).

³⁷ Council Regulation (EU) No 557/2014 of 6 May 2014 establishing the Innovative Medicines Initiative 2 Joint Undertaking (IMI2 JU).

³⁸ http://www.who.int/medicines/areas/priority_medicines/en/

³⁹ 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.

⁴⁰ http://www.imi.europa.eu/sites/default/files/uploads/documents/IMI2_SRA_March2014.pdf

⁴¹ 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>

⁴² http://www.imi.europa.eu/sites/default/files/uploads/documents/IMI2_CallDocs/Manual_SubEvalAward_IMI2_v1.4_Oct2016.pdf

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 results⁴³ 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 on a national level, avoid dispersion of the results, and contribute to maintaining European competitiveness in the field of biomedical research and innovation.

⁴³ For the purposes of this Call, results are defined as that foreground generated under a IMI project from IMI Calls launched between 2008-2013.

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 JU⁴⁴, 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 agreement⁴⁵, 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 leveraging the latest knowledge and learning, allowing the results to enable further research beyond the state of the art.

⁴⁴ 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.

⁴⁵

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 action⁴⁶ significant enough to ensure meeting the proposal specific objectives and contribute to the IMI2 JU objectives as a public-private partnership.

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.

⁴⁶ 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.

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.
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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
<p>EMTRAIN European Medicines Research Training Network 115015</p>	<ul style="list-style-type: none"> ▪ 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. 	<ul style="list-style-type: none"> ▪ Databases ▪ Learning platforms 	<ol style="list-style-type: none"> 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 	<p>www.emtrain.eu</p> <p>michael.wolzt@m-eduniwien.ac.at</p>

Project acronym, title & number	Project results (IMI1 project foreground)	Foreground type	Reference to scientific publications / other public sources	Project website and contacts
<p>EUPATI European Patients' Academy on Therapeutic Innovation 115334</p>	<ul style="list-style-type: none"> ▪ 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. 	<ul style="list-style-type: none"> ▪ 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 	<ol style="list-style-type: none"> 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. 	<p>www.eupati.eu</p> <p>jan@patientsacademy.eu</p> <p>walter.atzori@eupatient.eu</p>

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	<ul style="list-style-type: none"> ▪ 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. 	<ul style="list-style-type: none"> ▪ 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 	<ol style="list-style-type: none"> 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. <i>European Journal of Pharmaceutical Sciences</i> 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. <i>Frontiers in Pharmacology</i> 2013; 4: 112. 	<p>www.pharmatrain.eu</p> <p>ingrid.klingmann@pharmatrain.eu</p>

Project acronym, title & number	Project results (IMI1 project foreground)	Foreground type	Reference to scientific publications / other public sources	Project website and contacts
<p>Open PHACTS The Open Pharmacological Concepts Triple Store 115191</p>	<p>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.</p>	<ul style="list-style-type: none"> ▪ Semantically integrated life science data 	<ol style="list-style-type: none"> 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 	<p>www.openphacts.org</p> <p>gerhard.f.ecker@univie.ac.at</p> <p>stefan.x.senger@gsk.com</p>
<p>RAPP-ID Development of RApid Point-of-Care test Platforms for Infectious Diseases 115153</p>	<p>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.</p> <p>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.</p> <p>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.</p>	<ul style="list-style-type: none"> ▪ Prototype 	<ol style="list-style-type: none"> 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 	<p>www.rapp-id.eu</p> <p>jvillaci@its.jnj.com</p> <p>herman.goossens@uza.be</p> <p>pieter.moons@uantwerpen.be</p>

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	<p>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.</p> <p>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.</p>	<ul style="list-style-type: none"> ▪ Databases ▪ Technology platform 	<ol style="list-style-type: none"> 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 	<p>www.web-radr.eu</p> <p>phil.tregunno@mhra.gsi.gov.uk</p>
GetReal Incorporating real-life clinical data into drug development 115546 ⁴⁷	<ul style="list-style-type: none"> ▪ The web-based navigator tool has been designed to: <ol style="list-style-type: none"> 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); 	<ul style="list-style-type: none"> ▪ Website ▪ Software tools ▪ Online education and Training programme 	<p>Information on all aspects of the project foreground included in this call are publically available at the following sources:</p> <ol style="list-style-type: none"> 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 found at: https://www.imi-getreal.eu/Events/Stakeholder-Conference 	<p>www.imi-getreal.eu</p> <p>elaine.a.irving@qsk.com</p> <p>d.e.grobbee@umcutrecht.nl</p> <p>p.stolk@umcutrecht.nl</p>

⁴⁷ 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 created⁴⁸ 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 World⁴⁹.

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 companies⁵⁰, 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)⁵¹ 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 protection⁵².

Before submitting a proposal, applicant consortia should familiarise themselves with all Call documents such as the IMI2 Manual for evaluation, submission and grant award⁵³, and the IMI2 evaluation criteria. Applicants should refer to the specific templates and evaluation procedures associated with the topic type: Research and Innovation Actions (RIA), Coordination and Support Action (CSA).

⁴⁸ Council Regulation (EU) No 557/2014 of 6 May 2014 establishing the Innovative Medicines Initiative 2 Joint Undertaking (IMI2 JU).

⁴⁹ http://www.who.int/medicines/areas/priority_medicines/en/

⁵⁰ 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.

⁵¹ http://www.imi.europa.eu/sites/default/files/uploads/documents/IMI2_SRA_March2014.pdf

⁵² 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>

⁵³ http://www.imi.europa.eu/sites/default/files/uploads/documents/IMI2_CallDocs/Manual_SubEvalAward_IMI2_v1.4_Oct2016.pdf

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.

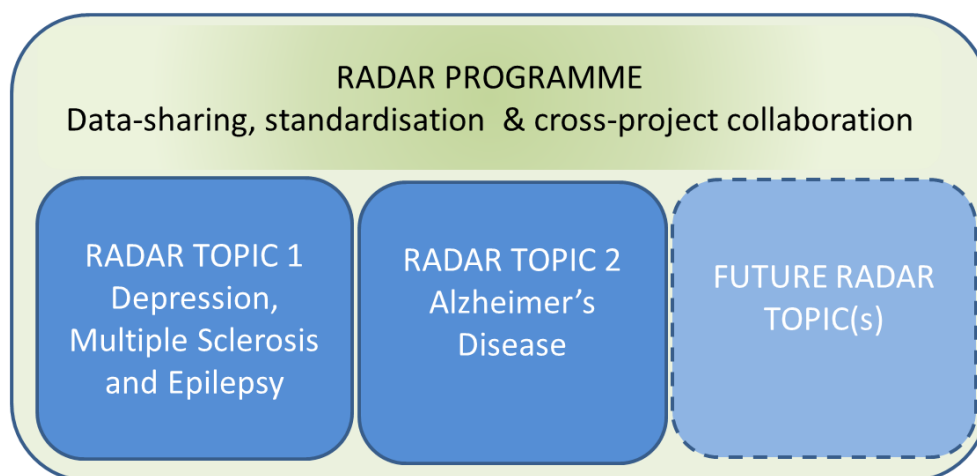
Introducing a drug development and a clinical care strategy based on such science and technology requires a second type of public-private research to be undertaken to: 1) develop policy for the regulatory and licensing pathways to deliver a digital intervention; 2) understand and develop a framework 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 (approximately 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=16hxaa8ljrm1arbzf32dbt5>
- 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 contribution⁵⁴.

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:

⁵⁴ 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 endpoints 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)^{55 56} 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 ELIXIR⁵⁷, but also in global organisations such as the G20 countries⁵⁸. Very similar principles for data stewardship are described in the H2020 Guideline for data management⁵⁹ as part of the H2020 Open Research Data Pilot (ORDP, Art. 29.3 of the MGA) and the IMI2 Data Management Plan template⁶⁰.

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:

⁵⁵ <https://www.force11.org/group/fairgroup/fairprinciples>

⁵⁶ 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>

⁵⁷ <https://www.elixir-europe.org>

⁵⁸ http://europa.eu/rapid/press-release_STATEMENT-16-2967_en.htm

⁵⁹ http://ec.europa.eu/research/participants/data/ref/h2020/grants_manual/hi/oa_pilot/h2020-hi-oa-data-mgt_en.pdf

⁶⁰ 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 ELIXIR⁶¹ 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.⁶²

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.

⁶¹ <https://www.elixir-europe.org>

⁶² 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.⁶³
- 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.⁶⁴

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.

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

⁶³ Grant Agreement option 28.2a will apply

⁶⁴ Grant Agreement options 29.1a and 29.1b will apply

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 contributions⁶⁵

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

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

⁶⁵ Note: This does not however constitute the justification referred to in Article 4(2) of the IMI 2 JU regulation.

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) standards⁶⁶). 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 sources⁶⁷. 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.

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.

⁶⁶ 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>

⁶⁷ <http://www.dtls.nl/fair-data/byod/>

- 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 exocrine glands leading to sicca symptoms of the eyes and the mouth⁶⁸. 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 productivity⁶⁹. Moreover, pSS patients have 9-fold higher risk of developing B cell lymphomas⁷⁰. 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 stratification⁷¹. 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 scarce⁷². 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)^{73 74}, their recent use in clinical trials has yielded mixed results^{75 76}. 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

⁶⁸ Rischmueller M, Tieu J, Lester S. Primary Sjögren's syndrome. *Best Pract Res Clin Rheumatol*. 2016;30:189-220.

⁶⁹ 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

⁷⁰ See footnote above

⁷¹ 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

⁷² See footnote above

⁷³ 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.

⁷⁴ 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

⁷⁵ 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.

⁷⁶ 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.

measures/biomarkers of improvement are needed to increase the likelihood of success of drug development in pSS⁷⁷.

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.

⁷⁷ 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

- 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 objectives⁷⁸) 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 Syndrome⁷⁹.

⁷⁸ 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

⁷⁹ Brito Zeron P, Kostov BA, Seror R, Baldini C, Quartuccio L, Kvarnstrom M et al. Big Data Sjogren Project (EULAR-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.

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
- 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 contributions⁸⁰.

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;
- 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.

⁸⁰ Note: This does not however constitute the justification referred to in Article 4(2) of the IMI 2 JU regulation.

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 I 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 or other 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.

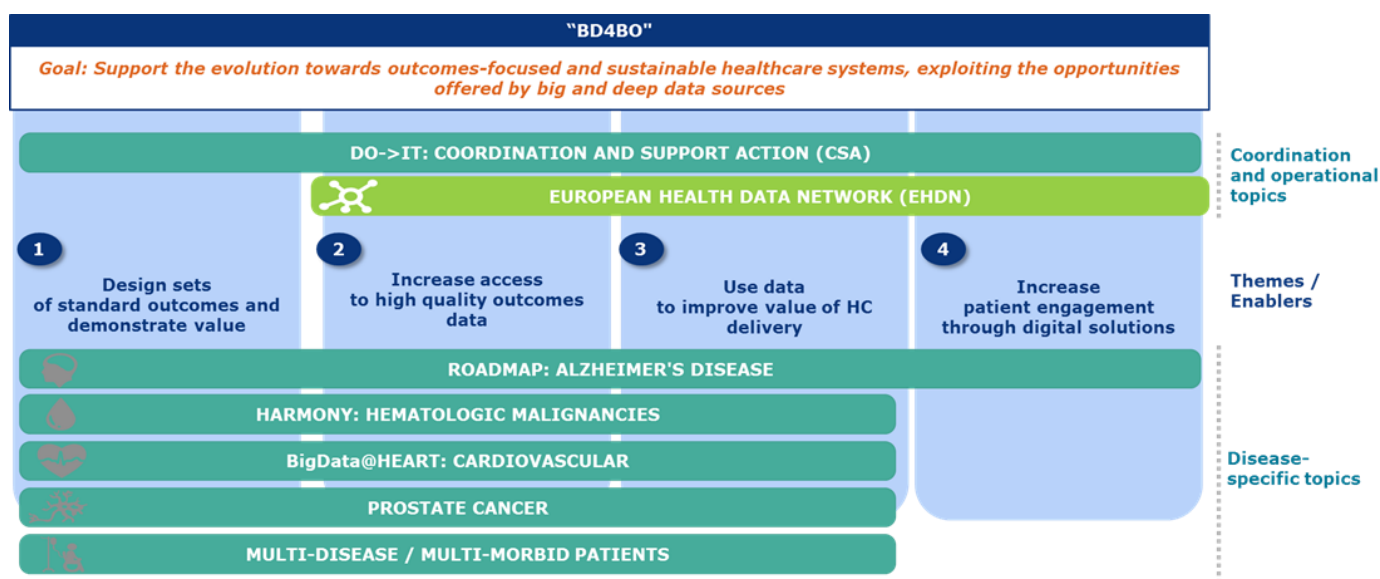


Figure 1: Programme structure, themes / enablers and CSA

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 programme⁸¹ 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.

⁸¹ 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) standards⁸².

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/>) project⁸³. 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 Model⁸⁴, originally developed as part of the Observational Medical Outcomes Partnership (OMOP)⁸⁵, 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 Model⁸⁶; this number may

⁸² <http://www.ichom.org/>

⁸³ Hripcsak G, et al. (2015) Observational Health Data Sciences and Informatics (OHDSI): Opportunities for observational researchers. *Stud Health Technol Inform* 216:574–578

⁸⁴ 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.

⁸⁵ 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.

⁸⁶ Hripcsak G, et al. (2015) Observational Health Data Sciences and Informatics (OHDSI): Opportunities for observational researchers. *Stud Health Technol Inform* 216:574–578

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 standards⁸² 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 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.

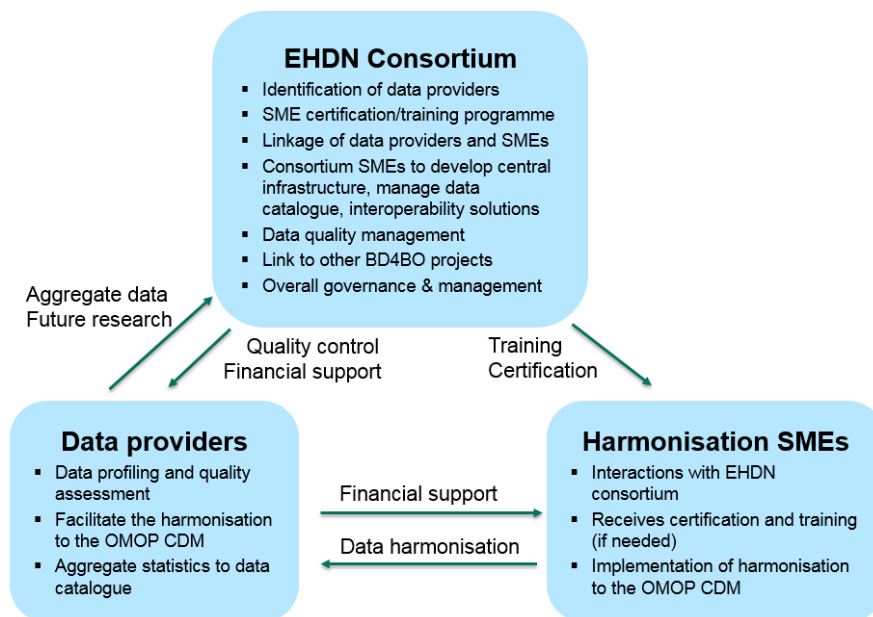
The third goal of EHDN is to stimulate development of new and augmented health services through available and expanded technologies, in the interest of health outcomes.

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 an 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.

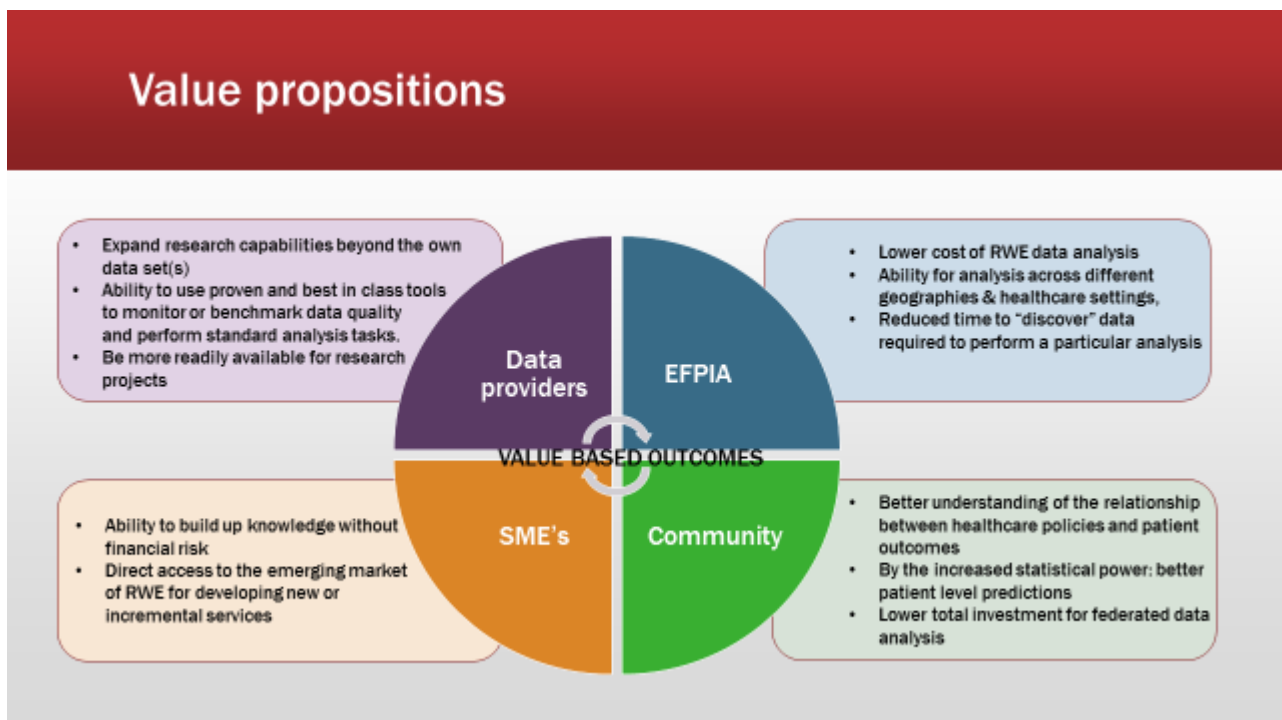
The validation of harmonised data sets as compliant with the EHDN suite of tools for accessing data thereby providing the opportunity for the data owners to participate in BD4BO and other research projects. This will imply the existence of an operational data quality management framework for real world 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 000⁸⁷.

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

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).⁸⁸ 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.

⁸⁷ This figure includes both in-kind and financial contributions.

⁸⁸ 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.

- 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. some work going on in the Institute for Innovation through Health Data (iHD) and other EU initiatives such as SPOR and IDMP⁸⁹. 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.

⁸⁹ See http://www.ema.europa.eu/ema/index.jsp?curl=pages/regulation/general/general_content_000645.jsp

- Ability to render structured content harmonised to the applicable data standards from unstructured text (text mining).

Financial support to third parties⁹⁰ 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 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 party⁹¹, 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.

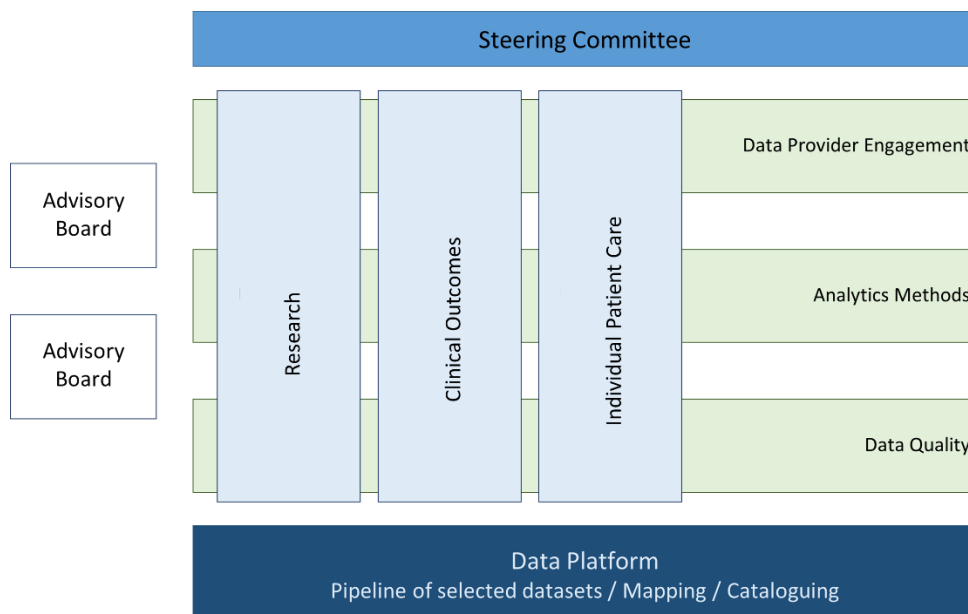
In the spirit of the partnership, and to reflect how IMI 2 JU call topics are built on identified scientific priorities agreed together with EFPIA beneficiaries/large industrial beneficiaries, these beneficiaries intend to significantly contribute to the programme leadership and project and financial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

⁹⁰ In accordance with Annex K of the Horizon 2020 Work Programme and the article 15 of the IMI2 Model Grant Agreement.

⁹¹ 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.

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 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 proposal⁹². 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, ...)

⁹² In compliance with article 15.1 of the IMI2 Grant Agreement.

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 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, eCOP⁹³) 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.

⁹³ 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^{94 95}. 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 longer⁹⁶. But older people are more vulnerable to infectious diseases because their immune system becomes weaker with age⁹⁷. 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 suffering⁹⁸. 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 life⁹⁹. 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 exposure¹⁰⁰, immune response to vaccination¹⁰¹, 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;

⁹⁴ EUROSTAT (2017). "Population structure and aging".

⁹⁵ Flinch, C (2010). Evolution of the human lifespan and diseases of aging: roles of infection, inflammation, and nutrition. PNAS, 107 (1).

⁹⁶ Gloersen, E (2016). The impact of demographic change on European regions: 147

⁹⁷ 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.

⁹⁸ Westendorp R, (2006). What is healthy aging in the 21st century? *AM J Clin Nutr* 83(2):404S-409S.

⁹⁹ 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

¹⁰⁰ 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.

¹⁰¹ Gruver, A. L., et al. (2007). "Immunosenescence of ageing." *J Pathol* 211(2): 144-156.

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 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^{102 103 104 105}, identifying external factors that could influence the process, epidemiology and the cost of vaccine preventable infectious diseases in elderly¹⁰⁶. 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^{107 108 109 110}. 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

¹⁰² Gruver, A. L., et al. (2007). "Immunosenescence of ageing." *J Pathol* 211(2): 144-156.

¹⁰³ 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

¹⁰⁴ Ovsyannikova I, (2012). Impact of cytokine and cytokine receptor gene polymorphisms on cellular immunity after smallpox vaccination. *Gene*, 510(1): 59-65.

¹⁰⁵ Boraschi, D., et al. (2013). "The gracefully aging immune system." *Sci Transl Med* 5(185): 185ps188.

¹⁰⁶ 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.

¹⁰⁷ DiazGranados C, et al (2014). Efficacy of high-dose versus standard-dose influenza vaccine in older adults. *N Engl J Med*, 371(1): 635-45.

¹⁰⁸ Bonten M, et al. (2015). Vaccine against pneumococcal pneumonia in adults. *N Engl J Med*, 373(1): 93.

¹⁰⁹ Lal H, et al (2015). Efficacy of an adjuvanted herpes zoster subunit vaccine in older adults. *N Engl J Med*, 372 (22): 2087-96.

¹¹⁰

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.

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 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 (T_{fh}), 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 (T_{fh}), 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 cerebrovascular 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 molecules¹¹¹. 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 market¹¹². 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 BBB¹¹³. 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, liposomes¹¹⁴, nanoparticles, and more recently exosomes¹¹⁵ 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.

¹¹¹ 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. Daneman and R. M. Ransohoff, Development, maintenance and disruption of the blood-brain barrier, *Nature Medicine* 19, 1584–1596 (2013).

¹¹² PhRMA, March 25, 2014.

¹¹³ 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)

¹¹⁴ F. Lai, A. M. Fadda and C. Sinico, Liposomes for brain delivery, *Expert Opinion on Drug Delivery*, 10:7, 1003-1022, 2013.

¹¹⁵ L. Alvarez-Erviti, Y. Seow, H. Yin, C. Betts, S. Lakhai 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 models¹¹⁶, their robustness and predictability remain to be assessed, and no fully reconstituted human model convincingly mimicking the neurovascular unit has been successfully developed to-date¹¹⁷. To this end, 3D- or spheroid models and microfluidics could be ideally suited and a few interesting directions are starting to emerge in the literature¹¹⁸ 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**¹¹⁹. 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)¹²⁰. 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 drugs¹²¹. 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.

¹¹⁶ 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.

¹¹⁷ 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.

¹¹⁸ 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.

¹¹⁹ 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 al *Nature Rev Neuroscience* (2011), 12(3), 169-182

¹²⁰ 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.

¹²¹ 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 approaches¹²² 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

¹²² Y. Zhang, K. Chen, S. A. Sloan, M. L. Bennett, A. R. Scholze, S. O'Keefe, 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^{123 124}. 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.

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.

¹²⁴ 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 al *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 metabolism¹²⁵.

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 endeavour¹²⁶, 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 biopharmaceuticals 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.

¹²⁵ 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

¹²⁶ 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 contributions¹²⁷.

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.

¹²⁷ 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 biopharmaceuticals 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.

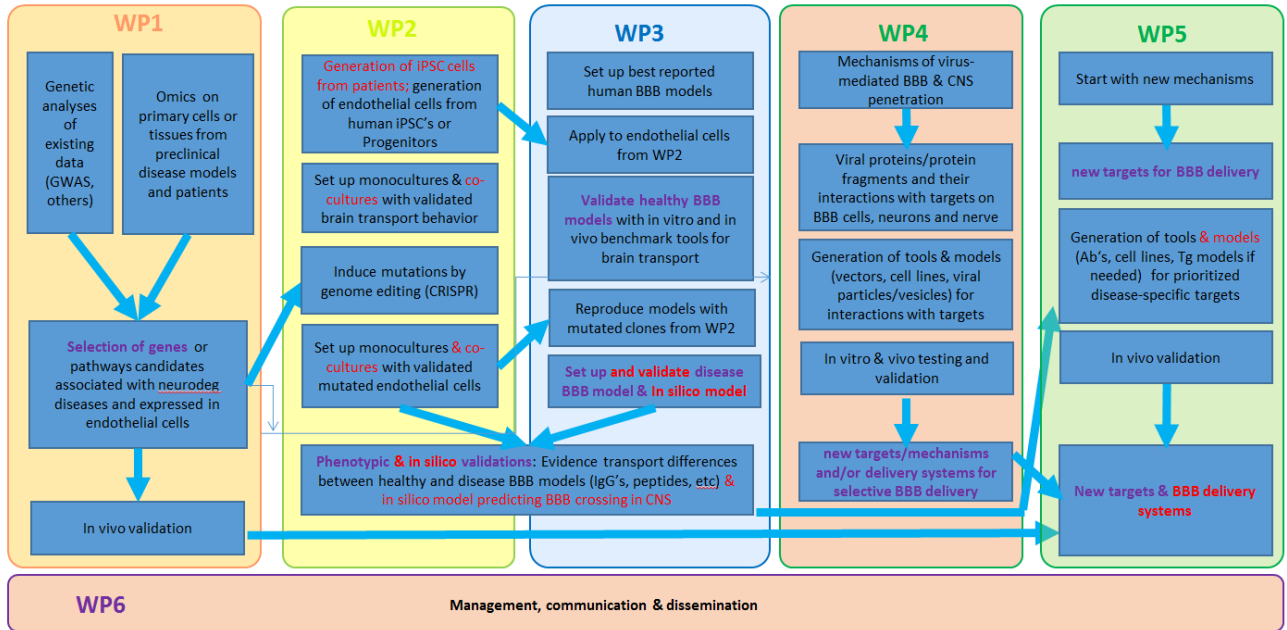
Applicant consortium contribution: tools for validation of the new mechanisms (Ab's, ligands, cell lines); *in vivo* PK; disease models.

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 disease¹²⁸. 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>)^{129 130} 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 owners¹³¹, 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.

¹²⁸ C.H. Arrowsmith et al. "The promise and peril of chemical probes" *Nature Chem. Biol.* 2015, 11, 536-541.

¹²⁹ 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.

¹³⁰ 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.

¹³¹ The term 'public target owners' used throughout this text refers to academic groups, biotechs, SMEs, charity organizations and patient foundations.

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 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 (sp³ 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^{132 133 134}.

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

¹³² 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.

¹³³ 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.

¹³⁴ S. Dandapani, L. A. Marcaurelle, "Grand challenge commentary: Accessing new chemical space for 'undruggable' targets", *Nature Chem. Biol.* 2010, 6, 861–863.

support assay development and perform HTS campaigns & follow-up tests for academic groups, biotechs, SMEs, charity organisations and patient foundations.

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 diseases¹³⁵, 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-OPENSREEN (www.eu-openscreen.eu) and other initiatives outside the EU. With respect to IMI projects:

- European Lead Factory (www.europeanleadfactory.eu/)

¹³⁵ 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.prelect.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	<p>The indicative EFPIA in-kind contribution will be EUR 8 200 000</p> <p>The financial contribution from IMI2 JU will be a maximum of EUR 8 200 000</p>	<p>Research and Innovation Actions (RIA)</p> <p>Two-stage submission and evaluation process.</p> <p>Only the applicant consortium whose proposal is ranked first at the first stage is invited for the second stage.</p>
IMI2-2017-12-04	<p>The indicative EFPIA in-kind contribution will be EUR 14 127 000</p> <p>The financial contribution from IMI2 JU will be a maximum of EUR 14 127 000</p>	<p>Research and Innovation Actions (RIA)</p> <p>Two-stage submission and evaluation process.</p> <p>Only the applicant consortium whose proposal is ranked first at the first stage is invited for the second stage.</p>
IMI2-2017-12-05	<p>The indicative EFPIA in-kind contribution will be EUR 5 500 000</p> <p>The financial contribution from IMI2 JU will be a maximum of EUR 5 500 000</p>	<p>Research and Innovation Actions (RIA)</p> <p>Two-stage submission and evaluation process.</p> <p>Only the applicant consortium whose proposal is ranked first at the first stage is invited for the second stage.</p>
IMI2-2017-12-06	<p>The indicative EFPIA in-kind contribution will be EUR 9 000 000</p> <p>The financial contribution from IMI2 JU will be a maximum of EUR 9 000 000</p>	<p>Research and Innovation Actions (RIA)</p> <p>Two-stage submission and evaluation process.</p> <p>Only the applicant consortium whose proposal is ranked first at the first stage is invited for the second stage.</p>
IMI2-2017-12-07	<p>The indicative EFPIA in-kind contribution will be EUR 17 500 000</p> <p>The indicative IMI2 JU Associated Partners contribution will be 750 000</p> <p>The financial contribution from IMI2 JU will be a maximum of EUR 18 250 000</p>	<p>Research and Innovation Actions (RIA)</p> <p>Two-stage submission and evaluation process.</p> <p>Only the applicant consortium whose proposal is ranked first at the first stage is invited for the second stage.</p>

LIST OF ACRONYMS

Acronym	Meaning
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
ADMET	Absorption, Distribution, Metabolism, Excretion, Toxicity
AMR	Antimicrobial Resistance
API	Application Programming Interface
ASD	Autism spectrum disorder
AST	Assistant
AWP2016	Annual Work Plan 2016
BBB	Blood brain barrier
BD4BO	Big Data for Better Outcomes
BRIDG	Biomedical Research Integrated Domain Group
BIT	Booking of IT material application
BMI	Body Max Index

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
CMT	carrier-mediated transcytosis
CNS	Central Nervous System
COPD	chronic obstructive pulmonary disease
C-Path	Critical Path Institute
CPD	Continuing professional development
CRC	Australian Cooperative Research Centres
CRO	Contract research organisation
CSC	Common Support Centre
CTCAE	Common Terminology Criteria for Adverse Events
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
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
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

ESSDAI	EULAR Sjögren's syndrome disease activity index
ESSPRI	EULAR Sjogren's Syndrome Patient Reported Index
eTRIKS	European Translational Information & Knowledge Management Services
EU-ADR	Exploring and Understanding Adverse Drug Reactions
EULAR	European League against Rheumatism
EUPCTN	Sustainable pan-EU paediatric CT network
ESFRI	European Strategy Forum on Research Infrastructures
eTOXdb	eTOX rich preclinical database
eTOXsys	eTOX <i>in silico</i> toxicology prediction system
EU	European Union
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	Governing Board

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
HCT	Human challenge trials
Helmsley Charitable Trust	Leona M. and Harry B. Helmsley Charitable Trust
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
ICD	International Classification of Diseases
ICHOM	International Consortium for Health Outcomes Measurement
ICH S 1	International Conference on Harmonisation's Safety (S) 1
ICS	Internal Control Standards
ICT	Information Communications Technology
I-HD	European Institute for Innovation through Health Data
ILG	Industry Liaison Group
IMI 1 JU	Innovative Medicines Initiative 1 Joint Undertaking
IMI 2 JU	Innovative Medicines Initiative 2 Joint Undertaking

IMI JU	Innovative Medicines Initiative Joint Undertaking
IP	Intellectual Property
iPS cells	Induced pluripotent stem cells
ISA	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
LEAP	Longitudinal European Autism Project
MAPPs	Medicines adaptive pathways to patients
MCI	Mild Cognitive Impairment
MEP	Member of the European Parliament
MIAME	A Minimum Information About a Microarray Experiment
MRI	Magnetic resonance imaging
MS	Multiple sclerosis
MSD	Merck Sharp & Dohme Corp
MTA	Material transfer agreement
NAFLD	Non-alcoholic fatty liver disease
NASH	Non-alcoholic Steatohepatitis
ND4BB	New Drugs for Bad Bugs
NICE	The National Institute for Health and Care Excellence

NIMH	National Institute of Mental Health
NMDA-Receptor	N-methyl-D-aspartate receptor
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
PET	Positron emission tomography
PM	Person/month
PMDA	Pharmaceuticals and Medical Devices Agency
PONDS	Province of Ontario Neurodevelopmental Disorders
PPP	Public-private partnership
PRO	Patient reported outcomes
pSS	primary Sjögren`s syndrome
PSTC	Predictive Safety Testing Consortium
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

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
ROADMAP	Real World outcomes across the AD spectrum for better care: Multi-Modal data Access Platform
RWD	Real World Data
SAR	Structure activity relationship
SC	Scientific Committee
SDTM	Study Data Tabulation Model
SEND	CDISC SEND Controlled Terminology
SGGs	Strategic Governing Groups
SMEs	Small and medium-sized enterprises
SLC	Solute carriers
SOFIA	Submission of Information Application
SOP	Standard operating procedure
SP	Short Proposal
SRA	Strategic Research Agenda
SRG	States Representatives Group
SW	Semantic Web

SWOT	Strengths-Weaknesses-Opportunities and Threats analysis
T1D	Type 1 diabetes
T2D	Type 2 diabetes
TA	Temporary Agent
TB	Tuberculosis
TSD	Total sleep deprivation
TTG	Time to Grant
TTP	Time to Pay
UPSA	Ultrasound-based plaque structure analysis
US	United States
VC	Venture capital
WHO	World Health Organisation
WP(s)	Work Package(s)

