IMI2

20th Call for proposals

Annex I to the Decision of the IMI2 JU Governing Board No. IMI2-GB-DEC-2019-24 adopted on 13 December 2019

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Contents

Introduction

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

The Innovative Medicines Initiative 2 Joint Undertaking (IMI2 JU) has been created[1] following the principles below:

Research related to the future of medicine should be undertaken in areas where societal, public health and biomedical industry competitiveness goals are aligned and require the pooling of resources and greater collaboration between the public and private sectors, with the involvement of Small and Medium-sized Enterprises (SMEs).

The scope of the initiative should be expanded to all areas of life science research and innovation.

The areas should be of public health interest, as identified by the World Health Organisation (WHO) report on priority medicines for Europe and the World[2].

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

The initiative should therefore seek to involve a broader range of partners, including mid-sized companies[3], 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)[4] is the main reference for the implementation of research priorities for IMI2 JU. The scientific priorities for 2020 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.

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[1] Council Regulation (EU) No 557/2014 of 6 May 2014 establishing the Innovative Medicines Initiative 2 Joint Undertaking (IMI2 JU), OJ L 169, 7.6.2014, p. 54–76.
[2] http://www.who.int/medicines/areas/priority_medicines/en/
[3] Under IMI2 JU, mid-sized companies having an annual turnover of E
UR 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.
[4] http://www.imi.europa.eu/sites/default/files/uploads/documents/About-IMI/research-agenda/IMI2_SRA_March2014.pdf

Applicant consortia shall ensure that where relevant their proposals are in compliance with the General Data Protection Regulation (EU) 2016/679[5] and Clinical Trial Regulation (EU) 536/2014[6] (and/or Directive 2001/20/EC[7)] and any relevant legislation[8].

Before submitting a proposal, applicant consortia should familiarise themselves with all Call documents such as the IMI2 JU Manual for submission, evaluation and grant award[9], 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).

[5] Regulation (EU) 2016/679 of the European Parliament and of the Council of 27 April 2016 on the protection of natural persons with regard to the processing of personal data and on the free movement of such data, and repealing Directive 95/46/EC (General Data Protection Regulation), OJ L 119, 4.5.2016, p. 1–88.
[6] Regulation (EU) No 536/2014 of the European Parliament and of the Council of 16 April 2014 on clinical trials on medicinal products for human use, and repealing Directive 2001/20/EC, OJ L 158, 27.5.2014, p. 1-76.
[7] Directive 2001/20/EC of the European Parliament and of the Council of 4 April 2001 on the approximation of the laws, regulations and administrative provisions of the Member States relating to the implementation of good clinical practice in the conduct of clinical trials on medicinal products for human use (the "Clinical Trials Directive), OJ L 121, 1.5.2001, p. 34.
8 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, OJ L 281, 23.11.1995, p. 31–50.
[9] https://www.imi.europa.eu/sites/default/files/uploads/documents/apply-for-funding/call-documents/imi2/IMI2_ManualForSubmission_v1.7_November2018.pdf

Topic 1: Early diagnosis, prediction of radiographic outcomes and development of rational, personalised treatment strategies to improve long-term outcomes in psoriatic arthritis

Topic details

Topic code	IMI2-2020-20-01
Action type	Research and Innovation Action (RIA)
Submission and evaluation process	2 stages
IMI2 Strategic Research Agenda - Axis of Research	Target validation and biomarker research (efficacy and safety)
IMI2 Strategic Research Agenda - Health Priority	Immune-mediated diseases

Specific challenges to be addressed by public-private collaborative research

Psoriatic arthritis (PsA) is a chronic immune-mediated disease involving axial and peripheral joints, nails, skin and enthesis. Cutaneous manifestations often precede articular symptoms and it has been estimated that about 20-30 % of psoriatic patients develop arthritis or enthesitis over time [1]. In fact, the precedence of cutaneous symptoms may give as much as about 7 years to predict, detect and potentially treat PsA [2].

Although still a matter of debate, the pathogenesis of PsA is multifactorial and includes genetic and environmental triggers, like dysbiosis, infections or a mechanic stress, which could induce and maintain the aberrant activation of the innate and adaptive immune system.

Current therapeutic approaches aim to cover the entire clinical spectrum of PsA, from nail and skin involvement to joint, tendon and enthesis damage and inflammation. The newest discoveries in PsA pathogenesis have promoted the development of several drugs with different mechanisms of action targeting molecules involved in both musculoskeletal and cutaneous manifestations. The choice of the best treatment for PsA patients should rely on a global evaluation, including the predominant clinical manifestations, comorbidities or contraindications to the therapy [3].

There are still a large number of patients suffering from PsA that are diagnosed after several years of signs and symptoms (late diagnosis) and fail to respond to current standard of care treatments, or quickly relapse on, or following treatment. Currently, it is felt that the earlier PsA can be diagnosed, the better the chances that treatment could influence the disease. It also seems that the physiopathology of PsA evolves with the “age” of the disease, and this may provide opportunities to discover new targets in early PsA patients.

The Group for Research and Assessment of Psoriasis and Psoriatic Arthritis (GRAPPA) identified the following major unmet medical needs:

- Early diagnosis of PsA either in psoriasis (PsO) patients or in patients without initial psoriasis skin manifestations. Significant delay in diagnosis contributes to poor clinical and radiographic outcome;
- Early identification of patients at risk of progression to PsA. Defining the predictors of progression to PsA in patients with skin PsO will enable earlier intervention and possibly even prevent development of PsA;

- Definition of the clinical, genetic, immune factors or protein biomarkers that predict disease progression in PsA patients at time of diagnosis;

- Better prediction, at diagnosis, for prognosis and stratification by therapeutic needs.

The focus of this topic is a multifactorial disease represented by its different forms through a wide patient population. It goes beyond the more homogeneous patients enrolled in clinical trials for the registration of new drugs. A broad spectrum of expertise is required for this challenge to be adequately addressed. In this context, collaborative efforts among pharmaceutical industries, academia, small and medium-sized enterprises (SMEs) and patient organisations in a public-private partnership are most likely to harness all the skills and expertise required. Lastly, the involvement of representatives of health and regulatory authorities will ensure the necessary regulatory guidance paving the way towards the regulatory acceptance of “early PsA” diagnostic methods and personalised treatments. A synergy is expected from industry and other stakeholders joining forces in this particular area of medicines innovation.

Scope

The overall scope of this topic is to provide patients and physicians with new tools including clinical data patterns, biomarker profile patterns and imaging analysis for a better control of PsA. The aim of this topic is to characterise the natural history of PsA from psoriasis to “early” PsA to “full-fledged” PsA, as diagnosed by the Classification Criteria for Psoriatic Arthritis (CASPAR). This characterisation will be based on discovering new biomarkers and endotypes, constructed on genetic, epigenetic, transcriptomic, proteomic and/or clinical markers. To identify those endotypes, artificial intelligence (AI) and machine learning (ML) processes will be needed.

In particular, the topic aims to achieve the following specific objectives:

- to enable rheumatologists, dermatologists and general practitioners to make an early diagnosis of PsA in patients with PsO and other rheumatic disorders;

- to identify early patients at risk of progression to PsA in order to enable earlier interventions and possibly prevent PsA development;

- to define the factors that predict disease progression in PsA patients, including early prediction of bone/joint damages, leading to the development of more adapted treatment strategies;

- to develop rational and personalised treatment strategies (e.g. select the optimal first line or second line treatment based on patient characteristics) with optimised outcomes in PsA patients and reduce the disease burden.

Expected key deliverables

- Early diagnosis of PsA in PsO patients:

    - identification of predictors of disease progression, e.g. genetic, epigenetic, transcriptomic, proteomic and/or clinical biomarkers assessed through longitudinal follow-up until evidence of CASPAR;

    - identification and characterisation of biomarkers to predict, diagnose and monitor PsA in patients with PsO and to assess treatment response;

    - biomarkers of tissue damage, predicting disease progression among PsA patients;

    - ML/AI tools to identify novel biomarker signatures;

    - digital tool(s) developed for use by physicians and/or patients.

- Early prediction of bone/joint damages in PsA patients:

- identification of poor radiographic outcomes;
- biomarker assay(s) to identify patients that may rapidly develop bone or joint damages, indicating that these patients need strict control of PsA.

- Prediction of best treatment for patients at diagnosis:
  - biomarker assay(s) to assess response/non-response for various treatments of PsA;
  - development of a PsA specific algorithm to estimate the expected response to treatments.
  - Creation of a tissue library, accessible by all involved parties, comprising skin, synovial tissue, synovial fluid and/or peripheral blood cells (including CD4+ and/or CD8+ T cells and/or other lymphocytes, monocytes) for analysis. This tissue library will have to be organised by the consortium with a perspective of sustainability incorporated in its foundation documents. Existing libraries will also be considered and be contacted for possible sustainable collaboration;
- Development and implementation of new techniques for diagnostic use e.g. peptide immunoaffinity enrichment with targeted mass spectrometry (immuno-multiple reaction monitoring, iMRM), mass cytometry (e.g. CyTOF), (single cell) investigation of autoantibodies / DNA methylation (e.g. as marks for tissue damage), and other techniques for single cell analysis to support detailed investigation of signalling cross-talk within and between relevant cell populations;
- Novel methods for data mining and AI-driven information extraction;
- Letter of support from regulatory bodies (e.g. the European Medicines Agency, EMA and/or Food and Drug Administration FDA) on the potential for qualification/validation of the biomarker(s) and their clinical applications (context of use) in PsA.

It is expected that applicants should propose a coherent, strategic plan to cover how they plan to address the key deliverables (identification of predictors of disease progression e.g. genetic, epigenetic, transcriptomic, proteomic and/or clinical biomarkers assessed through longitudinal follow-up until evidence of CASPAR; identification and characterisation of biomarkers to predict, diagnose and monitor PsA in patients with PsO and to assess treatment response).

Expected impact

In their proposals, applicants should describe how the outputs of the project will contribute to the following impacts and include wherever possible baseline, targets and metrics to measure impact:

- “Early PsA” diagnosis and earlier personalised treatments for patients would impact the disease progression and ultimately prevent PsA development. AI would help identifying endotypes which could take into account the clinical and biological heterogeneities of PsA;
- Development of objective and sensitive functional measures would enable the early diagnosis of PsA in PsO patients and the early prediction of bone/joint damages in PsA patients, yielding long-lived reduction in disease and improvement of patients’ quality of life;
- Improved rates of treatment successes through better understanding of the relation between molecular characteristics of PsA and treatment responses would reduce costs to patients (side effects) and society (economics).

In their proposals, applicants should outline how the project plans to leverage the public-private partnership model to maximise impacts on innovation, research & development; regulatory, clinical and healthcare practices, as relevant. This could include a strategy for the engagement with patients, healthcare professional associations, healthcare providers, regulators, HTA (health technology assessment) agencies, payers, etc., where relevant.

In addition, applicants should describe how the project will impact on the competitiveness and growth of companies including SMEs.

In their proposals, applicants should outline how the project will:

- Manage research data including use of data standards;[10]
- Disseminate, exploit, and sustain the project results. This may involve engaging with suitable biological and medical sciences research infrastructures;[11]
- Communicate the project's activities to relevant target audiences.

Potential synergies with existing consortia

Synergies and complementarities should be considered with relevant national, European and non-European initiatives (including suitable biological and medical sciences research infrastructures[2]) in order to incorporate past achievements, available data and lessons learnt where possible, thus avoiding unnecessary overlap, and duplication of efforts and funding.

Industry consortium

The industry consortium is composed of the following EFPIA partner(s):

- Novartis (lead)
- UCB (co-lead)
- BMS
- Pfizer

The industry consortium plans to contribute the following expertise and assets:

- translational medicine expert: leading role from a strategic, scientific, organisational and project management perspective;
- data manager: support to organise and control database systems within the project generated from this topic and interoperability with other relevant IMI-funded or open public projects;
- biomarker expert: scientific adviser to make sure that the selected biomarkers are relevant or sufficiently innovative;
- bioinformatics expert: analysis of large datasets (big data) to find predictive signatures of disease and response to therapy;
- statistical expert: scientific adviser to make sure that the statistical approaches are relevant or sufficiently innovative;

[10] Guidance on data management is available at http://ec.europa.eu/research/participants/docs/h2020-funding-guide/cross-cuttingissues/open-access-data-management/data-management_en.htm
[11] http://www.corbel-project.eu/about-corbel/research-infrastructures.html

- pharmacometric expert: scientific adviser to make sure that the pharmacometric approaches are relevant or sufficiently innovative;

- regulatory affairs expert: regulatory adviser to make sure that the selected biomarkers or new tools (e.g. questionnaire) are relevant.

During the funded action, members of the industry consortium plan to contribute scientifically relevant activities for generating data / collecting samples in prospective activities that are part of broader clinical studies independent from, but carried out in connection with the action and necessary for achieving its objectives. The generation of the data constitutes an in-kind contribution which entails access rights to these project results in line with IMI2 JU intellectual property (IP) rules. The estimated in kind contribution for the prospective activities to generate these data and samples is EUR 9 880 000.

The data and samples collected are planned to come from the prospective studies described below, and consist of the following data/samples types & volume:

Company	**Study description**	**Data/sample description**	**Estimated number of involved patients**
Novartis	Phase 3, 2 arm study in PsA	Placebo arm only, 16 week treatment duration	190
UCB	Phase 3 or 3B PsA study	Baseline data	300
BMS	Ph3 PsA subset of PBO	Data only (no samples)	200

These data and samples are essential for achieving the objectives of the project. Disclaimer: the final quantitative contribution in the form of data and samples is contingent on successful study readouts. The industry consortium partners will team up to address any unexpected changes in the above so that the estimated total in-kind contribution remains at its planned level.

The industry consortium may contribute additional prospective cohorts of patients, including PsO patients, as they become available.

In addition, retrospective industry historical data may be contributed as background as relevant.

Indicative duration of the action

The indicative duration of the action is 60 months.

This duration is indicative only. At stage 2, the consortium selected at stage 1 and the predefined industry consortium may jointly agree on a different duration when submitting the stage 2 proposal.

Indicative budget

The financial contribution from IMI2 JU is a maximum of EUR 10 211 000.

The indicative in-kind contribution from EFPIA partners is EUR 13 880 000.

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

Expertise and resources expected from applicants at stage 1

The stage 1 applicant consortium is expected, in the submitted short proposal, to address all the objectives and key deliverables of the topic, taking into account the expected contribution from the industry consortium which will join at stage 2 to form the full consortium.

The stage 1 submitted short proposals should include suggestions for creating a full proposal architecture.

This may require mobilising, as appropriate the following expertise:

- SMEs & academia / research and technology organisations (RTOs) with past and present experience on genetic, epigenetic, transcriptomic, proteomic, biomarkers, AI/ML techniques and "big data" management techniques. Experience and capacity to manage large volumes of various data (clinical, biological, genetic, imaging) to potentially identify endotypes by using AI and ML systems;
- Patient associations and/or patient advocacy groups in PsO/PsA to ensure access to data and information;
- Regulatory agencies and/or HTA agencies and/or health authorities interested in innovative PsO/PsA assessments and new diagnostic tools to build a strategy for regulatory qualification/acceptance of project outputs;
- Academics, physicians (both rheumatologists and dermatologists) and/or clinical trial centres experienced in PsO/PsA clinical, biological and imaging assessments; capable of justifying (1) their expertise in recruiting PsO & PsA patients; and (2) the number they envisage to support a valid statistical conclusion; capable of organising prospective longitudinal assessments of PsO patients;
- Strong data management experience in managing and coordinating a multi-centre, multi-node clinical research data generation activity of comparable scope. This must include the ability to design and execute an effective and feasible scientific work plan and related robust processes to deliver objectives and deliverables on time. Essential experience should also cover the legal and ethical challenges associated with integrating multi-centre, patient-derived data, as well as physical data processing/data management practices (privacy, security);
- Demonstrated ability to deliver analytical platforms for a range of scientific/medical and analytical communities;
- Expertise in a) clinical characterisation and patient access/recruitment (incl. samples and/or data from ongoing prospective collections/trials for PsO and/or PsA); b) biological specimen-based profiling; and c) advanced informatics;
- Expertise in access to and use of medical record-based information. Other publicly available data or cohorts could be incorporated into the action generated by this topic;
- Skills in molecular epidemiology, clinical science, and the integration of biological profiling with relevant datasets;
- Proven expertise in rigorous programme management of large and complex multi-stakeholder projects, including expertise in risk management and sustainability of results.

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

- Access to clinical cohorts and corresponding datasets of PsO and PsA patients, particularly longitudinal timed assessments. For a successful project, samples and data will need to be accessible to the whole consortium. Since access to clinical information and specimens is critical to the overall success of defining endotypes and the project goals, applicants should demonstrate their capacity (e.g. patient consent or waiver to consent) and the process by which they can provide access to these. Applicants may involve

academics, medical centres with existing materials, biobanks, or organisations planning or actively participating in clinical trials and able to obtain consent. Access to large numbers of patients is essential to ensuring the statistical power for definition of endotypes. Value is seen in both cross-sectional and longitudinal approaches but longitudinal data (e.g. patients before and after therapy) is of higher value.

Partners providing medical record-based information as project background must be mindful that they, as background contributor, should have sufficient title to the said background to authorise its use within the project pursuant to the IMI2 JU IP and legal framework.

Considerations for the outline of project work plan

In their stage 1 proposal, applicants should:

- Give due visibility on data management; dissemination, exploitation and sustainability; and communication activities. This should include the allocation of sufficient resources for these tasks which will be further developed in stage 2 proposal;

- Consider including a strategy for ensuring the translation of the projects results to drug development, regulatory/HTA settings (e.g. through scientific advice/qualification advice/opinion, etc.), clinical and healthcare practices and/or decision making processes.

Additional considerations to be taken into account at the stage 2 full proposal

At stage 2, the consortium selected at stage 1 and the predefined industry consortium jointly submit the full proposal developed in partnership. The full proposal is based upon the selected short proposal at stage 1.

In the spirit of the partnership, and to reflect how IMI2 JU call topics are built on identified scientific priorities agreed together with EFPIA beneficiaries/large industrial beneficiaries, these beneficiaries intend to significantly contribute to the programme and project leadership as well as project financial management. The final architecture of the full proposal will be defined by the participants in compliance with the IMI2 JU rules and with a view to the achievement of the project objectives. The allocation of a leading role within the consortium will be discussed in the course of the drafting of the full proposal to be submitted at stage 2. To facilitate the formation of the final consortium, until the roles are formally appointed through the consortium agreement, the proposed project leader from among EFPIA beneficiaries/large industrial beneficiaries shall facilitate an efficient negotiation of project content and required agreements. All beneficiaries are encouraged to discuss the project architecture and governance and the weighting of responsibilities and priorities therein.

Data management

In their stage 2 proposal, applicants should give due visibility to data management including use of data standards. A full 'data management plan' (DMP) as a distinct deliverable must be delivered within the first 6 months of the project. The DMP needs to be kept up to date with the needs of the project and as such be updated as necessary during its lifetime.[12]

Dissemination, exploitation and sustainability of results

In their stage 2 proposal, applicants must provide a draft plan for dissemination and exploitation, including sustainability of results. A full plan as a distinct deliverable must be delivered within the first 6 months of the project[13], and updated during the project lifetime and could include identification of:

[12] Guidance on data management is available at http://ec.europa.eu/research/participants/docs/h2020-funding-guide/cross-cuttingissues/open-access-data-management/data-management_en.htm

[13] As an additional dissemination obligation under Article 29.1 of the IMI2 Grant Agreement will apply

- different types of exploitable results;
- potential end users of the results;
- results that may need sustainability and proposed sustainability roadmap solutions.

From its creation, the consortium will dedicate a group of participants to think of a process for sustainability.

Sufficient resources should be foreseen for activities related to dissemination and exploitation, including the plan for the sustainability of the project results. This may involve engaging with suitable biological and medical sciences research infrastructures (RIs).[14] Alternatively, if a sustainable organisation can be implemented as a follow-up to some activities generated by this topic consortium, and possibly in coordination with other related projects (e.g. BIOMAP (www.biomap-imi.eu/), this will be investigated.

Communication

The proposed communication measures for promoting the project and its findings during the period of the grant should also be described and could include a possible public event to showcase the results of the project.

[14] http://www.corbel-project.eu/about-corbel/research-infrastructures.html

References

[1] Mease PJ. Psoriatic arthritis assessment and treatment update. Curr Opin Rheumatol. 2009;21(4):348-55.

[2] Scher, JU, Ogdie A, Merola JF and Ritchlin C. Preventing psoriatic arthritis: focusing on patients with psoriasis at increased risk of transition. Nat Rev Rheum, 2019, 15;153-166

[3] Talotta R, Atzeni F, Sarzi-Puttini P. Psoriatic arthritis: from pathogenesis to pharmacologic management. Pharmacol Res. 2019 Sep 7:104394. doi: 10.1016/j.phrs.2019.104394.

Topic 2: Innovations to accelerate vaccine development and manufacture

Topic details

Topic code	IMI2-2020-20-02
Action type	Research and Innovation Action (RIA)
Submission and evaluation process	2 stages
IMI2 Strategic Research Agenda - Axis of Research	Innovative medicines
IMI2 Strategic Research Agenda - Health Priority	Vaccines

Specific challenges to be addressed by public-private collaborative research

Vaccination is one of the greatest achievements in healthcare. However, developing a vaccine remains costly, time consuming, and risky (approximately EUR 800 million, 11 years in clinical development with <10% chance of entering the market) [1]-[3].

Advances in immunology, disease modelling, in silico modelling, including the analysis of big data and the application of machine learning (ML) artificial intelligence (AI), provide opportunities to innovate, de-risk and accelerate the vaccine-development process. Many of these advances have occurred in the academic sector.

These advances can be harnessed to tackle scientific bottlenecks in vaccine development and to nurture and expand a vaccines innovation ecosystem by bringing together academics, small and medium-sized enterprises (SMEs) and industry to collaborate in four areas:

- In silico platform for knowledge management and mathematical modelling of the immune system;
- Novel controlled human infection models (CHIMs);
- Next-generation human in vitro systems and assays; and
- Mathematical modelling platforms for vaccine substance and product attributes in biomanufacturing.

Currently, computational models have been applied to immunology data, but these models are limited to particular aspects [4]-[11]. There is the potential for these models to become more sophisticated and to predict how responses to pathogens and vaccines are affected by pre-disposing factors [12][13]. In biomanufacturing, in silico modelling could be applied to predicting optimal conditions for maintaining vaccine attributes with changes to processes or in the cold chain, thus replacing more expensive and time-consuming empirical methods.

CHIMs are especially helpful for the development of vaccines and can provide early evidence of clinical efficacy and samples for cutting-edge immunological research[14]-[22]. In particular, suitable CHIMs are needed for the development of universal or broadly protective vaccines against influenza, respiratory syncytial virus (RSV) and Clostridium difficile[23]-[29].

Next-generation in vitro systems (i.e. organoids and other self-organised in vitro-derived tissue culture systems that exhibit human organ functionality) and assays related to them, have the potential to model and evaluate host-pathogen interactions in the mucosa; the tissue in which the majority of pathogens enter the human body[30]-[47]. Some of these in vitro systems utilise human-induced pluripotent stem (iPS) cells, allowing the potential to evaluate

human pathogens with consideration to particular pre-disposing factors in the donor[30]-[41]. Also, in vitro systems and assays are needed to phase out animal models[48].

A consortium of academics, SMEs and industry will provide the opportunity to gather the best experts to address these challenges. Academia is at the forefront of scientific and technological advances; SMEs are adept at providing services and innovating those services; and industry has broad overlapping expertise in vaccine development and manufacture. Although the topic covers distinct scientific domains, there are numerous synergies among them. Hence, to address the challenges and to maximise these synergies, collaborations within the sector and with other sectors are needed, and therefore investment in a public-private partnership can provide the impetus to bring academics and SMEs into an alliance with industry partners.

Scope

The overall objective is to accelerate and de-risk the development of new vaccines by incorporating scientific and technological advances from the academic and biotech sectors into industry, and to develop more predictive biological and mathematical models of vaccine performance. The topic is composed of four subtopics, which constitute the four respective challenges described above. Subtopics 1 and 4 are centred on developing in silico model platforms for the immune system and biomanufacturing, respectively, which should be sustainable after the completion of the project; and subtopics 2 and 3 seek to widen the use of CHIMs and next-generation in vitro models and assays in vaccine development.

All subtopics in the programme relate to the use of novel modelling technologies (biological or mathematical) to accelerate the development of vaccines. Hence, by bringing together stakeholders from all areas of vaccine R&D (preclinical, clinical and manufacturing), the programme offers a unique opportunity to explore and open up an interdisciplinary dialogue on the future use, acceptance and further co-ordinated development of these technologies.

For each of the subtopics the specific objectives are as follows:

Subtopic 1: Systems-immunology platform for model development

To develop an open-data/open-source in silico platform focussed on immunobiological processes, and not on a given disease or vaccine indication, for the prediction of:

- immune responses to vaccines and pathogens and how those responses are affected by pre-disposing factors, using a combination of data sets to predict vaccination response of individuals (e.g. multi-layer omics and immunophenotyping);
- antigen and pathogen features most likely to induce protective immunity, and the anticipated immune responses to those features;
- emerging medical needs (via AI systems) such as infectious disease outbreaks, and the associated required investment in vaccination development and implementation.

Subtopic 2: CHIMs

To develop improved or novel CHIMs for influenza, RSV and *C. difficile*, in order to facilitate the generation of early efficacy data for vaccine candidates. This will include the:

- identification, characterisation and manufacture of pathogen strains;
- identification of key parameters for CHIM standardisation, generalised adoption, and ultimately, regulatory acceptance.

Subtopic 3: State-of-art innovations in human in vitro mucosa models and assays

(i) To develop prototype next-generation in vitro systems (self-organised in vitro tissue-culture systems derived from human stem cells or human primary tissue that exhibit organ-like functionality) for antigen identification/validation and drug substance and drug product characterisation/validation.

(ii) To develop associated functional immune assays (e.g. miniaturised, medium to high throughput) for clinically-relevant (surrogate) endpoints.

- At least one in vitro model should be included for each of the following mucosae: gastro-intestinal, respiratory and urovaginal;
- Pathogens of interest are those relevant for global health, such as those with pandemic potential (influenza), or those for which vaccines are not yet available, including RSV, *C. difficile*, *Bordetella pertussis*, *Moraxella catarrhalis*, nontypeable *Haemophilus influenzae*, *Chlamydia trachomatis*, *Neisseria gonorrhoeae*, herpes simplex virus, norovirus, *Pseudomonas aeruginosa*, ExPEC (extra-intestinal pathogenic *Escherichia coli*) and cytomegalovirus.[15]

Subtopic 4: Biomanufacturing platforms using mathematical modelling

To develop an open data/open source in silico biomanufacturing platform incorporating models for predicting:

- Vaccine-product stability (drug substance/product);
- The parameters to maintain process robustness for unit-operation scale up or scale down, and for process transfer.

This will also include:

- Defining the new approach to working which integrates these models in the biomanufacturing regime;
- Initiating a dialogue with relevant regulatory authorities, that paves the way for future use of predictive stability and process scale-up modelling in chemistry, manufacturing, and control (CMC) dossiers for new and improved vaccines.

Subtopics and the Call process

The Call process has two stages.

At stage 1, applicant consortia should submit short proposals to one of the four subtopics (1–4). An applicant consortium can submit a short proposal for more than one subtopic, on condition that a separate short proposal is submitted for each subtopic.

To achieve the project objectives, maximise cross-learning and enable data sharing, it is envisaged that a single full proposal should be submitted at stage 2. This full proposal will include activities covering all four subtopics and their specific work packages (Figure 1). Thus, at stage 2, the full proposal will be submitted by the consortium composed by the successful applicant subconsortia of all four subtopics and the industry consortium.

[15]Pathogens not of interest include: fungi, parasites, syphilis, *Acinetobacter*, *Enterococcus*, *Klebsiella pneumoniae*, *Mycoplasma pneumoniae*, *legionella*, enteroviruses, coxsackieviruses, adenovirus, bocavirus, Chikungunya/Zika, hantavirus, hepatitis viruses C and E, HIV-1, human herpesvirus 6 (HHV-6), MERS/SARS, parvovirus B19, and West-Nile virus

An overall coordinator, selected from the winning consortium of Subtopic 3 (State-of-art innovations in human in vitro mucosa models and assays), and an overall project leader from the industry consortium, will be nominated by the consortium at the start of the preparation of the full proposal.

In the event that no short proposal is over the threshold for one or two subtopics, stage 2 of the Call will still be initiated by the merger of the remaining consortia and the industry consortium. The overall IMI2 JU maximum financial contribution and the EFPIA in-kind contributions will be adapted accordingly, based upon the allocation provided under the section 'Indicative budget'.

If no short proposal is selected for Subtopic 3, activities related to the overall coordination and project management (proposed work package [WP] 1), as well as the overall communication and dissemination activities (proposed WP6), will be preferentially transferred to the Subtopic 2 leader, together with the amount of the relevant financial contribution identified for these activities under section 'Indicative budget'.

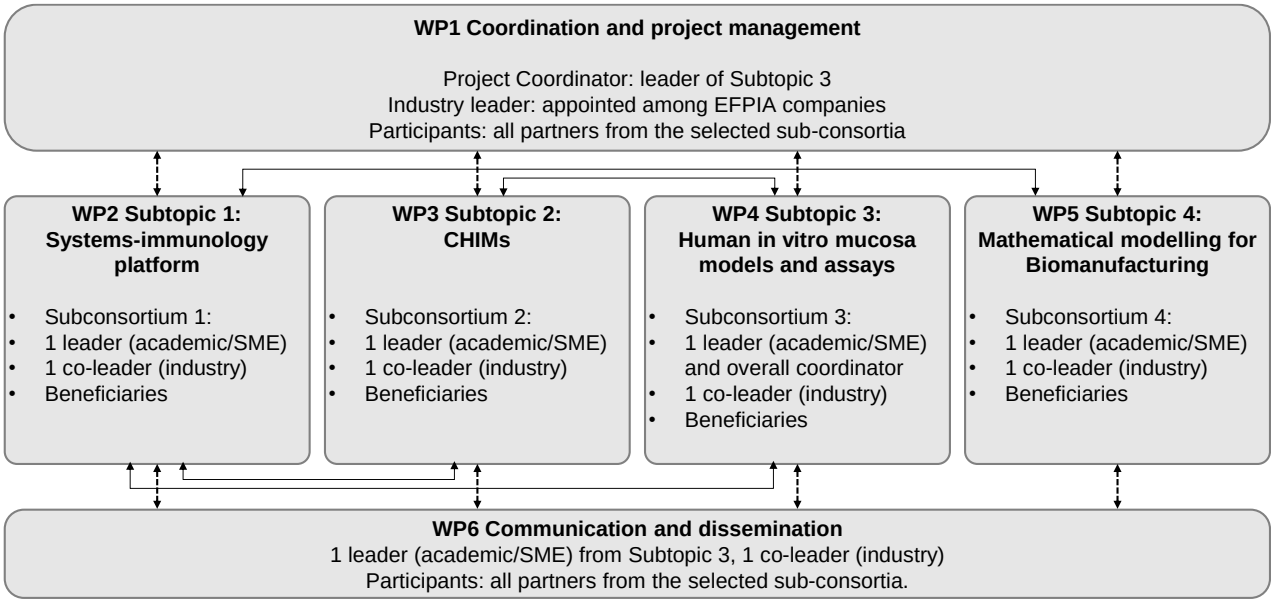

Figure 1: Consortia composition and interactions between suggested work packages (WPs), where each of the four subtopics will constitute distinct work packages.

Expected key deliverables

Based on the objectives of the topic, the following key deliverables have been identified.

All subtopics (under the direction of the coordinator)

- Data-management and data-sharing procedures, tools and infrastructures to support collaborations between subtopics;
- Sustainability plan for datasets and data management;
- Joint subtopic workshops to identify/develop/ratify collaborations between subtopics;
- Scientific publications.

Subtopic 1

- Sustainable open-access and cloud-based in silico platform incorporating knowledge management tools with links to databases of existing knowledge, omics data and validated computational knowledge-driven models and data-driven models, including data from related disease fields.

Subtopic 2

- New CHIMs that can accelerate the development of vaccines against, influenza, RSV and *C. difficile*;
- Definition of clinical and laboratory (molecular, immunological and microbiological) endpoints for efficacy and/or safety, for use in larger field trials;
- Improved or new comprehensive pre-screening methodologies that capture relevant pre-disposing factors, e.g. deep immunophenotyping and multi-layer omics;
- Clear definitions of rescue therapy including appropriate infection control and contingency plans, and for using CHIMs in at-risk populations that could be included in the contemplated CHIMs studies;
- Identification of key parameters for CHIM standardisation, generalised adoption, and ultimately, regulatory acceptance.

Subtopic 3

- Prototype next-generation in vitro models (as defined above) and assays for clinically-relevant (surrogate) endpoints with guidelines for good laboratory practice (GLP) implementation including robust biostatistical plans for:
    - evaluating the interactions between pathogens or their antigens with human gastro-intestinal, respiratory and urovaginal mucosae, ideally including interfaces with immune-system components such as innate-immune cells, antibodies or T cells;
    - addressing immunological mechanisms during convalescence from naturally-acquired infection or disease;
    - addressing heterogeneity within a particular human population;
    - evaluating human samples from biobanks, including serum, stool, vomitus, or mucosal secretions from vaccine recipients or individuals infected with a relevant human pathogen.

Scientific validation of selected prototype model(s) could be performed in a clinically-relevant setting, e.g. in parallel with a CHIM.

Subtopic 4

- Sustainable cloud-based in silico platform for:
    - vaccine substance and product stability for different types of vaccines (e.g. subunit, virus, conjugates, etc.);
    - biomanufacturing process robustness (applicable to unit operation scale up or scale down, and process transfer).

Expected impact

The overall expected impacts are: a greater success rate in bringing vaccine candidates through clinical development; increased efficiencies in the transitioning of biomanufacturing processes during vaccine development; and a more vibrant ecosystem of vaccine innovation in Europe. This impact will be demonstrated by more extensive alliances between academia, SMEs and industry through sustainable in silico platforms, CHIMs, CHIM-challenge strains and next-generation in vitro systems and assays, as potential services and products, and case-study based guidance for the use of CHIMs and next-generation in vitro systems and assays. This should also result in the increased probability of successful phase 3 efficacy trials and the acceleration of vaccine development, leading to benefits for trial participants and ultimately those with the medical need for the vaccine.

In their proposals, applicants should describe how the outputs of the project will contribute to the following impacts and include wherever possible baseline, targets and metrics to measure impact.

All subtopics

- The extent of the collaborative engagement of multiple partners across academia, SMEs and industry in developing and potentially sustaining the outcomes of the project.

Subtopic 1

- Better understanding of the immune response to disease, host-pathogen interactions, vaccine mechanisms of action and the associated contribution of genetic/epigenetic/environmental factors on immunobiology.

Subtopic 2

- The likelihood of the CHIMs being incorporated into vaccine-development programmes on a wider scale, and how their associated guidelines for use will support this incorporation.

Subtopic 3

- The likelihood of the next-generation in vitro models and assays being incorporated into vaccine-development programmes on a wider scale, and how their potential versatilities and associated guidelines for use will support this incorporation;

- The potential for the next-generation in vitro models and assays to replace the use of animal testing in research, licensure and release of vaccines (with regulatory agency approval) in the future.

Subtopic 4

- Better understanding of how scale-up and scale-down transitions affect vaccine manufacturing, and can be modulated to ensure vaccine quality and stability/shelf-life;

- More efficient vaccine-manufacturing processes that could also allow affordable vaccine development for small or restricted target populations, personalised vaccines, or sustainable vaccine development for diseases in low-to-middle income countries.

In their proposals, all applicants should outline how their specific subtopic plans to leverage the public private partnership model to maximise impact on innovation, research & development; regulatory, clinical and healthcare practices, as relevant. This could include a strategy for engagement with citizens, patients, healthcare professional associations, healthcare providers, regulators, HTA agencies, payers etc., where relevant.

In addition, all applicants should describe how their specific subtopic will impact competitiveness and growth of companies including SMEs;

In their proposals, all applicants should outline how their specific subtopic will:

- manage research data, including use of data standards;[16]
- disseminate, exploit, and sustain the project results. This may involve engaging with suitable biological and medical sciences Research Infrastructures;[17]
- communicate the project activities to relevant target audiences.

In addition, the following additional exploitation[18]/dissemination[19] obligations must be considered to maximise impact:

- The in silico immune-systems platform and biomanufacturing platform should be open-access cloud-based resources.

Potential synergies with existing Consortia

Synergies and complementarities should be considered with relevant national, European and non-European initiatives (including suitable biological and medical sciences research infrastructures[487]) to incorporate, whenever possible, past achievements, available data and lessons learnt, thus avoiding unnecessary overlap, and duplication of efforts and funding.

Industry consortium

The industry consortium is composed of the following EFPIA partners:

- GSK (Lead) - contribution to Subtopics 1, 2, 3 and 4;
- Sanofi Pasteur (Co-lead) - contribution to Subtopics 1, 2, 3 and 4;
- Takeda - contribution to Subtopic 3;
- CureVac AG - contribution to Subtopic 3.

The industry consortium plans to contribute the following expertise and assets:

All subtopics:

- Expertise in vaccine development, manufacturing processes and global regulatory affairs;
- Industry leadership in IMI projects;
- Establishing links with other major existing initiatives (e.g. Human Vaccines Project, HIC-Vac in the United Kingdom, IMI2-Periscope, IMI2-VITAL, IMI2-FLUCOP, IMI2-RESCEU, IMI2-iConsensus, etc.), and where possible, obtaining access to relevant databases or datasets.

Subtopic 1

- Expertise:

[16] Guidance on data management is available at http://ec.europa.eu/research/participants/docs/h2020-funding-guide/cross-cutting-issues/open-access-data-management/data-management_en.htm
[17] http://www.corbel-project.eu/about-corbel/research-infrastructures.html
[18] Article 28.1 (Additional exploitation obligations) of the IMI2 Grant Agreement will apply
[19] Article 29.1 (Additional dissemination obligations) of the IMI2 Grant Agreement will apply

- Mathematical modelling, knowledge-management system for data integration;
- Immunology.
- Assets:
    - Data from non-clinical and clinical studies. This may include suitable datasets, adapted experiments or analytical experiments (e.g. in vitro data from ongoing or past research projects) to support the project. The specific nature of contribution may be refined at stage 2 of the application process to be more appropriately aligned with the project proposed by the applicant consortium.

Subtopic 2

- Expertise:
    - Clinical and translational research, virology, immunology, biostatistics, bioinformatics, quantitative mathematics;
    - Good-manufacturing-practice (GMP) production of material and/or viral and bacterial strains for CHIM development;
    - Phenotypic and genetic characterisation of microbial strains.
- Contributions to clinical studies:
    - GSK intends to cover the cost of characterisation and GMP manufacturing of relevant challenge strains;
    - Sanofi Pasteur intends to contribute to the production of GMP RSV stocks;
    - Sanofi Pasteur also intends to contribute data on experimental human infection with RSV, obtained via in-house study (or studies) to be conducted within 24 months of the start of the project. These data are expected to be used to inform and refine the design of RSV CHIM studies in the project.

Subtopic 3

- Expertise:
    - Translational preclinical models and in vitro infection models, including organoids;
    - Biomarkers of vaccine safety, reactogenicity, immunogenicity and efficacy, and infectious disease outcomes;
    - Assay miniaturisation;
    - Phenotypic and genetic characterisation of microbial strains.
- Assets:
    - Samples/data from non-clinical and clinical studies conducted with the pathogens of choice to help define how findings in the models developed by the consortium relate to natural/controlled infection in humans and how they concord with data from preclinical in vivo studies used historically to predict the behaviour of vaccines in humans.
- Contributions to studies for the development of next generation in vitro systems:

- Pending the final choice of pathogens for the in vitro models and assay development, GSK may contribute by providing relevant materials (antigens, antibodies, preclinical or clinical samples);

- Takeda intends to provide an in-cash contribution for the development and evaluation of in vitro gastro-intestinal models of infection and/or immunity.

- Contributions to services:

  - Sanofi Pasteur intends to provide a contribution for investigating the use of next-generation in vitro systems in evaluating vaccine safety.

Subtopic 4

- Expertise:

  - Process modelling support and revision;

  - Knowledge-management system for data integration.

- Assets:

  - To help build the in silico models, EFPIA companies will provide retrospective data on stability of drug substance and/or process intermediaries and on bioprocess scale-up/scale-down, collected for different classes of vaccines (e.g. native and recombinant proteins, viruses, conjugated protein-polysaccharide, and others);

  - EFPIA companies will conduct prospective empirical studies to support qualification/validation of the resulting in-silico models (i.e. proof-of-concept studies) for both stability and process development. These will be designed in consultation with the consortium partners to best suit the project objectives.

Indicative duration of the action

The indicative duration of the action is 66 months.

- Within each subtopic, it is expected that scientific activities should be completed within 60 months after project start;

- Activities related to communication, dissemination, exploitation and management (reporting) should continue for an additional 6-months (i.e. up to Month 66) to focus on communication of the results, including publications, and implementation of the sustainability plan.

This duration is indicative only. At stage 2, the subconsortia selected for all subtopics at stage 1 and the predefined industry consortium may jointly agree on a different duration when submitting the full proposal.

Indicative budget

Overall budget

The financial contribution from IMI2 JU is a maximum of EUR 18 600 000 for the four subtopics and open calls listed below.

The indicative in-kind and financial contribution from EFPIA partners is EUR 19 870 000 for the four subtopics and open calls listed below. The total financial contribution available from the EFPIA partners for activities in relation to the objectives of this action is EUR 2 000 000.

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

Subtopic 1 budget

The financial contribution from IMI2 JU is a maximum of EUR 2 100 000.

The indicative in-kind contribution from EFPIA partners is EUR 4 100 000.

Therefore, at stage 1, the applicant consortium may allocate up to EUR 2 100 000 (IMI2 JU financial contribution) in the budget of their stage 1 proposal.

Subtopic 2 budget

The financial contribution from IMI2 JU is a maximum of EUR 9 825 000.

The indicative in-kind contribution from EFPIA partners is EUR 7 210 000.

Therefore, at stage 1, the applicant consortium may allocate up to EUR 9 825 000 (IMI2 JU financial contribution) in the budget of their stage 1 proposal.

Subtopic 3 budget

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

The indicative in-kind and financial contribution from EFPIA partners is EUR 5 385 000. The total financial contribution available from the EFPIA partners for activities in relation to objectives of this subtopics (i.e. the conduct of pre-clinical studies) is EUR 1 000 000.

At stage 1, the applicant consortium may allocate up to EUR 5 000 000 in the budget of their stage 1 proposal. This amount is subdivided in the following categories:

- Scientific activities:
    - EUR 4 000 000 of which EUR 1 000 000 for the conduct of pre-clinical studies (development and evaluation of gastro-intestinal models of infection and/or immunity)
- Coordination and management activities (for entire project, not a specific subtopic):
    - EUR 1 000 000 for the management, communication and dissemination activities for the whole consortium and to the data management and sustainability plan for the whole consortium

Subtopic 4 budget

The financial contribution from IMI2 JU is a maximum of EUR 2 175 000.

The indicative in-kind contribution from EFPIA partners is EUR 2 175 000.

Therefore, at stage 1, the applicant consortium may allocate up to EUR 2 175 000 (IMI2 JU financial contribution) in the budget of their stage 1 proposal.

Financial contribution for open calls for proposals

To ensure access to state-of-the-art technologies that may become available after the start of the project and could support the development of new platforms and tools (e.g. CHIMs and organoids, algorithms), the consortium may consider enrolling additional participants, after year 2, to fulfil the tasks identified by the consortium. The need for enrolling additional participants will be based on the identification of objectives that could be better addressed by

those new technologies, and should be endorsed by the independent panel of experts during the interim project review conducted by IMI2 JU.

This will be achieved by launching at least two open calls: one call per year, the first one being planned after year 2. These open calls (which will specify the needs, type of technologies, selection criteria, etc.) will constitute project activities. Each open call will be prepared by a dedicated working group and endorsed by the entire consortium. In principle, new beneficiaries identified by means of the open calls will join the consortium for carrying out activities additional to those already planned. The detailed mechanism and procedure for conducting these calls will be established in the full proposal.

A maximum financial contribution of EUR 1 500 000 (composed by financial contributions of EUR 500 000 from IMI2 JU and EUR 1 000 000 from EFPIA) will be allocated for the implementation of the open calls. This amount has not been included in any of the subtopic budgets at stage 1, as it will be allocated in the budget of the stage 2 proposal by the full consortium. This financial contribution is a fixed amount and will not be modified in the event that no short proposals are not selected under one or two subtopics at stage 1.

Expertise and resources expected from applicants at stage 1

The stage 1 applicant consortium to each subtopic is expected, in the submitted short proposal, to address all the objectives and key deliverables of the subtopic, taking into account the expected contribution to the subtopic from the industry consortium which will join at stage 2 to form the full consortium.

The stage 1 submitted short proposals should include suggestions for creating a full-proposal architecture for the subtopic, which could be in line with the suggested architecture described below, though this architecture is only a suggestion. It should also recognise potential inter-subtopic interactions within the project.

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

Subtopic 1

- Expertise in computational and mathematical modelling, and immunology;
- Front-end and back-end in silico platform development;
- Knowledge-management systems for data integration;
- Evaluation/curation of open-source data and knowledge that can be utilised for mathematical modelling;
- Project management skills (subtopic coordination);
- Communication and dissemination skills;
- Business sustainability plans.

Subtopic 2

- Expertise in microbiology, virology, microbial genetics;
- Clinical expertise in ethics, immunology, big data analyses and establishment of large databases, regulatory science;
- Project management skills (subtopic coordination);
- Communication and dissemination skills.

It may also require mobilising, as appropriate, the following resources: clinical infrastructures for inpatients, data on previous CHIM activities with specific pathogens, and existing ethical and regulatory frameworks (ethical aspects and guidance will have to be considered).

Subtopic 3

- Expertise in next-generation in vitro systems (organ on chip, 3D tissue models, organoids etc.);
- Advanced biostatistics and data analysis;
- Novel immunological assays;
- Novel reagents for interrogating immune responses to complex epitopes on pathogens;
- Expertise in association of peripheral immune responses to mucosal pathogens to potentially protective mucosal immune responses;
- Expertise in prospective clinical cohort studies and in the identification of immune correlates of protection;
- Given that the project coordinator will be appointed from Subtopic 3, strong expertise and track record in EU project management of large consortia, including reporting, legal and financial aspects, is required;
- Communication and dissemination skills: development and implementation of communication, dissemination and use plan.

In light of the scope of the project and its four aspects, the applicant consortium for Subtopic 3 should have a global vision and a profound understanding of the challenges and activities to ensure good oversight.

Subtopic 4

- Bio pharmaceutical process knowledge;
- Process Modelling expertise;
- Front-end and back-end platform development;
- Knowledge-management system for data integration;
- Evaluation/curation of open-source data and knowledge that can be utilised for the modelling;
- Project management skills (subtopic coordination);
- Communication and dissemination skills;
- Business sustainability plans.

SMEs

Suitable SMEs could be considered in the four subtopics for the following activities:

- Back-end and front-end IT infrastructure construction for in silico platforms.
- Manufacture (and associated optimisation) of challenge pathogens for CHIMs.
- Design/production of monitoring devices for biomanufacturing.
- Project management activities.

The size of the consortium for each subtopic should be proportionate to the objectives of the topic while ensuring its manageability.

Considerations for the outline of project work plan (for all subtopics)

In their stage-1 proposals applicants should:

- Give due visibility to data management; dissemination, exploitation and sustainability; and communication activities. This should be described by each submitting applicant consortium, and should include the elements necessary to ensure the proper functioning of each subtopic as well as sufficient resources for these tasks, bearing in mind that some modifications will be necessary at the stage 2 full proposal and several activities will be shared among all participants of the full consortium to ensure integration and avoid redundancy;

- Consider including a strategy for ensuring the translation of the project results to drug development, regulatory/health technology assessment (HTA) settings (e.g. through scientific advice/qualification advice/opinion, etc.), clinical and healthcare practices and/or decision-making processes.

Suggested architecture

The architecture of the proposed project is described in Figure 2.

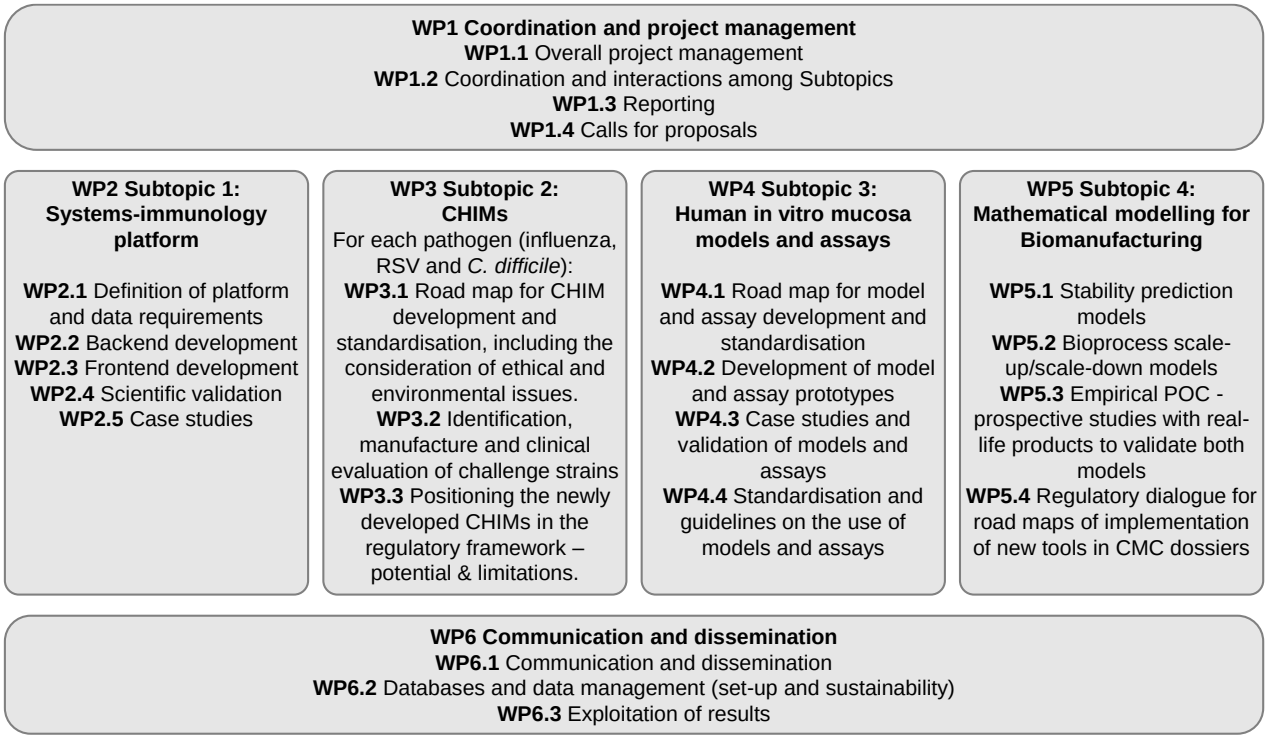

Figure 2: The project could be composed of two horizontal work packages (WPs) for project management and communication and four subtopics, each comprising several work streams.

The governance structure should reflect the specific setting of this topic, i.e. the inclusion of four subconsortia into one single consortium managed under a single grant agreement and a single consortium agreement.

Within Subtopic 4, it is proposed that scientific activities would be completed within 48 months after project start to be in coordination with internal activities of EFPIA members. Dissemination and exploitation activities within this subtopic (specifically for data exchange with other subtopics) and some new activities (arising from open calls for proposals) could be extended until the end of the project (Month 66).

Additional considerations to be taken into account at the stage 2 full proposal

In the spirit of the partnership, and to reflect how IMI2 JU call topics are built on identified scientific priorities agreed together with EFPIA beneficiaries/large industrial beneficiaries, these beneficiaries intend to significantly contribute to the programme and project leadership as well as project financial management. The final architecture of the full proposal will be defined by the participants in compliance with the IMI2 JU rules and with a view to the achievement of the project objectives. The allocation of a leading role within the consortium will be discussed in the course of the drafting of the full proposal to be submitted at stage 2. To facilitate the formation of the final consortium, until the roles are formally appointed through the consortium agreement, the proposed project leader from among EFPIA beneficiaries/large industrial beneficiaries shall facilitate an efficient negotiation of project content and required agreements. All beneficiaries are encouraged to discuss the project architecture and governance and the weighting of responsibilities and priorities therein.

In consideration of the nature of the consortium (potentially large with the merger of four subconsortia into one single consortium), all beneficiaries should be prepared to start discussing the main terms of the consortium agreement (i.e. governance, liabilities, intellectual property, publication, data protection, financial management) during the preparation of the full proposal.

Data Management

In their stage 2 proposal, applicants should give due visibility to data management including use of data standards. A full 'data management plan' (DMP) as a distinct deliverable must be delivered within the first 6 months of the project. The DMP needs to be kept up to date with the needs of the project and as such be updated as necessary during its lifetime.[20]

Dissemination, exploitation and sustainability of results

In their stage 2 proposal, applicants must provide a draft plan for dissemination and the exploitation, including sustainability of results. A full plan as a distinct deliverable must be delivered within the first 6 months of the project[21], and updated during the project lifetime and could include identification of:

- Different types of exploitable results;
- Potential end-users of the results;
- Results that may need sustainability and proposed sustainability roadmap solutions.

Sufficient resources should be foreseen for activities related to dissemination and exploitation, including the plan for the sustainability of the project results. This may involve engaging with suitable biological and medical sciences Research Infrastructures (RIs).[22]

Communication

The proposed communication measures for promoting the project and its findings during the period of the grant should also be described and could include a possible public event to showcase the results of the project.

[20] Guidance on data management is available at http://ec.europa.eu/research/participants/docs/h2020-funding-guide/cross-cutting-issues/open-access-data-management/data-management_en.htm
[21] As an additional dissemination obligation under Article 29.1 of the IMI2 Grant Agreement will apply
[22] http://www.corbel-project.eu/about-corbel/research-infrastructures.html

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Introduction to the IMI2 Antimicrobial Resistance (AMR) Accelerator programme

Background and problem statement

The discovery and development of new preventions and treatments to address antimicrobial resistance (AMR) is an undisputed European and global challenge. The challenge is compounded by a low return on investment (RoI) for the pharmaceutical sector driven largely by the lack of established reimbursement models and standard methods to express the true societal value for new technologies addressing AMR. This has subsequently led to a reduction in resources applied across the pharmaceutical industry and a decline in scientific discoveries. Overall, this situation has compromised the delivery of new options to treat and prevent resistant infections. This was highlighted in the European One Health Action Plan against Antimicrobial Resistance (for more info please visit the following link: https://ec.europa.eu/health/amr/sites/amr/files/amr_action_plan_2017_en.pdf). Beyond Europe, it is of note that AMR is one of four public health concerns that has been raised to the level of discussion at the UN General Assembly (September 2016), putting it on par with subjects such as HIV and Ebola. Additionally, drug resistant tuberculosis (TB) is the largest single contributor to AMR health, mortality, and economic impact.

There are significant scientific challenges to the discovery and development of new agents to treat and prevent AMR infections, including those caused by Gram-positive and Gram-negative bacteria, *Mycobacterium tuberculosis*, and non-tubercular mycobacteria (NTM). As an example, despite there being an extensive number of essential bacterial targets, no antibiotics with novel mechanism for Gram-negative infections have been approved in 40 years.

Furthermore, despite some recent progress, we have a poor understanding of how to rationally design potent small molecules that are optimised to treat life-threatening multi-drug resistant (MDR) Gram-negative pathogens. Models, approaches, and tools developed by large pharma or public entities to support antibiotic drug development need to be validated and shared more widely to serve the AMR community at large. At the same time, alternative approaches to treating infections require robust validation. The same is true for platforms that enhance the success of vaccines and monoclonal antibodies, or new imaging platforms to measure pharmacodynamic responses at the site of action.

In the case of TB, the world's leading infectious disease killer with 1.7 million deaths in 2016, (from WHO TB report 2017 Executive Summary at the following link, http://www.who.int/tb/publications/global_report/Exec_Summary_13Nov2017.pdf) there is an acute need for the development of a novel combination regimen with an indication for the treatment of any form of TB ('pan-TB regimen') that will be more effective, shorter, and safer than current existing options. This applies to all types of TB (drug-sensitive (DS), multi-drug resistant (MDR) and extensively-drug resistant (XDR-TB)). A pan-TB regimen would encompass at least three new chemical entities, with properties better suited to protect against emerging resistance both individually as well as in combination. Many scientific hurdles must be overcome to understand how multiple chemical entities can be combined most successfully, keeping synergistic drug activity, drug-drug interactions, and translational aspects in mind. Regimen development in TB has provided and will continue to lead to knowledge that will help to develop new treatments, including combination regimens, for other infections that have relied on mono-therapy thus far.

Overall objectives of the AMR Accelerator

The aim of the AMR Accelerator is to progress a pipeline of potential medicines, including but not limited to new antibiotics, to treat patients with resistant bacterial infections in Europe and across the globe, or to prevent them. Specifically, if successful, projects in the Accelerator are expected to deliver up to >10 new preclinical candidates and >5 'phase 2-ready' assets over a period of approximately seven years.

The AMR Accelerator will provide, under one operational structure, a wide-ranging series of projects that will address many of the scientific challenges in AMR. The scientific scope will be broad, including prevention (vaccines, monoclonal antibodies (mAbs), immunoprophylaxis, other means) and treatment (new antibiotics, non-antibiotic alternatives, and combinations). For clarity, the term 'AMR' should be interpreted to include Gram-positive

and Gram-negative bacteria, tuberculosis (TB) and non-tubercular mycobacteria (NTM). Within this broad scope, projects in the Accelerator will develop new pre-clinical tools and methods, validate alternative or 'non-traditional' approaches, and progress potential new treatments through phase 1-3 clinical trials. They will also analyse data from EFPIA-funded clinical trials to assist in the translation of preclinical data to clinical results of novel anti-infective agents and vaccines. The Accelerator will also potentially generate new clinical/regulatory phase 2-3 pathways. Over the past years, IMI's New Drugs for Bad Bugs (ND4BB) programme has created a vibrant drug discovery and development network in AMR, and met important milestones. The AMR Accelerator will complement and augment the capabilities of the IMI ND4BB programme.

Progression of successful assets beyond the scope of the Accelerator (pillar-dependent, see below) may occur, as appropriate, by other mechanisms. Such mechanisms might include EU funding programmes within Horizon 2020 (including SME instruments) or future framework programmes, InnovFin instruments, structural funds, venture capitals, other internal R&D funding mechanisms, etc. In addition, the applicable principles from the Davos Declaration on Antimicrobial Resistance (January 2016) or the Industry Roadmap for Progress on Combatting Antimicrobial Resistance (September 2016: https://www.ifpma.org/wp-content/uploads/2016/09/Roadmap-for-Progress-on-AMR-FINAL.pdf[23]) should be taken into account.

The Accelerator will contribute to one of the three pillars of the European One Health Action Plan against Antimicrobial Resistance 'Boosting research and development and innovation in AMR' (June 2017: https://ec.europa.eu/health/amr/sites/amr/files/amr_action_plan_2017_en.pdf). The Accelerator will also directly address the IMI2 JU objective to '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' (Article 2(b)(iii) of the Council Regulation establishing IMI2 JU: http://eur-lex.europa.eu/legal-content/EN/TXT/?uri=celex%3A32014R0557)

AMR Accelerator programme structure

The AMR Accelerator programme consists of three pillars under which multiple actions are expected:

- **Pillar A**: Capability Building Network (CBN)
- **Pillar B:** Tuberculosis Drug Development Network (TBDDN)
- **Pillar C:** Company-specific Portfolio Building Networks (PBNs)

The overall IMI2 JU financial contribution to the AMR Accelerator topics under Pillars A, B and C will be a maximum of EUR 237 230 000.

The EFPIA and Associated Partner in-kind contribution will be matched by IMI2 JU funding across the whole of the Accelerator and not necessarily 1:1 on an individual project or pillar basis.

The two-stage IMI2 JU Call 20 includes one topic (topic 3) under Pillar B to complement the actions funded under IMI2 JU Call 15 and IMI2 JU Call 16.

Future calls for proposals could be launched at a later stage to select under each pillar additional research projects or networks depending on developing scientific needs and objectives in AMR research.

Pillar A: Capability Building Network (CBN) to accelerate and validate scientific discoveries.

The CBN will: 1) create a coordination and support group to assist in the effective management of projects across the Accelerator and; 2) deliver pre-competitive science to accelerate scientific discoveries in AMR, the results of which will be disseminated widely. The CBN will include projects to further basic science, and discoveries to enable future drug discovery and development in the prevention (vaccines, mAbs, immunoprophylaxis, and others) and

[23] For example, points 3 and 4 from the 'Roadmap for Progress'.

treatment of MDR bacterial infections including tuberculosis (TB), and non-tubercular mycobacteria (NTM). Although most research in the Accelerator related to TB will be conducted in the TBDDN (below), TB projects could occur in the CBN if the scientific concepts are of broader applicability (e.g. immunoprophylaxis).

The initial action in the CBN resulting from topic 7 in IMI2 JU Call 15 will implement a coordination and support group that will support operations of all projects in the AMR Accelerator with effective management, communication, and data capture capabilities. The initial CBN action also will focus on the collection, sharing, and analysis of vaccine and/or antibacterial clinical trial data and the optimisation of animal infection models for bacterial infections.

Pillar B: Tuberculosis Drug Development Network (TBDDN) to accelerate and validate scientific discoveries and advance the R&D pipeline of new and innovative agents to address the global TB epidemic.

The TBDDN will work to address the innovation gap in the discovery and development of a pan-TB regimen by combining access to novel drug candidates with innovative tools and incorporation of clinical trial data to accelerate the discovery of new combination regimens for the treatment of TB.

The platform will be self-sustained and independent from other similar activities (Integrated Research Platform (IRP), TB Drug Accelerator (TBDA)). It is anticipated that there will be linkages with the TBDA (for more info on TBDA, please visit: http://partnerships.ifpma.org/partnership/tb-drug-accelerator-program). It will provide ready-to-use services for rapid progression of available (1st line) new and innovative candidates. The platform will be partly supported by the coordination and support group from Pillar A, but will include management resources to self-sustain its scientific and financial reporting as well as innovation management procedures.

Topic 8 of IMI2 JU Call 15 will result in the creation of a group to profile and progress anti-TB compounds from advanced lead through phase 1 and to collect, share, and analyse TB clinical trial data. Additionally, it will address the development of new alternative anti-tubercular drugs (for example, host-defence or virulence approaches).

Topic 3 of IMI2 JU Call 20 will result in the development and implementation of innovative, state of the art adaptive clinical trial designs for the field of TB regimen development, able to define the therapeutic dose for existing experimental New Chemical Entities (NCE's) within treatment combinations. Additionally, it will exploit innovative technologies (including biomarkers and diagnostics) to facilitate and monitor adherence in resource-poor settings, while generating evidence that shorter regimens improve adherence.

Pillar C: Portfolio Building Networks (PBN) to advance the R&D pipeline of new and innovative agents to address AMR.

As in the CBN, the overall scientific scope in the PBN will be broad, including prevention (vaccines, mAbs, immunoprophylaxis, and others) and treatment (new antibiotics, non-antibiotic alternatives, formulation strategies, and combinations). Within this broad scope, the PBN will provide a mechanism for dedicated partnerships between EFPIA companies and SMEs and/or academic teams for the discovery and development of new antibacterial assets, including in select cases TB and NTM. Assets and projects can originate from SMEs, academia, or EFPIA companies, and will be jointly progressed or studied, including both pre-clinical work and potentially phase 1-3 clinical development. The PBN will also potentially be useful to generate new clinical/regulatory phase 3 pathways for pathogens such as NTM and to conduct phase 2 trials in TB.

Consortia selected under this pillar may have a limited number of partners, and will require the participation of an EFPIA partner (e.g. 1 EFPIA partner + 1 SME/academic partner)[24]. IMI2 JU Call 16, the first call under Pillar C, is divided in several topics, each dedicated to specific individual asset or research area. Additional single-stage calls, one or two per year, may be launched in the future pending budget availability. A total of at least 8-10 grant agreements are anticipated in the PBN (indicative number only).

[24] See 'Applicant consortium' section of IMI2 JU Call 16 topic text (Pillar C, "Portfolio Building Networks").

Collaboration agreements

To ensure smooth operation of the projects in the AMR Accelerator, the grant agreement of the first CBN action (COMBINE- 853967 selected under Pillar A from IMI2 JU Call 15 topic 7, and containing the coordination and support group[25]) is complementary to all the grant agreements of actions selected under Pillars B and C (via IMI2 JU Call 15 topic 8, IMI2 JU Call 16 topics, IMI2 JU Call 20 topic 3 and potential future additional calls for proposals), as well as probable future grant agreements from actions selected under Pillar A. In addition, all grant agreements of actions under pillar B will be complementary between them. The respective options of Article 2, Article 31.6 and Article 41.4 of the IMI2 JU Model Grant Agreement[26] will be applied. Accordingly, the consortia selected under Pillars A, B, and C will conclude collaboration agreements with the COMBINE- 853967 consortium selected from IMI2 JU Call 15 topic 7. These collaboration agreements will provide the framework for COMBINE-853967 to provide day-to-day support of projects in the Accelerator, and will ensure exchange of relevant information, exploration of synergies, collaboration where appropriate, and avoid duplication of efforts.

Furthermore, a memorandum of understanding (MoU) will be pursued between the Pillar B TBDDN actions (IMI2 JU Call 15 topic 8 and Call 20 topic 3) and the Integrated Research Platforms (IRP) action of IMI2 JU Call 15 topic 1 (EU-PEARL 853966) to cover collaboration and sharing of information on TB-related activities. The MoU should constitute one deliverable in each action resulting from topic 8 of IMI2 JU Call 15 and topic 3 of IMI2 JU Call 20. Similarly, when reasonable, a MoU should be pursued between potential TB-focused actions under Pillar C of the Accelerator (resulting from IMI2 JU Call 16) and TBDDN actions, as well as the IRP action of IMI2 JU Call 15 topic 1 (EU-PEARL 853966), with appropriate provisions to protect confidentiality of the interactions between the consortia and their intellectual property rights.

Need and opportunity for public-private collaborative research

The discovery and development of new antibiotics and alternative treatment and prevention options for multi-drug resistant infections is a high medical and societal need. The AMR Accelerator will address multiple challenges in a coordinated programme, which offers excellent opportunities for collaborative work between different sectors and disciplines. Moreover, operating with the support of the coordination and support group in the CBN will allow for greater efficiency, by reducing the need for duplicative management structures or processes.

Due to the current low return on investment that developers can expect for agents to address AMR, this scientific area has not received the investment that was seen in the ‘call to action’ to address HIV/AIDS and on par with the public health threat. Consequently, public-private partnerships (PPPs) such as the framework provided by the IMI2 JU continue to be critical to that effort.

Excellent examples include previous and current investments by the European Union and IMI (ND4BB, Model-based preclinical development of anti-tuberculosis drug combinations (PreDiCT-TB), More Medicines for Tuberculosis (MM4TB), Open Collaborative Model for Tuberculosis Lead Optimisation (ORCHID), anTBiotic), the NIH (Tuberculosis Research Units Network, TBRU-N) and the Bill & Melinda Gates Foundation (TB Drug Development Accelerator and TB Alliance discovery portfolio)). Multiple new drug candidates are in the pipeline for the treatment of TB for the first time in decades, and are reaching or about to reach the clinic. Existing drugs are being repurposed or optimised for TB with the potential of shortened treatment duration for drug-sensitive TB and safer, shorter treatments for MDR-TB. In ND4BB, immense progress has been made from basic science to discovery of novel lead molecules through to running interventional clinical trials.

However, more work is critical to continue to address the constantly emerging global challenge of AMR. For example, there is a challenge in maturing the TB pipeline from the selection of candidates to progression through phase 1 studies, in addition to parallel studies to determine the optimal combinations to create new pan-TB

[25] For additional details see the topic 7 “Capability Building Network” of IMI2 JU Call 15.
[26] See: https://www.imi.europa.eu/sites/default/files/uploads/documents/reference-documents/h2020-mga-imi_en_v5.pdf

regimens. Also, the ever-evolving resistance landscape requires additional investment to validate new tools and approaches, in addition to progressing potential new therapies to prevent and treat bacterial infections.

Acting to address these challenges in a single, coordinated Accelerator offers excellent opportunities for collaborative work between different sectors and disciplines on an area of critical scientific need.

The development of the Accelerator will contribute to a vibrant AMR community in Europe and will offer potential opportunities for individual partners, such as:

- Capability Building Network:
    - play a key role in a EU AMR programme with links to the broader global agenda on AMR;
    - enable SME, and/or academic groups to progress pre-competitive basic science projects in the AMR field;
    - offer the opportunity to work within a broad network of researchers focused on AMR science and gain additional experience in AMR science and drug discovery.
- Tuberculosis Drug Development Network:
    - enable SME and/or academic groups to progress pre-competitive basic science projects in the TB field;
    - enable SME and/or academic groups to progress potential drugs from pre-candidate status through to 'ready for phase 2' status, including, but not limited to GLP and GMP scale-up, formulation, toxicology studies, and phase 1 clinical studies, including preclinical combinations of drugs;
    - offer the opportunity to work within a broad network on researchers focused on TB drug discovery.
- Portfolio Building Network:
    - offer the opportunity for SMEs and/or academic groups to partner with EFPIA companies to enable progression of promising assets or technologies to key milestones, creating value, and sharing risk. There will be potential to further extend such partnerships with EFPIA companies beyond the scope of the Accelerator following completion of project;
    - will allow a vibrant partnering ecosystem that will benefit SMEs or academics with early stage assets based on pre-agreed conditions and milestone decision points.

Applicants to Calls launched as part of the Accelerator should consult the IMI2 JU Model Grant Agreement and IMI2 JU Annotated Model Grant Agreement, as well as a short questions and answers document available at https://www.imi.europa.eu/sites/default/files/uploads/documents/apply-for-funding/open-calls/Questions_and_answers_on_the_AMR_accelerator_programme.pdf

Topic 3: Academia and industry united innovation and treatment for tuberculosis (UNITE4TB)

Topic details

Topic code	IMI2-2020-20-07
Action type	Research and Innovation Action (RIA)
Submission and evaluation process	2 stages
IMI2 Strategic Research Agenda - Axis of Research	Innovative medicines
IMI2 Strategic Research Agenda - Health Priority	Antimicrobial resistance

Specific challenges to be addressed by public-private collaborative research

Tuberculosis (TB) is the leading infectious cause of death worldwide [1]. To achieve the target of TB elimination by 2035, the WHO estimates that there is a funding shortfall of over USD1 billion per year in TB research. The treatment of drug-sensitive TB is an onerous regimen of four drugs for two months followed by two drugs for four months (six-months total), and multidrug-resistant TB may require treatment for up to two years. Many patients find adherence difficult, and the current drugs are associated with significant tolerability issues. Shorter and safer treatment regimens are urgently needed. Tuberculosis has a low or negative expected return on investment and therefore fails to attract funding: this call addresses this acute unmet medical and public health need.

Currently, TB drug development involves 14-day monotherapy trials for early bactericidal activity (EBA) to identify the maximally efficacious dose for a new chemical entity (NCE). The standard trial design contains no option to change doses or de-escalate in-stream in response to emerging Pharmacokinetic-pharmacodynamic (PKPD) or safety data, resulting in a flat dose-response [2]. In Phase 2B, the efficacy of treatment combinations is then studied in eight weeks of dosing, with time-to-sputum-culture-conversion as the primary endpoint. This paradigm has multiple weaknesses: inadequate exploration of dose response; lack of innovative study designs to empirically determine optimal duration of therapy, as well as inability to study multiple regimens in parallel. Moreover, there is a lack of Phase 2 biomarkers that adequately predict phase 3 outcome (relapse-free cure) [3][4][5].

Therefore, there is a critical need for innovative trial designs in TB. Efficient adaptive trial designs would accelerate clinical development in Phase 2, but cannot currently be implemented due to the lack of in-stream biomarkers for sterilising cure/relapse. Several RNA expression, cytokine, bacterial and radiological biomarkers have been proposed in the literature, but to date there has been neither comparison nor prospective validation of these biomarkers. A biomarker that predicts relapse at an individual level may further create opportunities for individualised medicine, or even permit creation/validation of trial simulations. These trial simulations could help optimise trial design, and facilitate in-stream decision-making in adaptive trials.

Private and public investment has been made in the discovery of NCEs but there is at present no mechanism for clinical exploration of these NCEs in innovative combinations. The collaboration of industry academics, clinicians and SME partners pooling resources and NCE's, developing adaptive trial designs alongside implementation of biomarkers, diagnostics and digital technology will make this a unique partnership. It will accelerate the development of combination regimens for the treatment of the world's biggest cause of mortality in infectious disease, aligned with the World Health Organisation's sustainable development goals.

Scope

The objectives of this Call Topic are to develop and implement innovative, state of the art adaptive clinical trial designs for the field of TB regimen development able to define the therapeutic dose for existing experimental New Chemical Entities (NCE's) within treatment combinations. The funded action will define the duration and composition of novel treatment combinations that will shorten or simplify the standard of care, for drug resistant TB as well as prospectively validating biomarkers against the relapse endpoint. In addition, the funded action is expected to develop clinical trial simulations, evaluate new technologies to monitor and enhance treatment adherence, and develop an understanding of population pharmacogenomics in all forms of active TB.

The funded action will develop a portfolio of ten NCEs that have completed first-in-human studies from a pool of existing NCE's supplied by EFPIA/Associated partners, and carry out Phase 2A (EBA) studies followed by Phase 2B/C efficacy and relapse assessment. The funded action will also study high-quality NCEs that are either owned or controlled by (with the right to further develop) EFPIA, academics or SMEs that wish to perform TB Phase 2 studies performed by the consortium on their compounds (in monotherapy (Phase 2a) or combination (Phase 2b/c)). It is expected that minimum requirements for compounds entering the consortium would include lack of pre-existence resistance in the field (focus on drug-resistant tuberculosis), a suitable safety and efficacy profile alongside suitable supplies of formulated product. Only molecules with a novel mechanism of action, not already existing within the portfolio, or with proof of a substantial improvement over existing compounds, would be accepted for Phase 2A EBA studies (please refer to EFPIA/AP contribution for pipeline current target classes under **NCEs portfolio**). Acceptance of suitable molecules will be subject to due diligence by the governing bodies of the consortium. These NCEs will be studied alone in early clinical efficacy EBA studies and in combinations for relapse studies, including with recently approved drugs in innovative Phase 2 trials designed to accelerate drug development and maximise the chance of success in Phase 3. These trials may include innovative ways of combining drugs and new formulations in different phases of a regimen.

The funded action will develop innovative trial designs able to define optimal treatment duration against endpoints that better predict the current Phase 3 endpoint of relapse and will improve efficiency by comparing multiple regimens in parallel within the same study [6][7]. Early interims will stop failing/futile arms, resulting in even greater efficiencies.

The funded action should also prospectively validate biomarkers against a relapse endpoint. The primary objectives of the biomarker work is to validate i) biomarkers able to accurately prioritise regimens for evaluation in phase 3, ii) biomarkers that are able to predict sterilising cure/relapse at the individual patient level, and iii) a third, more ambitious objective to identify biomarkers that permit the building of a clinical trial simulation platform.

A combination of biomarkers that predicts relapse and guides treatment duration alongside innovative adaptive trials, would greatly accelerate drug development in TB by enabling in-stream adaptation of a clinical trial to prioritise evaluation of the most promising regimens. The simulation platform should embrace and validate data-driven technologies such as artificial intelligence/ machine learning (AI/ML) to set criteria for stopping arms and to determine treatment duration.

Clinical data generated in one population are not always applicable to other populations. The understanding of how host genetics influence TB outcomes are critical, but are often missing in early-stage development. This can result in failures when therapies which have been validated in one population are then implemented in other populations. The applicant consortium is expected to study the influence of host genomic factors on drug factors, such as drug exposures and clearance in the patient, and to match these against a relapse endpoint. This would permit the selection of drugs and doses that are appropriate to particular populations or even to specific patients. It is anticipated that a proportion of the data generated in the funded action will be generated outside of Europe and this pharmacogenomic activity will therefore be critical to ensuring the applicability of that data to a European population.

Adherence is critical for the efficacy of a treatment regimen. The proposed activities should exploit innovative technologies (including biomarkers and diagnostics) to facilitate and monitor adherence in resource-poor settings, while generating evidence that shorter regimens improve adherence.

The consortium will develop and execute innovative adaptive trial designs to evaluate approximately ten NCEs and approximately ten combination regimens. To complete recruitment within relevant timeframes, the trial network should be able to enrol about one thousand TB patients annually. To achieve this level of recruitment, a proportion of patients may have to be recruited from highly endemic countries outside Europe. The consortium should propose a mechanism for the allocation of financial resources matched to actual patient recruitment costs per site which ensures objectives are met. A significant proportion of funding for sites should be linked to the actual number of study participants recruited.

Collaboration agreement(s)

The action funded under this call topic will be the second one launched under 'Pillar B TBDDN (Tuberculosis Drug Development Network),' of the AMR accelerator. Please refer to Call 15 and 16 topic texts regarding 'collaboration agreements', and 'Questions and answers'[27] associated with both calls. This topic will be complimentary to the actions funded under Pillar A and B of the AMR accelerator:

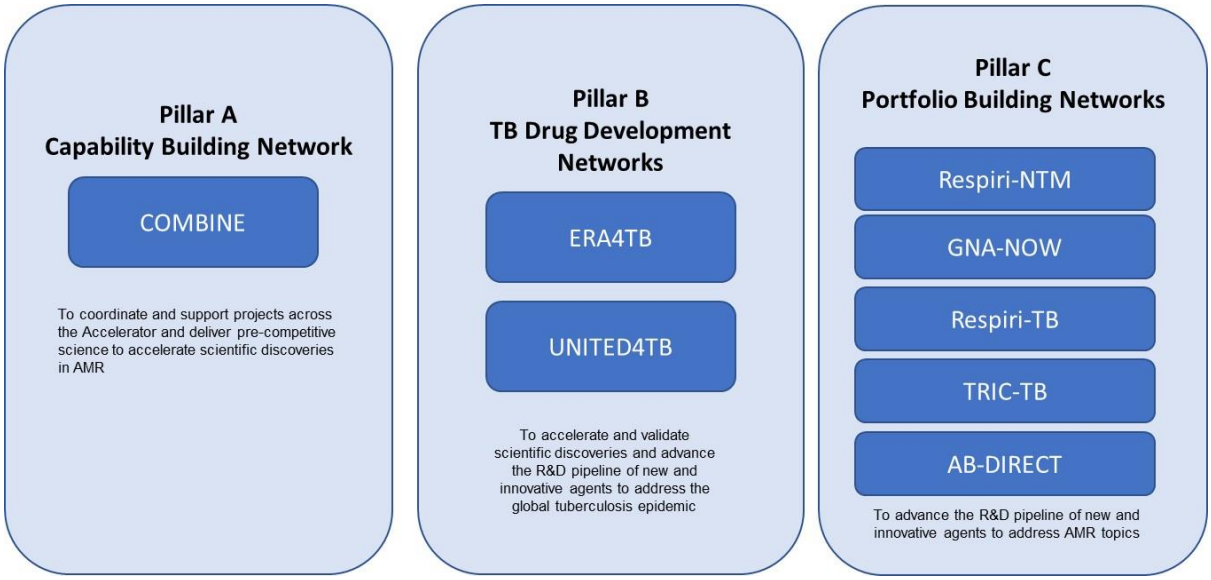

Figure 1 The structure of the AMR accelerator

- IMI2 JU Call 15 topic 8 – (ERA4TB), for using the generated pre-clinical regimen prioritisation to guide regimen selection for Phase 2B/C studies;

- IMI2 JU Call 15 topic 7 AMR Pillar A (COMBINE) on selection of biomarkers for validation, standardisation and quality control of assays that are common to AMR consortia.

The options regarding 'complementary grants' of the IMI2 JU Model Grant Agreement and the provisions therein (Articles 2, 31.6 and 41.4) will be enabled in the corresponding IMI2 JU grant agreements for all the concerned AMR accelerator projects.

Moreover, this action will seek cooperation through memoranda of understanding (MoU) with the actions that are funded under the following topic:

- **IMI2 JU Call 15 topic 1** - **EU-PEARL**, the proposed phase 2 trial designs will be presented to the EMA and FDA for scientific advice and the proposed biomarker development framework will be presented to the EMA

[27] https://www.imi.europa.eu/sites/default/files/uploads/documents/apply-for-funding/open-calls/Questions_and_answers_on_the_AMR_accelerator_programme.pdf

and FDA for biomarker qualification advice in co-ordination with **EU-PEARL** and TB Drug Translational Development Collaboration (TDTDC) as necessary;

- Individual-level patient data will be made publicly available through a sustainable data-sharing platform developed in co-ordination with **COMBINE (Call 15 topic 7)**, **ERA4TB** (**Call 15 topic 8)**, and **EU-PEARL (Call 15 topic 1)**

Additionally, where reasonable, a MoU should be pursued between potential TB-focused actions under Pillar C of the Accelerator (resulting from IMI2 JU Call 16) and TBDDN actions (i.e. Call 15 topic 8, and Call 20 topic 3) with appropriate provisions to protect confidentiality of the interactions between the consortia and their intellectual property rights.

Expected key deliverables

The proposed activities will be expected to achieve the following deliverables for the implementation of innovative state-of-the-art adaptive clinical trials, the development of biomarkers and the development of Artificial Intelligence:

- Innovative, adaptive clinical trials
  - To develop strategies for adaptive dosing (escalation/de-escalation) and trial-stopping criteria based on in-stream pharmacokinetic, efficacy and safety read-outs while building a pharmacokinetic-pharmacodynamic model, as appropriate;
  - Successful submission of documents to EMA and FDA for scientific advice on proposed innovative trial designs by the end of the first year, and for innovative trials with novel endpoints, designs and analysis plans prior to study start as required;
  - An approved plan for quality assurance (clinical data collection and analysis; laboratory assays and standardisation across a global study) and compliance with ICH GCP, European Clinical Trial Regulations, EMA and FDA clinical trial guidelines. The proposed plan should include provisions for independent study monitoring and audit; and for laboratory quality assurance;
  - A strategy for the standardisation of sample collection, laboratory assays, imaging protocols, radiation safety for subjects across a global study. This should include a plan for collaborating with **IMI2 JU Call 15 topic 7 AMR Pillar A;**
  - Established clinical trial capacity with the ability to recruit approximately 1 000 patients per year, spanning at least two WHO regions able to deliver regulatory trials in TB by the end of the first year;
  - An established Target Product Profile (TPP), Target Regimen Profile (TRP), aligned with that described by WHO, and due diligence criteria for the progression of assets within the consortium;
  - The consortium should publish a Phase 2A (EBA) design that permits in-stream adaptation of dosing in response to pharmacokinetic and pharmacodynamic readouts, so as to permit the full characterisation of the dose-response curve;
  - The consortium should publish a Phase 2B/C design that evaluates multiple regimens in parallel against novel endpoints related to the current Phase 3 endpoint (relapse and poor outcome), an ability to determine the optimal duration for a regimen, and interim(s) for futility that permit efficiency to increase as arms are dropped;
  - Establish a plan for quality assurance (clinical data collection and analysis; laboratory assays and standardisation across a global study) and compliance with ICH GCP, European Clinical Trial Regulations, EMA and FDA clinical trial guidelines. The proposed plan should include provisions for independent study monitoring and audit; and for laboratory quality assurance.

- Completed clinical trial data: Dose selection criteria for the UNITE4TB portfolio of Innovative NCEs based on completion and results from Phase 2A EBA, and Phase 2B/C combination studies. Identification of at least one viable regimen for Phase 3 clinical trials, or a ranked list of viable treatment regimens (maximum four NCEs each), capable of shortening therapy and/or with a safety/tolerability/accessibility profile better than the current standard-of-care, and which are ready to enter Phase 3;

- An established data sharing platform where individual level patient data are FAIR (Findable, accessible, Interoperable and Recoverable) and publicly available beyond the life of the consortium;

- Reporting outcomes in compliance with the European Clinical Trial Directive. The applicant consortia must present a publication strategy that does not delay the external availability of individual level patient data beyond the lifetime of the consortium;

- Innovative biomarkers
  - A strategy for how published biomarkers will be prioritised and selected for evaluation and validation and subsequently implemented within ongoing trials. For the avoidance of doubt, novel biomarker development is outside the scope of this action;

  - A strategy for early scientific engagement with the EMA and FDA, prior to clinical study start, to obtain regulatory buy-in for the proposed biomarker validation framework;

  - A methodological framework to prospectively validate biomarkers to be used in adaptive trial designs to shorten drug development and expand clinical trial capacity, and ideally used as a surrogate marker of sputum culture conversion and sterilising cure;

  - Data package of prospectively validated model/panel of biomarkers to be used in clinical trials to shorten TB drug/regimen development duration, and ready for submission to the EMA and FDA for regulatory qualification.

- Pharmacogenomics
  - Pharmacogenomics strategy for exploring how host genetic variation may influence drug absorption, target exposure, clearance, and patient outcomes resulting in pharmacogenomic PKPD models for individual NCEs.

- Clinical trial simulation tool
  - Developed clinical trial simulation tool(s) incorporating AI/ML to inform trial design, facilitate in-trial adaptation and, possibly, phase 2 trial waiver.

- Digital health technologies
  - A strategy for the evaluation of the impact of these technologies on adherence, and the impact of varying treatment durations on adherence in the field

  - Technology to evaluate the impact of treatment duration on adherence. Implement and validate digital health technologies to improve adherence to TB regimens within the currently proposed studies.

- Artificial Intelligence/Machine Learning

- A strategy for regulatory agency advice and alignment with proposed AI/ML-based models;
- Establish models that describe the role of individual biomarkers suitable for regulatory acceptance.
- Biobank.
- Establish a sustainable biobank to make samples with linked de-identified clinical data collected from the consortium clinical trials publicly available beyond the life of the consortium.
- Human biological samples collected as part of the clinical studies should be banked and made available to external researchers beyond the lifetime of the consortium. Samples provided to researchers should be linked to de-identified demographic and clinical study data in a manner compliant with GDPR;
- The applicant consortia should provide a strategy for human biological sample tracking, access and management that is compliant with relevant European legislation;
- A strategy for granting access to samples should also be presented (e.g., an independent panel for evaluation of proposed research plans).

Expected impact

The objectives, deliverables and impact of the resulting action are well aligned with the mission and goals of IMI2 JU to deliver increased success rate of biomarkers and priority medicines in innovative clinical trials. The expected impact of the funded action will also help attain 2030 UN Sustainable Development Goals and WHO 2035 End TB Targets by:

- providing new tools and understanding on how to progress TB science for the discovery and development of new clinical candidates and combinations thereof across the TB R&D landscape, with special emphasis on innovative clinical trial design and development of novel biomarkers;
- contributing to the EU's ambition of being a 'best practice region' for addressing AMR, and profit from its medical capacity to individualise and implement into medical practice combination therapies addressing MDR/XDR;
- developing new knowledge and tools, innovative clinical trial designs, imaging technology, biomarkers and pharmacogenomics diagnostics and exploiting artificial intelligence for the development of new clinical candidates and combinations;
- enabling the progression of potential new, safe, efficacious, shorter and affordable treatment solutions for TB patients worldwide, with the intent to improve the quality of life and life expectancy of TB patients;
- contributing to the development of a vibrant TB research environment in the EU, fostering private-public collaboration across EFPIA, academia, NGO's and SME's and strengthening the competitiveness and industrial leadership of Europe;
- providing a legal frame and agreement on IP terms and exploitation, as a paradigm of public and private international collaboration in the development of combination regimes;
- implementing agreement with other consortia facilitating prompt data sharing and data exploitation to accelerate TB drug regimen development.

In addition, the following additional exploitation[28]/dissemination[29] obligations must be considered to maximise impact: the applicant consortium is expected to have a strategy on the translation of the relevant project outputs into regulatory, clinical and healthcare practice. These strategies aim to ensure fast access and uptake in high TB burden countries to secure maximum impact on the TB epidemic.

A plan for interactions with regulatory agencies/health technology assessment bodies with relevant milestones and resources allocated should be proposed to ensure, for example, qualification advice on the proposed methods for novel methodologies for drug development.

The major outputs of the proposed activities, such as innovative clinical trial designs, biomarker evaluation and the evaluation of novel technologies to monitor and enhance adherence must be disseminated in peer-reviewed open access journals. Any clinical trial simulation created must be made available via an open access platform to external researchers beyond the lifetime of the funded action.

Clinical samples must be made available to researchers outside the consortium and beyond the lifetime of the consortium through a sustainable biobank.

In their proposals, applicants should outline how the proposed activities will:

- manage research data including use of data standards and a fully developed strategy for FAIR storage and access to data and models beyond the lifetime of the consortium;[30]
- disseminate, exploit, and sustain the project results. This may involve engaging with suitable biological and medical sciences research infrastructures;[31]
- communicate the project activities to relevant target audiences.

Potential synergies with existing consortia

Synergies and complementarities should be considered with relevant national, European and non-European initiatives (including suitable biological and medical sciences research infrastructures[22] 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 specifically consider synergies with partnerships that have existing TB clinical trial networks, TB drug discovery consortia, or with relevant not-for-profit organisations in the field.

The funded project is also expected to seek collaboration and establish a data-sharing framework agreement with the TB Drug Translational Development Collaboration (**TDTDC**) to ensure complementarity and sharing of results particularly with regards to efficacy, safety and experimental biomarkers.

Industry consortium

The industry consortium is composed of the following EFPIA partner(s):

- GlaxoSmithKline Investigación y Desarrollo S L (co-lead)

[28] Article 28.1 (Additional exploitation obligations) of the IMI2 Grant Agreement will apply
[29] Article 29.1 (Additional dissemination obligations) of the IMI2 Grant Agreement will apply
[30] Guidance on data management is available at http://ec.europa.eu/research/participants/docs/h2020-funding-guide/cross-cutting-issues/open-access-data-management/data-management_en.htm
[31] http://www.corbel-project.eu/about-corbel/research-infrastructures.html

- BioMérieux
- Janssen Pharmaceutical
- Otsuka Pharmaceutical Europe Ltd.

In addition, the industry consortium includes the following IMI2 JU Associated Partner(s)

- Deutsches Zentrum für Infektionsforschung (DZIF) (co-lead)
- Klinikum of the Ludwig-Maximilians-Universität München (KUM)

The industry consortium (EFPIA and Associated Partners) plan to contribute the following expertise and assets:

- **NCEs portfolio.** To ensure a working portfolio of ten assets, it is anticipated that EFPIA and Associated Partners will contribute a substantial number of assets to the pipeline to mitigate potential compound attrition. It is expected that in the region of eight NCEs will be made available to the consortium in the first year, consisting of ATPsynthse inhibitors, Nitroimidazoles, Decaprenylphosphoryl-β-d-ribose 2'-epimerase (Dpre1) inhibitors, b-lactams, Leucyl-tRNA synthetase (LeuRS) inhibitors and cholesterol catabolism inhibitors. Approximately seven additional NCE's may be included the years that follow, with at least four additional mechanisms of action including novel oxazolidinones, protein synthesis inhibitors, transcriptional repressors affecting the metabolism of medicines and new generation ATP synthase inhibitors. Molecules may become available via EFPIA members and/or IMI2 JU Associated Partners, (i.e.TB Alliance, Gates MRI) in other AMR Accelerator projects, e.g. ERA4TB, or through other initiatives. Selection of molecules will be subject to due diligence by the governance bodies of the consortium. For further information on the existing portfolio of TB assets please refer to the working group on new TB drugs (www.newtbdrugs.org).

- The Sponsor for each clinical trial within the consortium will be chosen from among the asset owners contributing NCEs to a study and will assume all legal and regulatory Sponsor accountabilities. In this capacity Sponsors will retain full responsibility only for the investigation and reporting of SUSARs and serious GCP breaches occurring within a trial. Other pharmacovigilance responsibilities will be agreed at the second stage of application.

- EFPIA members and Associated Partners will provide expertise and advice on core clinical trial activities and minimum standards expected as outlined in relevant regulatory guidelines which will be the responsibility of the applicant consortium including, but not limited to:

    - Clinical: protocols and informed consents, for data collection and quality management, privacy, reporting and disclosure. Minimum standards for monitoring and audit plans;

    - Statistical analysis plans and quality control processes;

    - Provision of regulatory documents such as investigator brochures and IMPD will be provided by asset owners. Asset owners will also be responsible for the creation of annual regulatory reporting for each asset (INDSR, DSUR, PSRI) using data provided by the applicant consortium. Asset owners will provide guidance on the construction of regulatory packages;

    - Pharmacovigilance: requirements for safety reporting within trials;

- Laboratory and imaging: requirements for assay standardisation/imaging protocol standardisation, results reporting and quality control and assurance. Legal obligations for tracking of human biological samples;

- Clinical pharmacology: standards for model building, quality assurance and reporting;

- Sample collection and banking protocol and standards for biomarkers and diagnostics. Assay protocol, reagents and equipment standardisation. Collaboration with applicants regarding selection of biomarkers and their validation/approval from regulatory agencies

- Investigational product: requirements for storage, transport, tracking and destruction of investigational product (both NCEs and licensed medicines);

- Agreements and contracting: requirements for transfer of Sponsor responsibilities, and compliance with relevant European regulations and legislation when contracting third parties or vendors.

Contribution of Data by industry and associated partners as "in-kind"

During the funded action, members of the industry consortium plan to contribute scientifically relevant activities for generating data/collecting samples in prospective activities that are part of broader clinical studies initiated independently of the Action. Certain of these studies activities, relevant to the Action and necessary for achieving its objectives, will be included in the project's Description of the Action but solely carried out by the contributing member of the industry consortium. The introduction of the data constitutes an in-kind contribution which entails access rights to these project results in line with IMI2 JU IP rules. The estimated in-kind contribution for the prospective activities to generate these data and samples will constitute a substantial proportion of the EFPIA-based in-kind contribution.

The prospective data and samples are planned to include preclinical and clinical studies with assets from the EFPIA partners that will be carried out to prepare assets to be potentially included as part of the UNITE4TB asset pipeline. These data and samples are essential for achieving all the objectives of the project as they will provide a basis for inclusion of compounds within the studies and access to data on the disease per se. Significant scientific contributions are also being delivered in the other pillars of the AMR accelerator and outputs from these activities are transferable to this project.

Indicative duration of the action

The indicative duration of the action is 84 months.

This duration is indicative only. At stage 2, the consortium selected at stage 1 and the predefined industry consortium may jointly agree on a different duration when submitting the stage 2 proposal.

Indicative budget

The financial contribution from IMI2 JU is a maximum of EUR 92 500 000.

The indicative in-kind from EFPIA partners and IMI2 JU Associated Partner(s)] is EUR 92 500 000.

This contribution comprises an indicative EFPIA in-kind contribution of EUR 62 500 000 and an indicative IMI2 JU Associated Partner(s) in-kind contribution EUR 30 000 000.

The EFPIA and Associated Partner in-kind contribution will be matched by IMI2 JU funding across the whole of the Accelerator and not necessarily 1:1 on an individual project or pillar basis

Due to the global nature of the participating industry partners and IMI2 Associated Partner(s), it is anticipated that some elements of the contributions will be non-EU/H2020 Associated Countries in-kind contributions.

Expertise and resources expected from applicants at stage 1

The stage 1 applicant consortium is expected, in the submitted short proposal, to address all the objectives and key deliverables of the topic, taking into account the expected contribution from the industry consortium which will join at stage 2 to form the full consortium.

The stage 1 submitted short proposals should include suggestions for creating a full proposal architecture which could be in line with the suggested architecture described below, though this architecture is only a suggestion.

Applicant consortia wishing to include their own NCE(s) will be subject to the same governance and acceptance criteria as other assets in the existing portfolio as determined by the decision-making bodies within the consortium. Any NCE brought into the consortium must be novel and clearly differentiated from any asset existing in the funded action pipeline according to guidelines proposed by the governing bodies. Applicants consortia may refer to the expected NCEs portfolio under industry contribution,

- **Innovative clinical trials**. Applicant consortia should include experienced TB investigators and sites with proven trial capacity (the number of sites should be limited to a reasonable number to facilitate management and coordination), capitalising on sites from previously established European networks, or from sites within endemic countries outside of Europe. The consortium should not attempt to set up a trial network *de novo* nor attempt to build capacity at sites with no previous TB clinical trial experience. Quality of data generated by the trials must be adequate for inclusion in a regulatory file, delivered in a timely fashion, and with appropriate cost efficiencies. The consortium may subcontract specific activities to CROs to seek for efficiency or additional expertise. Applicant consortia must have the expertise needed to execute and collect and analyse efficacy and safety data from an EBA study and for the analysis of data from phase 2B/C efficacy and relapse studies;

- **Innovative Biomarkers.** Expertise in the implementation of previously-identified biomarkers and regulatory buy-in for the proposed biomarker validation framework;

- **Clinical trial simulation.** Experience in building clinical trial simulations and regulatory qualification. Understanding of regulatory requirements for model specification and interrogation, with a specific understanding of the issues around black-box versus white-box approaches. Any AI/ML algorithms deployed to prioritise regimens and/or to predict sterilising cure should be complementary to existing mechanistic models;

- **Artificial Intelligence/Machine Learning (AI/ML)** The applicant consortia should have access to AI/ML expertise and its application in drug development/clinical trials;

- **Digital Health Technologies** The applicant consortia should have knowledge of digital health tools/technologies and expertise in deployment in resource-poor settings;

- **Pharmacogenomics** The applicant consortia should have expertise in pharmacogenomic techniques, collection, assay and analysis techniques.

This may require mobilising, as appropriate the following expertise:

- Experience in running clinical trials of a standard sufficient to support inclusion in a regulatory file in the field of TB. Including a deep understanding of relevant clinical trial guidelines, regulations and legislation and previous experience of engagement with the EMA and FDA;

- Expertise in analysis and interpretation of relevant biomarker modalities, including, but not limited to, the host response, bacterial antigens and radiology;

- Operational expertise in the transport and management of clinical trial supplies and human biological samples;
- Understanding of scientific and regulatory requirements for biomarker validation and qualification, appropriate to build a plausible validation/qualification strategy acceptable to the EMA and FDA, including an awareness of the scientific and regulatory issues relating to clinical trial simulations;
- Expertise in digital health technologies relevant to treatment adherence;
- Pharmacogenomic expertise in the collection of host DNA, and the ability to sequence and identify relevant pharmacogenomic variations in different populations. Ability to de-identify data and to store it in compliance with relevant guidelines and legislation. Ability to analyse genomic data and correlate this to drug PK and trial endpoints;
- GCP, GDPR, ethics, legal and data privacy expertise.

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

- Access to historical data archived by Critical Path to TB Drug Regimens (CPTR).

Considerations for the outline of project work plan

In their stage 1 proposals applicants should

- give due visibility to data management; dissemination, exploitation and sustainability; and communication activities. This should include the allocation of sufficient resources for these tasks which will be further developed in the stage 2 proposal;
- present a strategy for ensuring the translation of the project results to drug development: a key deliverable will be qualification advice from the EMA and FDA for the biomarker validation strategy.

Suggested architecture

The applicant consortium is expected to have a structure that address the following areas:

Administration. In view of the complexity and size of the action, the applicant consortium should make provisions for project management, general administration (including project co-ordination, communication strategy for consortium partners and between consortia, meeting management), compliance with IMI requirements (reporting and financial audit), including a suitable mechanism to adjust funding for clinical sites based on successful recruitment strategies. Applicants should refer to reflection paper EMA/121340/2011 [8].

Compliance and quality control. Compliance with relevant guidelines and regulations (ICH GCP, European Clinical Trial Directive, GDPR, human biological sample tracking and other sponsor obligations), selection of trial Sponsor, pharmacovigilance and safety reporting, mechanisms for oversight, clinical data quality, laboratory/radiological assay standardisation and internal and external quality control strategy, management of clinical trial supplies/investigational product. Applicants should refer to reflection paper EMA/121340/2011[8].

Clinical trial design. Co-ordination of regulatory activities and designs with **IMI2 JU Call 15 topic 1: EU-PEARL**, protocol development, statistical analysis and quality plans, publication plans.

Clinical operations. Implementation of consortium strategies for compliance and quality assurance, site selection (including provisions for flexible allocation of resources by recruitment rate) and set-up, logistics plans (transport of samples and consumables), equipment purchase, preparation of regulatory and ethics packages, annual regulatory and ethics reports, training of monitors and sites, creation of site files, creation/review of clinical and laboratory SOPs, and evaluation of innovative technologies for adherence.

Biomarkers. Create biomarker validation strategy, create infrastructure for transfer of samples and data between consortium partners, validate biomarkers against relapse endpoint and report results, create clinical trial simulation, prepare package for FDA/EMA biomarker qualification.

In addition, applicants should consider a suitable structure that incorporates all of the other Innovative key deliverables.

Additional considerations to be taken into account at the stage 2 full proposal

At stage 2, the consortium selected at stage 1 and the predefined industry consortium jointly submit the full proposal developed in partnership. The full proposal is based upon the selected short proposal at stage 1.

Decision-making. Following the first stage of the IMI2 JU Call process and selection of partners to receive IMI2 JU funding, it is expected that the consortium preparing the full proposal for the second stage of the IMI2 JU Call process will agree on a robust decision-making process (including escalation procedures) for progression of different NCEs, combination regimens and biomarkers. Overall plans and go/no-go milestones will be established during the stage 2 application that will assist in the decision-making process to help ensure that the overall portfolio remains dynamic and work on NCEs is appropriately prioritised across the portfolio. For the avoidance of doubt, any decisions directly affecting an existing NCE shall always require the consent of the NCE owner.

Such decisions will be made by a committee that includes representatives from all project partners. The composition of this committee will be detailed and agreed by all partners in the Consortium Agreement. A fair and efficient decision-making process will be presented in the full proposal at the second stage of the IMI2 JU Call process. This committee will track the progress of the project against its own internal milestones and will be empowered (to be outlined in the Consortium Agreement) to make progression/termination decisions based on pre-agreed go/no go milestones in a regular, streamlined, single-meeting process. The decision-making process by the committee may result, in case of a 'no-go' decision, in the recommendation from the committee/consortium to IMI2 JU for terminating the grant based on Art. 50.3.1 (h) of the IMI2 JU MGA. The final decision on project continuation or termination will be taken by IMI2 JU in line with the provisions of the Grant Agreement. However, the JU may also make such a decision without prejudice to any decision-making process at the level of the consortium, that is, even without the aforementioned recommendation.

In the spirit of the partnership, and to reflect how IMI2 JU call topics are built on identified scientific priorities agreed together with EFPIA beneficiaries/Associated Partners, these beneficiaries intend to significantly contribute to the programme and project leadership as well as project financial management. The final architecture of the full proposal will be defined by the participants in compliance with the IMI2 JU rules and with a view to the achievement of the project objectives. The allocation of a leading role within the consortium will be discussed in the course of the drafting of the full proposal to be submitted at stage 2. To facilitate the formation of the final consortium, until the roles are formally appointed through the consortium agreement, the proposed EFPIA co-project leader from among EFPIA beneficiaries/Associated Partners shall facilitate an efficient negotiation of the required legal consortium agreement. Project content and science shall jointly be facilitated by both co-project leaders.

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

Applicants to Calls launched as part of the Accelerator should consult the IMI2 JU Model Grant Agreement and IMI2 JU Annotated Model Grant Agreement, as well as a short questions and answers document available at https://www.imi.europa.eu/sites/default/files/uploads/documents/apply-for-funding/open-calls/Questions_and_answers_on_the_AMR_accelerator_programme.pdf.

Dissemination, exploitation and sustainability of results

In their stage 2 proposal, applicants must provide a draft plan for dissemination and exploitation, including sustainability of results. A full plan as a distinct deliverable must be delivered within the first 6 months of the project.[32], and updated during the project lifetime. It could include identification of:

- Different types of exploitable results;
- Potential end-users of the results;
- Results that may need sustainability and proposed sustainability roadmap solutions.

Sufficient resources should be foreseen for activities related to dissemination and exploitation, including the plan for the sustainability of the project results. This may involve engaging with suitable biological and medical sciences Research Infrastructures (RIs).[33]

Communication

The proposed communication measures for promoting the project and its findings during the period of the grant should also be described and could include a possible public event to showcase the results of the project.

[32] As an additional dissemination obligation under Article 29.1 of the IMI2 Grant Agreement will apply
[33] http://www.corbel-project.eu/about-corbel/research-infrastructures.html

References

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[2] A. H. Diacon, R. Dawson, et al. Randomized dose-ranging study of the 14-day early bactericidal activity of bedaquiline (TMC207) in patients with sputum. *Antimicrobial Agents and Chemotherapy* Volume 57, Issue 5, Pages 2199–2203 (2013). https://doi.org/10.1128/AAC.02243-12

[3] S. H. Gillespie, A. M. Crook, *et al*. Four-month moxifloxacin-based regimens for drug-sensitive tuberculosis. *New England Journal of Medicine* Volume 371, Issue 17, Pages 1577–1587 (2014). https://doi.org/10.1056/NEJMoa1407426

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[6] P. P. J. Phillips, K. E. Dooley, *et al.* A new trial design to accelerate tuberculosis drug development: The Phase IIC Selection Trial with Extended Posttreatment follow-up (STEP). *BMC Medicine* Volume 14, Issue 1, Pages 1–11 (2016). https://doi.org/10.1186/s12916-016-0597-3

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[8] European Medicines Agency. Reflection paper on ethical and GCP aspects of clinical trials of medicinal projects for human use conducted outside of the EU/EEA and submitted in marketing authorisation applications to the EU Regulatory Authorities

Topic 4: Tumour plasticity

Topic details

Topic code	IMI2-2020-20-04
Action type	Research and Innovation Action (RIA)
Submission and evaluation process	2 stages
IMI2 Strategic Research Agenda - Axis of Research	Innovative medicines
IMI2 Strategic Research Agenda - Health Priority	Cancer

Specific challenges to be addressed by public-private collaborative research

The last decade has seen tremendous advances in the development of effective targeted therapies as well as in immuno-oncology to more effectively treat cancer. Despite this, cures are still rare in the metastatic setting. In most cases, an initial response to treatment is followed by the eventual emergence of **drug resistance** [1]. Drug resistance in cancer is one of the greatest causes of mortality, and despite increasing success with targeted therapies in the clinic (including immunotherapy), the mechanisms by which cancer cells evade cell death are still not well understood. Drug combinations are likely to be critical to overcoming drug resistance but are dependent on identifying the cellular programmes that cancer cells use to resist therapeutic agents.

In tumours that initially respond to treatment, rare cancer cells can survive and withstand therapy **('drug tolerant persister' cells, DTPs**) and can act as a reservoir for the eventual emergence of drug resistance (**Figure 1**) [2]. Furthermore, these studies have shown that these cells are able to survive drug treatment by altering the transcriptional state of specific signalling pathways, and that in the early stages such changes are plastic and reversible, but that over time these changes become stable and fixed.

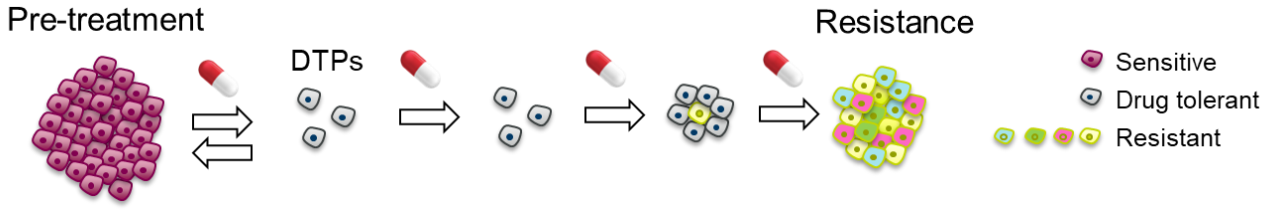

Figure 1. Diagram showing how drug tolerant persister cells (DTPs) arise from the bulk tumour following successful treatment, and ultimately contribute to the emergence of drug resistance.

Recent technological advances in **single-cell sequencing** have revolutionised the study of individual cells within cancer populations and, importantly, would allow the characterisation of DTPs, something previously impossible with bulk sequencing technologies [3]. Single-cell sequencing provides information that is not confounded by genotypic or phenotypic heterogeneity of bulk samples. Importantly, it has confirmed the existence of DTPs in patients following treatment response and, more importantly, the characterisation of the transcriptionally altered pathways in DTPs [2][4]. Characterising the transcriptionally altered pathways in persister cells, the biological processes they regulate and their druggability will be critical to **future drug combination strategies**, with the goal of preventing or significantly delaying the development of drug resistance.

There are numerous challenges in applying single cell sequencing to drug resistance- arguably one of the most important barriers to curing cancer today, and specifically:

- defining best sequencing protocols – single-cell RNA-sequencing (scRNA-seq) is a fast-moving field with a recent benchmarking paper comparing 13 different methods [5];
- computational approaches to big data – as with sequencing methods, the analysis framework is constantly evolving and there are challenges in integrating data across studies and platforms;
- standardisation of data formats;
- best practice single cell collection from *in vitro* and *in vivo* model systems;
- application of single-cell sequencing to clinical samples;
- spatial imaging technologies;
- biological interpretation of data, including novel target identification.

This topic proposes to apply state-of-the-art single-cell sequencing technologies to characterise cancer cell populations pre-treatment, at minimal residual disease (for DTPs), and upon the acquisition of drug resistance and from a variety of pre-clinical human and mouse models as well as clinical samples.

Scientific advances in singe-cell sequencing, use of patient-derived xenografts (PDX) and patient-derived organoids (PDO), and clinical tissue imaging have come together to create the perfect environment to address one of the most important challenges in cancer biology today: **drug resistance**. Each of these areas is a rapidly advancing field and, importantly, no single sector has complete expertise in all these areas. Additionally, the collection and sorting of cells in a standardised way is well-aligned with the capabilities of industry partners and is an activity that academic groups are typically not well set up to deliver at scale. Conversely, the techniques for evaluating single cells and the computational methods for interpretation of data are under constant development (mainly in academic labs). Finally, industry partners are ideally placed to interrogate different drug mechanisms against common tumour backgrounds (or vice versa). Taken together, these factors provide a compelling opportunity for private-public collaboration.

Therefore, to address such a wide range of complex issues, there is a need for strong cooperation amongst industry, biotechnology companies, academia, and patient organisations, bringing their diverse expertise in the following fields:

- acquisition of single-cells from pre-clinical and clinical models;
- adoption of best single-cell sequencing practice;
- standardisation of analytical methods, including data integration across studies;
- application of scRNA-seq to characterise non-malignant cells in the tumour microenvironment;
- spatial transcriptomics and imaging techniques;
- development of protocols for clinical single-cell sequencing.

This Call topic is an ideal opportunity to systematically address how viewing a patient's cancer not as a single homogeneous entity but rather as a population (containing diverse subpopulations with different behaviours) might ultimately alter the paradigm of drug resistance.

The strategic relationship between leading scientists and key opinion leaders in industry, small and medium-sized enterprises (SMEs) and academia will enable a better understanding of drug development post-novel target identification, and increase the likelihood of spin-off projects based on the better understanding of DTP biology.

Scope

The overall objective of the Call topic is to use state-of-the-art single-cell sequencing to understand and overcome drug resistance in cancer by **characterising the biology of drug tolerant persister cells**, building the capability for such studies across Europe.

The call topic will address primarily adult tumours, with the provision to include childhood tumours where appropriate models are available at a later stage of the programme. To optimise our ability to determine the role of tissue lineage on the biological processes observed in single-cells, we propose that the majority (>80 %) of the single cells should be provided from drug treatments in 3 adult cancers:

- non-small cell lung cancer (NSCLC);
- breast cancer;
- colorectal cancer.

Each industry partner will nominate five tumour types/drug treatments aligned to the tumour areas summarised above and it is expected that nomination of study systems will be in consultation with academic consortium partners. Upwards of 20 % of the studies can be proposed in tumour types in addition to these 3 core cancers, including childhood cancers.

We anticipate that most of the single cells from the models described above will be provided by the industry partners, while the academic consortium will provide expertise in single-cell sequencing and data analysis.

To facilitate data integration across studies, it is preferable to use a small number of sequencing technologies that are complementary, well supported and widely used, and which are able to analyse large numbers of single cells versus smaller number of cells at greater depth of coverage. For these reasons, the Chromium (10X Genomics) [6] and Smart-Seq2 [7] platforms are preferred as the main complementary single-cell sequencing technologies used for the implementation of the proposed activities. These are mature, commonly used protocols that have been extensively benchmarked.

The goals of the Call topic are:

- To characterise the biology of Drug Tolerant Persister cells - defining the signalling pathways and cellular processes that enable DTPs to survive drug treatment and thereby identify novel drug targets to overcome this – using state-of-the-art single-cell sequencing and spatial transcriptomics in a range of cancer models.
- To better understand the tumour microenvironment – to avoid solely focusing on cell intrinsic drug resistance programmes, a key element of the work packages should be to use spatial imaging techniques to explore the interaction between cancer cells and the microenvironment.
- Generation of single cell RNAseq data from adult and childhood cancers – although the pre-clinical models used to explore the biology of drug treatment in cancer are predominantly based on adult cancers, drug resistance is equally a major problem in childhood tumours. The applicants should anticipate that from year 3 of the funded project, specific childhood cancers (up to 20 % of the total studies proposed) could be considered for inclusion where the appropriate models are accessible and where there is a hypothesis relationship with drugs or tumours being investigated by the consortium. To develop best practice in clinical validation and single-cell sequencing – clinical validation will be key to translation of any findings and a change in clinical practice. To include informed patient consent forms that cover all intended uses, including clinical outcome data and sharing of data inside the consortium and with 3rd parties. General Data Protection Regulation (GDPR) compliant tracking of patient data, samples and PDXs.
- To create gold standard protocols for single cell collection – across a range of models and to include differing methods for isolating single cells from human (organoids, clinical biopsies) and mouse (PDX, genetically engineered mouse models (GEMM) and syngeneic mice) model systems.

- To develop core analytical methods – use pre-treatment, on treatment and post-treatment single-cell sequencing data to develop novel computational approaches to identify the different subtypes of cancer cells present, and the biological processes that are complicit in maintaining their survival following drug treatment.

- To build EU capability in single-cell sequencing – in the process of developing the protocols for single cell collection, sequencing and analysis, the funded project will put in place infrastructure to enable other groups in the EU to carry out similar single-cell sequencing studies in both cancer and non-cancer models.

Importantly, despite the fact that over the five years of the funded project we expect to adopt new technologies as and when they are developed and where they demonstrate significant advantages over current protocols, the goal of this Call topic is not the explicit development of such new methods and technologies *per se*. Additionally, we do not expect all of the drug-tumour combinations for study to be fixed at the outset. This will emerge as the industry partners identify agents and systems for study and will be managed by a consortium portfolio review process.

Expected key deliverables

The expected key deliverables should include the following:

Deliverable 1: Benchmarked and standardised protocols for single cell identification and collection from PDX/PDO models.

Deliverable 2: Gold standard methods for tissue-based spatial imaging. To include pre-clinical models as well as clinical samples for validation in relevant patient populations.

Deliverable 3: Multi-omics methods for characterising single cells. Incorporate new technologies such as CITE-seq (single-cell RNA sequencing and cell surface antibody expression), combined ATAC-seq/scRNA-seq and single-cell metabolomics protocols.

Deliverable 4: DTPs and metadata/annotation from human and mouse models. Provision of single cells from various time points (pre-treatment, on treatment and tumour progression) in (typically) 3-6 models per cancer type, and including pre-clinical (PDO, PDX, GEMM and syngeneic models) and clinical samples. Additional models from non-industry partners will also be permitted.

Deliverable 5: State-of-the-art analysis methods of single-cell sequencing. Define regulatory networks from transcriptional data as well as druggability of relevant targets and identify novel drug combinations to prevent the emergence of DTPs following treatment in the relevant cancers.

Deliverable 6: Single-cell measurement data combined with treatment and outcome data / clinical outcome data.

Deliverable 7: Gold standard methods for the validation of key transcriptional changes. To validate transcript(s) implicated in DTP biology using spatial imaging techniques applied to treated patient samples and combining CRISPR screens with scRNA-sequencing.

Deliverable 8: Tools to allow cross-study analyses of single-sequencing data. Develop novel methods and software packages to combine data across multiple studies for enhanced power and to detect novel biology not otherwise revealed by single study analyses.

Deliverable 9: **A raw data repository with access for all consortium partners.** A repository for data (measurement raw data, preclinical treatment and outcome data and clinical treatment and outcome data) with granular access rights that supports quality control and data queries in line with access and intellectual property (IP) rights according to the IMI2 JU Grant Agreement rules and as specified in the consortium agreement. The proposal should outline how sustainability of data access will be ensured. Where patient data is generated or used, this will be integrated across studies in a legally and ethically compliant way, including any GDPR requirements.

Deliverable 10: White paper on single-cell sequencing to characterise DTP biology.

Expected impact

A comprehensive effort to prevent drug resistance in cancer is generally lacking at the present time. This topic proposes the use of state-of-the-art single-cell sequencing technologies to address this challenge across a number of the most prevalent cancer types, in both adult and childhood cancers.

A comprehensive database, profiling DTPs across a range of cancers and therapies would enable a deeper understanding of the biology of DTPs and allow cross-tumour studies.

Impact for patients:

- identification of novel drug targets in DTPs and resulting drug combinations that delay or prevent the emergence of drug resistance in cancer;
- better understanding of the contribution of tumour heterogeneity and plasticity to disease outcome, progression and relapse.

Impact for academia and SMEs:

- harmonisation of protocols for single cell experiments;
- enhanced infrastructure in the EU for single cell sequencing;
- development of gold standards for the analysis of single-cell sequencing data;
- access to comparative data on different pre-clinical and clinical models and better understanding of the biology of DTPs in cancer with a high likelihood of spin-off projects;
- improvements in single cell sequencing and spatial imaging with potential for commercial development;
- better understanding of drug development post-novel target identification.

Impact for industry:

- access to a data source for further functional studies (e.g. knock-out, knock-in, target perturbation) that will lead to opportunities for identification of novel targets in the DTP space - pointing to new targets or rational drug combinations that alter the drug resistance paradigm;
- access to single cell measurement data combined with outcome data (models) and clinical outcome data;
- development of expertise in the analysis of single-cell sequencing data;
- gold standard methods for the delivery of single cell projects.

In their proposals, applicants should outline how the project plans to leverage the public-private partnership model to maximise impacts on innovation, research & development; regulatory, clinical and healthcare practices, as relevant.

In addition, applicants should describe how the project will impact the competitiveness and growth of companies including SMEs.

In their proposals, applicants should outline how the project will:

- manage research data including use of data standards[34]
- disseminate, exploit, and sustain the project results; this may involve engaging with suitable biological and medical sciences research infrastructures[35]
- communicate the project activities to relevant target audiences.

In addition, the following additional exploitation[36]/dissemination[37] obligations must be considered to maximise impact:

- Quality control (QC), standardisation data and the agreed standardised operating procedures will be made publicly available as soon as possible;
- A mechanism needs to be proposed to ensure that input data and results generated by an industry partner working together with an academic partner are kept confidential until the dataset and experiment is complete. A process for release to the rest of the consortium will also be agreed;
- A mechanism needs to be proposed to enable third party access to results at the end of the action. A plan for aspects related to sustainability should be proposed, especially ensuring that the database remains accessible and facilitating its population with additional clinical outcome data. This can include a proposal for options transferring the open access database into an existing structure and should include realistic ideas for long-term financial and operational sustainability of the database;
- Any publications arising from the action need to link to an open access area of the consortium database to coincide with publication.

Potential synergies with existing consortia

Synergies and complementarities should be considered with relevant national, European and non-European initiatives (including suitable biological and medical sciences research infrastructures[35]) in order to incorporate past achievements, available data and lessons learnt where possible, thus avoiding unnecessary overlap, and duplication of efforts and funding.

Key synergies with existing consortia that could be considered are:

- International programmes using single-cell sequencing to create reference maps of human cells (e.g. Cell Atlas programmes). In particular, dialogue with pre-existing working groups to develop standards in the generation and analysis of single-cell sequence data will be advantageous;
- Programmes that allow the inclusion of specific pre-clinical models would add value. Programmes directed towards developing an expanded range of adult and childhood cancer PDX models are particularly relevant;
- If aligned with the goals of the Call topic, programmes already collecting clinical samples for single-cell sequencing would be valuable as some of this data could be considered for integration.

[34] Guidance on data management is available at http://ec.europa.eu/research/participants/docs/h2020-funding-guide/cross-cutting-issues/open-access-data-management/data-management_en.htm
[35] http://www.corbel-project.eu/about-corbel/research-infrastructures.html
[36] Article 28.1 (Additional exploitation obligations) of the IMI2 Grant Agreement will apply
[37] Article 29.1 (Additional dissemination obligations) of the IMI2 Grant Agreement will apply

Industry consortium

The industry consortium is composed of the following EFPIA partners:

- AstraZeneca (lead)
- Bayer
- Eli Lilly
- Transgene SA
- Merck KG
- Charles River

The industry consortium anticipates contributing the following expertise and assets:

- work package co-leadership;
- contribution to database / IT solutions and bioinformatic analyses;
- contribution to samples, metadata and curation and models.

In particular, industry partners will **contribute single cell samples from the relevant human and mouse tumour models** and therapies as well as access to the relevant clinical samples. It is anticipated that nearly all of these will be in-kind, rather than background contributions. (In-kind samples will be the results of studies specifically designed for this programme and carried out during in the frame and duration of the project; if background contributions are introduced, they could include validation sets of cells collected prior to this action commencing).

During the funded action, members of the industry consortium plan to contribute scientifically relevant activities for generating data on single cells or collecting and sorting single cells in prospective activities that are part of broader industry clinical studies. The relevant activities will be included in the project's Description of the Action and are necessary for achieving its objectives. The introduction of the data constitutes an in-kind contribution which entails access rights to these project results in line with IMI2 JU IP rules. The single-cell samples will be collected from drug treatment studies in pre-clinical mouse or human tumour models (PDO, GEMM or PDX samples). The industry partners will provide samples corresponding to approximately 80 drug/tumour combinations in total. Each study will aim to collect cells at three time points. A small proportion (<20 %) of study samples will be provided for spatial and multi-omic analysis. Submitting these samples to scRNAseq analysis is an essential activity of the project and the data derived will drive better understanding of the origin of DTPs.

Optionally, prospective data will be provided by industry partners, derived from scRNAseq analysis of PDO or PDX samples and subjected to the same bioinformatic analysis as above.

In addition to project leadership, industry partners' staff efforts are expected to be largely spent on work packages 1-4 and 7 (please refer to the suggested architecture).

Indicative duration of the action

The indicative duration of the action is 60 months.

This duration is indicative only. At stage 2, the consortium selected at stage 1 and the predefined industry consortium may jointly agree on a different duration when submitting the stage 2 proposal.

Indicative budget

The financial contribution from IMI2 JU is a maximum of EUR 7 058 000.

The indicative in-kind contribution from EFPIA partners is EUR 8 500 000.

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

Expertise and resources expected from applicants at stage 1

The stage 1 applicant consortium is expected, in the submitted short proposal, to address all the objectives and key deliverables of the topic, taking into account the expected contribution from the industry consortium which will join at stage 2 to form the full consortium.

The stage 1 submitted short proposals should include suggestions for creating a full proposal architecture which could be in line with the suggested architecture described below, though this architecture is only a suggestion.

This may require mobilising, as appropriate the following expertise:

Relevant technology companies, in particular SMEs, along with academic centres that have expertise in single-cell sequencing and analysis of sequencing data, as well as spatial transcriptomics, should be part of the successful consortium.

The size and budget allocation of the applicant consortia should reflect the expertise needed to achieve the proposed objectives within the indicated budget while ensuring the 'manageability' of the consortium as well as efficient and effective teamwork. Therefore, the number of members of the applicant consortium needs to be thoroughly justified in the proposal and all partners involved should make a significant contribution to the proposed work.

Specifically, the applicant consortium should be able to demonstrate (through publications, consortia leadership, local capability development, grants):

- the technical expertise to carry out single-cell sequencing using technology platforms that are mature, well-supported and widely used, as well as technical expertise in spatial transcriptomics techniques;
- expertise in the development of new versions of single cell technology, plus a demonstrated ability to evaluate and rapidly internalise new single cell techniques;
- expertise in parallel single-cell sequencing technologies that capture epigenome-transcriptome interactions e.g. scNMT-seq (chromatin accessibility, methylation and transcription sequencing) [8];
- expertise in the bioinformatics analysis of single-cell sequencing data, spatial transcriptomics, gene regulatory network reconstruction, and computational approaches to novel target identification;
- expertise in the data integration of single-cell RNA-seq datasets across multiple platforms, individuals, and centres [9];
- to support standardisation of data, adherence to the FAIR principles ('findable, accessible, interoperable and reusable') [10];
- where there is a proposal for the applicant consortium to provide single-cells for sequencing, it should demonstrate the ability to deliver single cells from the relevant human (clinical, PDO) and mouse (PDX, GEMM, syngeneic) tumour models and from pre-treatment and treated models, with fixation/storage as specified in the consortium SOPs. Applicants should demonstrate the feasibility of collecting the outlined number of samples based on selected cancer types/therapies (see Deliverables);

- ability to coordinate a large research initiative and to create a scientific network.

The applicant consortium is expected to set up a governance structure that includes the necessary project management skills suitable for the consortium and activities. This could be ensured by one of the publicly funded partners, who in this case would need to have significant project management and coordination skills as well as the necessary experience in supporting complex – per size and composition – consortia in IMI/EU funded projects.

Considerations for the outline of project work plan

In their stage 1 proposals applicants should:

- Give due visibility to data management; dissemination, exploitation and sustainability; and communication activities. This should include the allocation of sufficient resources for these tasks which will be further developed in the stage 2 proposal;

- Consider including a strategy for ensuring the translation of the project results to drug development, regulatory/ health technology assessment (HTA) settings (e.g. through scientific advice/ qualification advice /opinion, etc.), clinical and healthcare practices and/or decision-making processes.

Suggested architecture

The public partners are expected to carry out most of the sequencing work whereas industry partners contribute in kind in the form of single cells (collected specifically for this programme) so that work can be carried out centrally with clear streamlined processes. Both industry and public partners will collaborate in the analysis of the data. Steering of the individual work packages and content decisions will be done jointly by the public and private partners.

For clarity, there will also be an opportunity for non-industry consortium partners to provide samples from up to 20 drug/tumour combinations, assuming that the models are appropriate with a hypothesis relationship with drugs or tumours being investigated by the consortium as agreed by the portfolio management process.

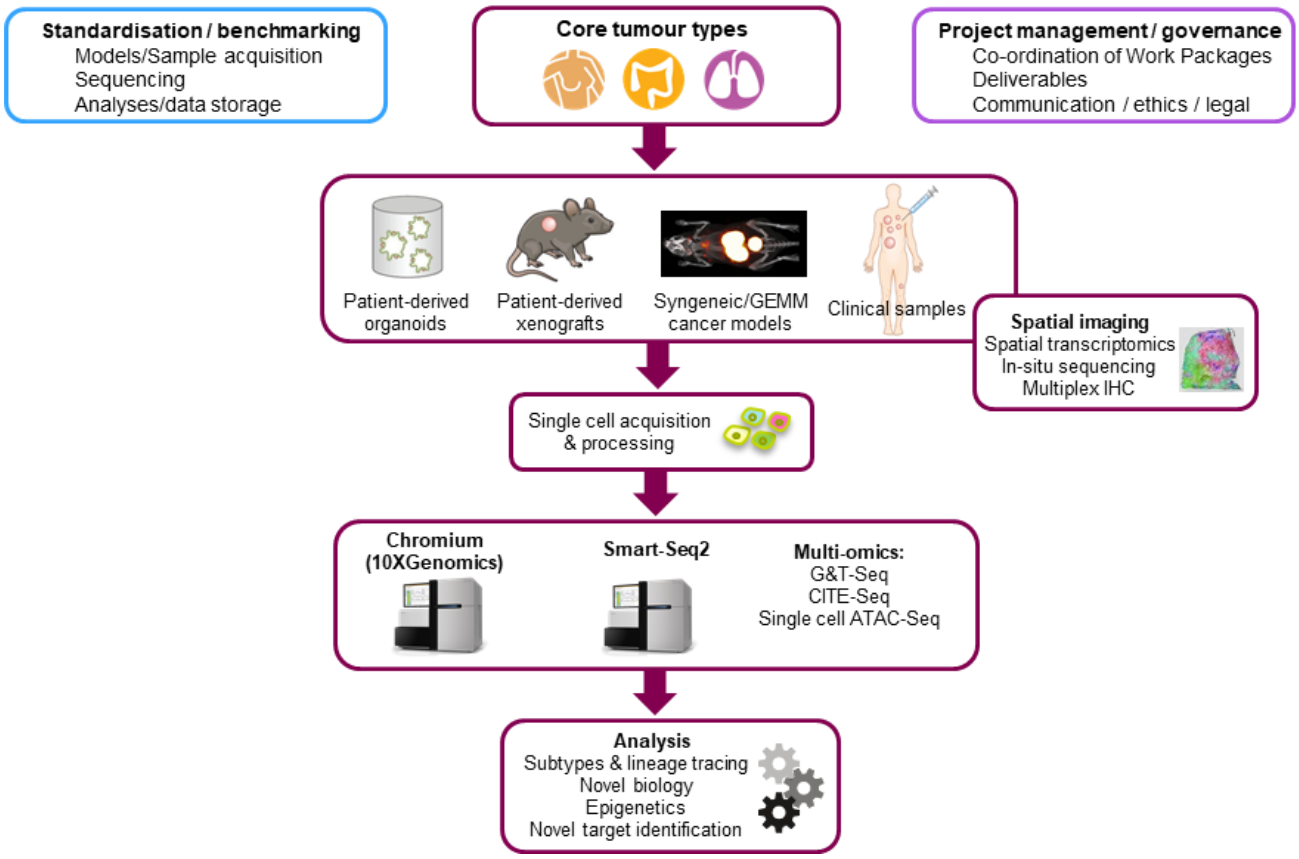

Figure 2. Work flow of the project. The various activities captured here form the basis for the 7 Work Packages detailed below.

Work Package 1 – Project management, coordination and long-term sustainability

Description: The goals of this work package are to support optimal project management in compliance with scientific and ethical standards, implement the strategy of the consortium, and ensure the appropriate dissemination of the project progress and outcomes.

Industry contribution: Project leader, coordination across different work packages (including overall scientific and strategic oversight).

Expected applicant consortium contribution: Project coordinator, project management expertise.

Work Package 2 – Portfolio management, coordination and prioritisation

Description: To direct and support optimal project delivery across tumour types, ensuring sufficient overlap that results are interpretable without wasteful duplication. To provide a mechanism for the identification and integration of bespoke test systems so that they have maximal impact.

- Proposed objectives:
    - set up a review and selection process for models to resolve duplication between tumour type/drug treatments and ensure quality and technical standards (as defined in WP3) are met;

- provide additional models– PDO, PDX, GEMMs or patient samples – complementary to the EFPIA set.

Industry contribution: Portfolio leader, technical advice on the quality of studies that are proposed. Portfolio management expertise. Allocation and prioritisation of studies in a transparent way. Allocation of time and resources for appropriate technical development.

Expected applicant consortium contribution: Portfolio coordinator, technical advice on the quality of studies that are proposed. Allocation and phasing/timing of studies.

Work Package 3 – Standardisation and benchmarking of standard operating procedures

Description: To ensure the standardisation and benchmarking of protocols, raw and meta-data used across the consortium, both for sequencing technologies and analytics.

Industry contribution: Knowledge of PDO, PDX, GEMM and syngeneic models.

Expected applicant consortium contribution: Expertise in single-cell sequencing protocols and current gold standard analysis techniques, including data integration across platforms and studies.

Work Package 4 – Single cell acquisition from models of tumour plasticity

Description: The acquisition of high-quality single cells from the relevant tumour models that are suitable for single-cell sequencing.

Industry contribution: Expertise in the use of biological models for single cell provision (PDO, PDX, GEMM, Syngeneic). Drug treatment regimes *in vivo*. Industry will be the source of most of the single cells for study.

Expected applicant consortium contribution: Knowledge of best practice for processing single cells. Methods to avoid batch effects in collection and processing. Provision of single cells from additional pre-clinical and clinical models where appropriate.

Work package 5 – Single-cell sequencing

Description: The generation of high quality single-cell sequencing data from single cells acquired from each study

- Proposed objectives should include:
  - high quality single-cell sequencing data in a format suitable for data Integration across studies (see work package below), using complementary technology platforms that are mature, well-supported and widely used;
  - specific single-cell sequencing technologies that address aspects of the epigenetic landscape of single cells (e.g. scATAC-seq) or cell surface protein expression (e.g. CITE-seq);
  - evaluation and internalisation/uptake of new and emerging single cell techniques.

Industry contribution: Single-cell sequence data from internal platforms where available. Data upload and annotation from scRNAseq experiments.

Expected applicant consortium contribution: Expertise in single-cell sequencing, including alternate non-transcriptomic platforms (e.g. scATAC-seq, CITE-seq, G&T-seq) that are nominated to be included in specific studies. Expertise in evaluating new techniques and platforms. Data upload and annotation from scRNAseq experiments.

Work package 6 – Spatial imaging technologies

Description: To add spatial context to single-cell sequence data using a variety of spatial imaging technologies in order to validate the observed transcriptional changes from the single-cell sequencing studies, and to understand the value of adding spatial orientation to these single cell observations. Apply to clinical samples as well as relevant pre-clinical models.

Industry contribution: Collection and curation of material from pre-clinical models as well as clinically relevant patient samples for analysis.

Expected applicant consortium contribution: Expert labs in spatial imaging of protein and transcript expression at single cell resolution.

Work package 7 – Analytical methods & integration of single cell datasets

Description:

a) To optimise/develop analytical methods and define the gold standard practice of single-cell sequencing data.
b) The integration of single-cell RNA-sequencing data and metadata/annotation across multiple platforms (including epigenetic), individuals, and studies and in addition to transfer information between datasets and spatial methods. Ultimately, to enable a more comprehensive comparison of cell populations in complex biological systems.

- Proposed objectives:
    - characterise the specific biological programs operative in Drug Tolerant Persister cells using single-cell sequencing datasets;
    - integrate single-cell sequencing data across studies and technologies to capture common biological processes;
    - identify novel drug targets.

Industry contribution: Pharma experience in novel target identification ligand affinity and druggability. IT expertise to support the data platform and analytics tools and ensure compatibility with industry requirements (e.g. FAIR requirements).

Expected applicant consortium contribution: Analysis expertise in single-cell sequencing data, both scRNA-seq as well as protocols addressing the epigenome. Expertise in data integration techniques, data storage solutions that allow interoperability. Academic experience in novel target ID.

Work package 8 – Communication/dissemination and ethics

Description:

a) to ensure effective communication and dissemination both within the consortium during the action, as well as external communication as appropriate with external synergy partners and stakeholders;
b) public engagement;
c) where clinical samples are to be used, appropriate planning and execution of correctly consented studies with corresponding ethical oversight and approval.

We anticipate that both industry and academic consortium partners will need to take full ownership and participation in this work package.

Additional considerations to be taken into account at the stage 2 full proposal

At stage 2, the consortium selected at stage 1 and the predefined industry consortium jointly submit the full proposal developed in partnership. The full proposal is based upon the selected short proposal at stage 1.

In the spirit of the partnership, and to reflect how IMI2 JU call topics are built on identified scientific priorities agreed together with EFPIA beneficiaries/large industrial beneficiaries, these beneficiaries intend to significantly contribute to the programme and project leadership as well as project financial management. The final architecture of the full proposal will be defined by the participants in compliance with the IMI2 JU rules and with a view to the achievement of the project objectives. The allocation of a leading role within the consortium will be discussed in the course of the drafting of the full proposal to be submitted at stage 2. To facilitate the formation of the final consortium, until the roles are formally appointed through the consortium agreement, the proposed project leader from among EFPIA beneficiaries/large industrial beneficiaries shall facilitate an efficient negotiation of project content and required agreements. All beneficiaries are encouraged to discuss the project architecture and governance and the weighting of responsibilities and priorities therein.

Data management

In their stage 2 proposal, applicants should give due visibility to data management including use of data standards. A full 'data management plan' (DMP) as a distinct deliverable must be delivered within the first 6 months of the project. The DMP needs to be kept up to date with the needs of the project and as such be updated as necessary during its lifetime.[38]

Dissemination, exploitation and sustainability of results

In their stage 2 proposal, applicants must provide a draft plan for dissemination and exploitation, including sustainability of results. A full plan as a distinct deliverable must be delivered within the first 6 months of the project[39], and updated during the project lifetime. It could include identification of:

- different types of exploitable results;
- potential end-users of the results;
- results that may need sustainability and proposed sustainability roadmap solutions.

Sufficient resources should be foreseen for activities related to dissemination and exploitation, including the plan for the sustainability of the project results. This may involve engaging with suitable biological and medical sciences research infrastructures (RIs).[40]

Communication

The proposed communication measures for promoting the project and its findings during the period of the grant should also be described and could include a possible public event to showcase the results of the project.

[38] Guidance on data management is available at http://ec.europa.eu/research/participants/docs/h2020-funding-guide/cross-cutting-issues/open-access-data-management/data-management_en.htm
[39] As an additional dissemination obligation under Article 29.1 of the IMI2 Grant Agreement will apply
[40] http://www.corbel-project.eu/about-corbel/research-infrastructures.html

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Topic 5: Proton versus photon therapy for oesophageal cancer – a trimodality strategy

Topic details

Topic code	IMI2-2020-20-05
Submission and evaluation process	2 stages
Action type	Research and Innovation Action (RIA)
IMI2 Strategic Research Agenda - Axis of Research	Adoption of innovative clinical trial paradigms
IMI2 Strategic Research Agenda - Health Priority	Cancer

Specific challenges to be addressed by public-private collaborative research

Alongside chemotherapy and surgery, radiotherapy (RT) has evolved to become one of the essential therapies for the treatment of cancer. However, radiotherapy is not suitable for all cancer types, and when used, the potential for negative side effects to surrounding organs can limit the dose administered leading to longer treatment times and reduced effectiveness. By delivering a high radiation dose, more precisely focused on the tumour site, proton therapy (PT) has the potential to reduce these adverse events and provide better outcomes for cancer patients.

Although the number of patients treated annually with PT is increasing, the clinical evidence supporting its effectiveness remains limited due to the lack of large multi-centre studies. There is a critical need[1] for high quality evidence from multi-centre trials to determine the potential role of PT for various cancer indications and to allow a consensus to be reached across Europe on the most suitable indications.

A robust evidence base on the effectiveness of PT has the potential to open a new treatment modality for cancers with currently very low survival rates, for example oesophageal cancer. Oesophageal cancer is the seventh most common cancer worldwide, with more than 570 000 new cases per year leading to more than 500 000 cancer deaths annually [2]. Until recently, surgery was the main treatment for patients with localised disease. In 2012, the results of the Chemoradiotherapy for Oesophageal Cancer Followed by Surgery Study (CROSS) randomised trial demonstrated that adding neoadjuvant chemo-radiation to surgery results in a beneficial effect on pathological complete response (pCR) and survival compared to surgery alone. However, with a pCR of 30 % and a five-year overall survival rate of 45-50 %, there is still a large unmet need.

The unique properties of PT allow oesophageal cancer patients the opportunity to receive more conformal radiotherapy with the possibility of reducing the dose to the surrounding normal organs including the lungs, heart and liver [5][6]. Treatment of oesophageal cancer patients with PT is under evaluation by several institutions. Recent publications present the role and the potential benefits PT offers to those patients [7]-[19] and could lead to better patient outcomes. Nevertheless, none of those publications provide level 1 evidence.

To build a robust evidence base to assess the potential of PT in oesophageal and other cancers, multi-centre international trials have to take place. The current diversity of reimbursement and coverage policies across the EU makes these trials difficult. A public-private collaboration of proton therapy oncologists, treatment centres, software developers and equipment manufacturers is needed to define a methodology to conduct clinical trials in PT at a European scale. In addition, a key factor is the generation of robust clinical evidence which is neutral and unbiased. A clinical trial conducted in a European framework, in a collaboration between industry and public partners, has an inherent degree of independence and neutrality required by the highest standards of clinical research.

Scope

The main objective of this topic is to examine the value of proton therapy as a treatment modality through a clinical study in oesophageal cancer. The study will compare outcomes between pencil-beam scanning proton therapy and intensity-modulated radiation therapy (IMRT). The study will determine if proton therapy in a trimodality (radiotherapy-chemotherapy-surgery) treatment;

(i) reduces treatment-related cardio-pulmonary toxicity;

(ii) increases loco-regional tumour control and pathological complete response and the influence of dose escalation;

(iii) improves disease-free and overall survival.

Oesophageal cancer is chosen due to its relatively high occurrence in the population and the possibility to extend findings to other cancer types.

A second objective is to use the evidence generated during the oesophageal cancer study to reach a consensus on which methodology is most suitable to evaluate PT treatment for other indications. To facilitate this objective, cost-effectiveness data should be collected during the duration of the action. This objective should be supported by engaging with selected stakeholders as advisors such as the broader oncology community including oncologists (e.g. through relevant European networks), healthcare providers, health technology assessment (HTA) agencies, payers, and patient associations. In addition, the findings of the proposed project should be disseminated via publications, presentations at relevant conferences, and other suitable dissemination methods.

Expected key deliverables

To achieve the objectives, the proposed project should deliver:

- A **study protocol** for a non-blinded multi-centre randomised phase III study on a statistically significant number of oesophageal cancer patients. Patients should be treated with pre-operative concomitant chemo-radiation and randomised between irradiation to be delivered as either RT or PT. This protocol should include a rapid, clinically relevant primary endpoint to allow effectiveness to be demonstrated as early as possible.
- **Annual updates** on the progress of the study to include:
  - recruitment reports;
  - data collection reports;
- A final **dataset** collected in compliance with the FAIR principles;[41]
- A proposal for a European methodology for multi-centric clinical trials in proton therapy;
- Publications & conference presentations on the results of the study;
- Publication and active dissemination of a **summary of results** to relevant authorities (e.g. healthcare providers, HTA bodies, payers.

[41] Findable, Accessible, Interoperable, Reusable, see: https://www.force11.org/group/fairgroup/fairprinciples

Expected impact

In their proposals, applicants should describe how the outputs of the project will contribute to the following impacts and include wherever possible baseline, targets and metrics to measure impact:

- The outcome of this research is potentially practice-changing as it may define a new and improved standard for the treatment of oesophageal cancer patients and potentially patients with other cancer indications.
- The morbidity data from the study will allow better understanding of the dose-volume relationships for normal tissue complications, enabling refined selection of patients for proton therapy in the future.
- The results should allow health authorities and healthcare providers to improve the quality of care through better evidence of benefits and patient outcomes and support reimbursement decisions.

In their proposals, applicants should outline how the project plans to leverage the public-private partnership model to maximise impacts on innovation, research & development; regulatory, clinical and healthcare practices, as relevant. This could include a strategy for the engagement with patients, healthcare professional associations, healthcare providers, regulators, HTA agencies, payers, etc., where relevant. An advisory group including these stakeholders should be set up.

In their proposals, applicants should outline how the project will:

- Manage research data including use of data standards.[42]
- Disseminate, exploit, and sustain the project results. This may involve engaging with suitable biological and medical sciences research infrastructures.[43]
- Communicate the project activities to relevant target audiences.

Potential synergies with existing consortia

Synergies and complementarities should be considered with relevant national, European and non-European initiatives (including suitable biological and medical sciences research infrastructures[48]) in order to incorporate past achievements, available data and lessons learnt where possible, thus avoiding unnecessary overlap, and duplication of efforts and funding.

Industry consortium

The industry consortium includes the following IMI2 JU Associated Partners:

- Ion Beam Applications SA
- Varian Medical Systems Particle Therapy GmbH

The industry consortium plans to contribute the following expertise and assets:

- in-depth knowledge of proton therapy solutions, including equipment and treatment planning software;

[42] Guidance on data management is available at https://ec.europa.eu/research/participants/docs/h2020-funding-guide/cross-cutting-issues/open-access-dissemination_en.htm
[43] http://www.corbel-project.eu/about-corbel/research-infrastructures.html

- contribution to the development of dissemination and communication materials;
- a financial contribution (detailed in the indicative budget section) to cover study related expenses.

Indicative duration of the action

The indicative duration of the action is 60 months.

This duration is indicative only. At stage 2, the consortium selected at stage 1 and the predefined industry consortium may jointly agree on a different duration when submitting the stage 2 proposal.

Indicative budget

The financial contribution from IMI2 JU is a maximum of EUR 1 500 000.

The indicative in-kind and financial contribution from the IMI2 JU Associated Partners is EUR 1 500 000, which includes a financial contribution of EUR 1 000 000.

Therefore, the stage 1 applicant consortium is expected to allocate up to **EUR 2 500 000** (IMI2 JU financial contribution + IMI2 Associated Partner financial contribution) in the budget of their stage 1 proposal. The allocation of the IMI2 Associated Partner financial contribution of EUR 1 000 000 to cover study related expenses may be fine-tuned by the full consortium when preparing the stage 2 proposal.

Expertise and resources expected from applicants at stage 1

The stage 1 applicant consortium is expected, in the submitted short proposal, to address all the objectives and key deliverables of the topic, taking into account the expected contribution from the industry consortium which will join at stage 2 to form the full consortium. The stage 1 submitted short proposals should include suggestions for creating a full proposal architecture

This may require mobilising, as appropriate the following expertise:

- Extensive experience in the application of radiotherapy and proton therapy;
- Clinical expertise in the area of oesophageal cancer;
- Proven ability to design and conduct relevant studies to obtain high quality clinical data;
- Experience in dealing with the legal and ethical challenges associated with integrating multi-centre patient-derived data, as well as data-processing and management practices (e.g. privacy). Candidates should mention how they plan to integrate possible bias resulting from centre-specificity in the data analysis;
- Strong project management expertise;
- Access to HTA expertise and expertise from oesophageal patients or patient groups in an advisory capacity would be considered an advantage.

The size of the consortium should be proportionate to the objectives of the topic while ensuring its manageability.

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

- Participating centres with the ability to include a statistically significant number of patients (with a minimum of 20 patients per centre) over the duration of the action;
- Applicants must demonstrate that they can secure access to:

- relevant, state-of-the art radiotherapy and proton therapy equipment;
- data centre and study monitoring infrastructure.
- Access to historical data that can be incorporated in the analysis would be considered an advantage. If relevant, applicants should indicate the volume and type of data they could bring to the project in their proposals.

Considerations for the outline of project work plan

In their stage 1 proposals applicants should:

- Provide the outline of a study protocol for the non-blinded multi-centre randomised phase III study. This should include a justified sample size of oesophageal cancer patients to ensure statistical significance. Applicants should also propose a rapid, clinically relevant primary endpoint to allow effectiveness to be demonstrated as early as possible.
- Give due visibility on data management; dissemination, exploitation and sustainability; and communication activities. This should include the allocation of sufficient resources for these tasks which will be further developed in stage 2 proposal.
- Consider including a strategy for ensuring the translation of the projects results to HTA settings (e.g. through scientific advice/ qualification advice /opinion, etc.), clinical and healthcare practices and/or decision-making processes.

Additional considerations to be taken into account at the stage 2 full proposal

At stage 2, the consortium selected at stage 1 and the predefined industry consortium jointly submit the full proposal developed in partnership. The full proposal is based upon the selected short proposal at stage 1.

In the spirit of the partnership, and to reflect how IMI2 JU call topics are built on identified scientific priorities agreed together with the IMI2 Associated Partners, these beneficiaries intend to significantly contribute to the programme and project leadership as well as project financial management. The final architecture of the full proposal will be defined by the participants in compliance with the IMI2 JU rules and with a view to the achievement of the project objectives. The allocation of a leading role within the consortium will be discussed in the course of the drafting of the full proposal to be submitted at stage 2. To facilitate the formation of the final consortium, until the roles are formally appointed through the consortium agreement, the proposed project leader from among IMI2 Associated Partners 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.

Data management

In their stage 2 proposal, applicants should give due visibility to data management including use of data standards. A full 'data management plan' (DMP) as a distinct deliverable must be delivered within the first 6 months of the project. The DMP needs to be kept up to date with the needs of the project and as such be updated as necessary during its lifetime.[44]

Dissemination, exploitation and sustainability of results

[44] Guidance on data management is available at http://ec.europa.eu/research/participants/docs/h2020-funding-guide/cross-cutting-issues/open-access-data-management/data-management_en.htm

In their stage 2 proposal, applicants must provide a draft plan for dissemination and the exploitation, including sustainability of results. A full plan as a distinct deliverable must be delivered within the first 6 months of the project.[45], and updated during the project lifetime and could include identification of:

- different types of exploitable results;
- potential end-users of the results;
- results that may need sustainability and proposed sustainability roadmap solutions.

Sufficient resources should be foreseen for activities related to dissemination and exploitation, including the plan for the sustainability of the project results. This may involve engaging with suitable medical sciences research infrastructures (RIs).[46]

Communication

The proposed communication measures for promoting the project and its findings during the period of the grant should also be described.

[45] As an additional dissemination obligation under Article 29.1 of the IMI2 Grant Agreement will apply
[46] http://www.corbel-project.eu/about-corbel/research-infrastructures.html

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Topic 6: Handling of protein drug products and stability concerns

Topic details

Topic code	IMI2-2020-20-06
Action type	Research and Innovation Action (RIA)
Submission and evaluation process	2 stages
IMI2 Strategic Research Agenda - Axis of Research	Patient-tailored adherence programmes.
IMI2 Strategic Research Agenda - Health Priority	Other

Specific challenges to be addressed by public-private collaborative research

In the past two decades, protein pharmaceuticals have become the fastest growing class of therapeutics owing to their beneficial impacts on the treatment of severe and life-threatening conditions and diseases. Development and manufacturing of protein pharmaceuticals is, however, challenging and requires overcoming various manufacturing hurdles such as issues with the purity of the protein product. The safety and efficacy of protein pharmaceuticals depend on their purity. Impurities in marketed protein pharmaceuticals may be present due to limitations in manufacturing processes or may also be a result of degradation processes occurring not only during manufacturing, but also during long-term storage of the bulk drug substance and/or final drug product (DP) [1]. Impurities within therapeutic protein products can cause severe adverse drug reactions (ADRs) in patients, that may be acute, as is the case for infusion-induced anaphylaxis and pseudo-allergy responses, which may even result in patient death, or long-term like unwanted immunogenicity.

Physical aggregation and chemical degradation can occur throughout a protein product's life history, and even modest environmental stresses can cause extensive damage. Development of effective upstream and downstream processes as well as robust formulations and filling processes are crucial for maintaining product quality, and hence, for the safety and efficacy of protein pharmaceuticals. The pharmaceutical industry has made great progress in improving bulk and DP manufacturing as well as storage and transportation conditions to minimise the level of degradation. However, there exists only low control over the many factors that may affect product quality after the protein pharmaceuticals are released and shipped. Routine handling or unintentional mishandling of therapeutic protein products may cause protein degradation that remains unnoticed but can potentially compromise the clinical safety and efficacy of the product [2]. Storage of the DP outside the recommended condition ranges, use of incompatible supply and/or technology, careless handling of drug during preparation for administration and during delivery to patient are just a few examples of such (mis)handling [3]. When it comes to handling of DP by patients, the social, cultural, logistical and environmental differences between different geographies and cultures can also impact the handling conditions.

There has been increasing expression of concern in the past decade regarding the significance of the post-production handling of protein pharmaceuticals. At the same time, studies revealed that the consequences of presence of impurities in DP can be severe. Potentially high likelihood and/or severity in consequences in combination with the low level of control over the processes by the industry make these concerns a significant risk that needs to be addressed in a public-private partnership that includes all relevant stakeholders.

DPs as described above are handled in pharmacies, hospitals and by patients after they have been released by the manufacturer. Consequently, although manufacturers can influence the process by making more robust DPs that that can withstand a certain level of stress during usage, and by providing training, the pharmaceutical industry does not have full control over handling processes. Collaboration with other stakeholders including those in the public sector is therefore necessary to address handling conditions, as already outlined in literature [1]. Indeed, understanding the handling conditions requires assistance from experts in pharmacies and medical institutions as

well as organisations that can gather and document information on the patients' side, e.g. academic and research organisations or structured patients communities, all of which are envisioned to become part of the applicant consortium.

Alongside a good understanding of the various (and probably most common) handling steps and the stresses they imply for protein drugs, there is a need for research in estimating the impact of each handling step on DP quality and potentially the safety and efficacy of the drug.

It is only through the above-mentioned process that the risky handling steps are identified and addressed. Working out a meaningful framework for sharing the information between the manufacturer and the healthcare professionals and/or patients (that might go beyond the current communication channels and exchange of standard pharmacy manuals and training) is only possible through close collaboration among all involved. A consortium comprised of the pharmaceutical industry, medical institutions, pharmacies, academia and SMEs and potentially patient organisations can fully address all the aspects of the complex topic and help to develop technological and process solutions.

Scope

The first objective of this topic is **to improve the understanding of real-world stressful drug product handling steps** and their **effects on protein product quality**.

- All protein DPs are considered to be within the scope of the topic though a subset of use cases may be identified upon formation of the full consortium during the stage 2 submission;
- All handling steps for preparation, transport and administration should be addressed:
    - Studying the effects of the handling steps on drug product quality is in the scope of the project;
    - Supplies that are used for handling of the protein pharmaceuticals are also to be investigated and evaluated. Evaluation of new technologies that are used to handle protein pharmaceuticals such as closed-system transfer devices are of interest;
    - Handling practices include the ones that are performed by healthcare professionals in hospital and compounding pharmacies and the ones in hands of patients. The understanding should be as thorough as possible and may be , obtained by the use of new technologies and digital tools that record details visually or by sensors of conditioning parameters during storage and administration processes, among other methods;
    - Routine handling procedures, i.e. the ones that are currently used as standard procedures for protein drug products in pharmacies and by patients should be addressed.
- These risks associated with the handling of protein DPs should be assessed and potential solutions developed;
- Mishandling cases with high level of likelihood or severe impacts should also be examined.

The second objective of this topic is to use this understanding **to develop guidelines and operating processes** to **improve the DP robustness and pharma processes**, and to develop **more efficient training** (see Figure 1)

- Improving the in-use studies and other processes in development of protein pharmaceuticals is in the scope of the topic;
- Innovative solutions that help to ensure the stability of DP during handling are welcome;
- Improving training materials and improving handling culture are in the scope of the topic. Training should target both professionals and patients;

- Utilisation of technologic tools (video, webinar, online media and creative manuals) for the development of novel training methods and materials is within the scope of the topic.

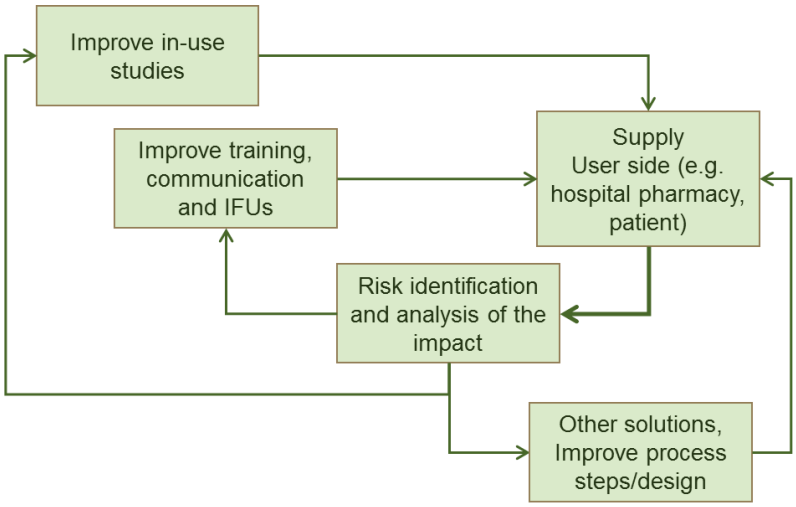

Figure 1: Good understanding of drug product handling at the user side can lead to the formulation of various solutions

Expected key deliverables

The expected deliverables from the action are the following:

Clear insight into the drug product handling procedures and their impact:

- Detailed outlining of handling procedures in pharmacies and homes, including all steps (irrespective of the delivery method/device);
- Evaluation of the real impact of handling steps on the stability of protein DP;
- Outlining of the protein drug preparation and administration supplies available to pharmacies and clinics considering the major geographic markets investigated in the project;
- Assessment of the potential impacts on delivered dose;
- Estimation of potential impacts on clinical safety and efficacy.

Improved protein drug product development processes

- Tools and methods to improve DP robustness (rational and realistic in-use studies);
- Determination of critical parameters, improvements in processes and definition of DP handling requirements.

Improved training on drug product handling

- Improved professional user training including development of training materials (e.g. videos) that can be used to educate and as reference in pharmacy manuals/instructions;
- Improved patient/caregiver training (at both strategy and execution levels).

Training materials and tools should be compatible with the needs of the different target groups. For instance, the training material for patients should have different characteristics than the SOPs and tools used for professional personnel in a pharmacy.

These key deliverables lead to improvements in assessment and management of the risks associated with handling of protein drug products and improved efficacy and safety of protein drug products for patients.

Expected impact

In their proposals, applicants should describe how the outputs of the project will contribute to the following impacts and include wherever possible baseline, targets and metrics to measure impact:

- Through this project, a better understanding of the handling procedures of protein DPs and associated stresses in hospitals and in the hands of patients will be obtained. The project will assess the risks associated with these handling steps and provide solutions to ensure high-quality delivery and administration of protein DP;
- The project will help participating pharmaceutical companies to improve their processes with regards to the development of more robust DPs that can withstand handling stresses;
- At the same time, access to the resulting improved methods to influence the handling culture can be used by both the private and public sectors in the interest of patients. Foremost amongst the expected impacts is the improved training for professionals and patient/caregivers to ensure the stability of protein DP. This will have global effects on the manufacturing side as well as the user side at pharmacies, hospitals and with patients, thus providing benefits to all healthcare stakeholders;
- Generation of knowledge in the area of stress-stability will help all the stakeholders involved and can be directly applied to the design of the processes and addressing important but challenging issues around the development of therapeutics and delivery to patients;
- Overall, the project is expected to lead to improvements in the safety and efficacy of protein drug therapies.
- While specific use cases may be chosen upon formation of the full consortium during the stage 2 submission, the results of the project should apply as broadly as possible to all protein DPs.

In their proposals, applicants should outline how the project plans to leverage the public private partnership model to maximise impact on innovation, research & development; regulatory, clinical and healthcare practices, as relevant. This could include a strategy for engagement with patients, healthcare professional associations, healthcare providers, regulators, health technology assessment agencies, payers etc., where relevant.

In addition, applicants should describe how the project will impact on competitiveness and growth of companies, including SMEs;

In their proposals, applicants should outline how the project will:

- manage research data, including use of data standards[47];
- Disseminate, exploit, and sustain the project results. This may involve engaging with suitable biological and medical sciences research Infrastructures[48];

[47] Guidance on data management is available at http://ec.europa.eu/research/participants/docs/h2020-funding-guide/cross-cutting-issues/open-access-data-management/data-management_en.htm
[48] http://www.corbel-project.eu/about-corbel/research-infrastructures.html

- Communicate the project activities to relevant target audiences.

Potential synergies with existing consortia

Synergies and complementarities should be considered with relevant national, European and non-European initiatives (including suitable biological and medical sciences research infrastructures[48]) in order to incorporate past achievements, available data and lessons learnt where possible, thus avoiding unnecessary overlap, and duplication of efforts and funding.

Industry consortium

The industry consortium is composed of the following EFPIA partners:

- Sanofi (lead)
- AbbVie
- AstraZeneca
- Boehringer Ingelheim
- Lonza
- Merck
- Pfizer
- Roche
- Teva

The industry consortium (EFPIA) plan to contribute the following expertise and assets:

- the development and manufacture of biologics;
- formulation and process development;
- clinical processes;
- protein and biologics analytics;

as well as interaction with public health stakeholders and authorities.

Indicative duration of the action

The indicative duration of the action is 48 months.

This duration is indicative only. At stage 2, the consortium selected at stage 1 and the predefined industry consortium may jointly agree on a different duration when submitting the stage 2 proposal.

Indicative budget

The financial contribution from IMI2 JU is a maximum of EUR 3 140 000.

The indicative in-kind and financial contribution from EFPIA partners is EUR 3 959 500.

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

Expertise and resources expected from applicants at stage 1

The stage 1 applicant consortium is expected, in the submitted short proposal, to address all the objectives and key deliverables of the topic, taking into account the expected contribution from the industry consortium which will join at stage 2 to form the full consortium.

The stage 1 submitted short proposals should include suggestions for creating a full proposal architecture.

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

- A global understanding of the protein DP handling, attained from first-hand knowledge;
- The capacity to investigate the real-world handling procedures in hospitals, pharmacies and at homes and assess their impact on the stability, and potentially safety and efficacy, of protein pharmaceuticals;
- Expertise in the available methods of communication and training for handling of protein DPs and a strong capacity to come up with novel training concepts and materials;
- The ability to implement new technologies to achieve relevant data for handling conditions and also to produce novel and efficient training materials and methods;
- Support for industry partners to address the challenge and influence the process of handling protein DP;
- The participation of SMEs with novel monitoring concepts and training tools is highly encouraged.

The size of the consortium should be proportionate to the objectives of the topic while ensuring its manageability.

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

- Resources, including data from past investigations or existing frameworks on DP handling;
- Technologies from SMEs that have been developed for other purposes but can be of use for this project;
- Networks and ecosystems the applicants are already members of.

Considerations for the outline of project work plan

In their stage 1 proposals, applicants should:

- Give due visibility to data management; dissemination, exploitation and sustainability; and communication activities. This should include the allocation of sufficient resources for the tasks which will be further developed in the stage 2 proposal;
- Consider including a strategy for ensuring the translation of the projects results to drug development, regulatory/ Health Technology Assessment settings (e.g. through scientific advice/ qualification advice /opinion, etc.), clinical and healthcare practices and/or decision-making processes.

- Applicants should not select specific protein DPs at stage 1. A subset of use cases may be identified upon formation of the full consortium during the stage 2 submission.

Additional considerations to be taken into account at the stage 2 full proposal

At stage 2, the consortium selected at stage 1 and the predefined industry consortium jointly submit the full proposal developed in partnership. The full proposal is based upon the selected short proposal at stage 1.

In the spirit of the partnership, and to reflect how IMI2 JU call topics are built on identified scientific priorities agreed together with EFPIA beneficiaries/large industrial beneficiaries, these beneficiaries intend to significantly contribute to the programme and project leadership as well as project financial management. The final architecture of the full proposal will be defined by the participants in compliance with the IMI2 JU rules and with a view to the achievement of the project objectives. The allocation of a leading role within the consortium will be discussed in the course of the drafting of the full proposal to be submitted at stage 2. To facilitate the formation of the final consortium, until the roles are formally appointed through the consortium agreement, the proposed project leader from among EFPIA beneficiaries/large industrial beneficiaries shall facilitate an efficient negotiation of project content and required agreements. All beneficiaries are encouraged to discuss the project architecture and governance and the weighting of responsibilities and priorities therein.

Data Management

In their stage 2 proposal, applicants should give due visibility to data management, including the use of data standards. A full 'data management plan' (DMP) as a distinct deliverable must be delivered within the first 6 months of the project. The DMP needs to be kept up to date with the needs of the project and as such be updated as necessary during its lifetime.[49]

Dissemination, exploitation and sustainability of results

In their stage 2 proposal, applicants must provide a draft plan for dissemination and the exploitation, including sustainability of results. A full plan as a distinct deliverable must be delivered within the first 6 months of the project[50] and updated during the project lifetime and could include identification of:

- Different types of exploitable results;
- Potential end-users of the results;
- Results that may need sustainability and proposed sustainability roadmap solutions.

Sufficient resources should be foreseen for activities related to dissemination and exploitation, including the plan for the sustainability of the project results. This may involve engaging with suitable biological and medical sciences Research Infrastructures (RIs).[51]

Communication

The proposed communication measures for promoting the project and its findings during the period of the grant should also be described and could include a possible public event to showcase the results of the project.

[49] Guidance on data management is available at http://ec.europa.eu/research/participants/docs/h2020-funding-guide/cross-cutting-issues/open-access-data-management/data-management_en.htm
[50] As an additional dissemination obligation under Article 29.1 of the IMI2 Grant Agreement will apply
[51] http://www.corbel-project.eu/about-corbel/research-infrastructures.html

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Conditions for this Call for proposals

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

The following conditions shall apply to this IMI2 JU Call for Proposals:

Applicants intending to submit a Short proposal in response to the IMI2 Call 20 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-IMI2-2020-20-two-stage**
Type of actions	**Research and Innovation Action (RIA)**
Publication Date	**21 January 2020**
Stage 1 Submission start date	**21 January 2020**
Stage 1 Submission deadline	**21 April 2020 (17:00:00 Brussels time)**
Stage 2 Submission deadline	**05 November 2020 (17:00:00 Brussels time)**

Indicative Budget

From EFPIA companies and IMI2 JU Associated Partners	EUR 140 209 500
From the IMI2 JU	EUR 133 009 000

Call Topics

IMI2-2020-20-01 **Early diagnosis, prediction of radiographic outcomes and development of rational, personalised treatment strategies to improve long-term outcomes in psoriatic arthritis**	The indicative contribution from EFPIA companies is EUR 13 880 000 The financial contribution from IMI2 JU is a maximum of EUR 10 211 000	Research and Innovation Action (RIA) Two-stage submission and evaluation process. Only the applicant consortium whose proposal is ranked first at the first stage is invited for the second stage.

IMI2-2020-20-02 **Innovations to accelerate vaccine development and manufacture**	The indicative contribution from EFPIA companies is EUR 19 870 000 The financial contribution from IMI2 JU is a maximum of EUR 18 600 000	Research and Innovation Action (RIA) Two-stage submission and evaluation process. Only the applicant consortium whose proposal is ranked first at the first stage is invited for the second stage.
IMI2-2020-20-03 **Academia and industry united innovation and treatment for tuberculosis (UNITE4TB)**	The indicative contribution from EFPIA companies is EUR 62 500 000 The indicative IMI2 JU Associated Partners contribution is EUR 30 000 000 The financial contribution from IMI2 JU is a maximum of EUR 92 500 000	Research and Innovation Action (RIA) Two-stage submission and evaluation process. Only the applicant consortium whose proposal is ranked first at the first stage is invited for the second stage.
IMI2-2020-20-04 **Tumour plasticity**	The indicative contribution from EFPIA companies is EUR 8 500 000 The financial contribution from IMI2 JU is a maximum of EUR 7 058 000	Research and Innovation Action (RIA) Two-stage submission and evaluation process. Only the applicant consortium whose proposal is ranked first at the first stage is invited for the second stage.
IMI2-2020-20-05 **Proton versus photon therapy for oesophageal cancer – a trimodality strategy**	The indicative IMI2 JU Associated Partners contribution is EUR 1 500 000 The financial contribution from IMI2 JU is a maximum of EUR 1 500 000	Research and Innovation Action (RIA) Two-stage submission and evaluation process. Only the applicant consortium whose proposal is ranked first at the first stage is invited for the second stage.
IMI2-2020-20-06 **Handling of protein drug products and stability concerns**	The indicative contribution from EFPIA companies is EUR 3 959 500 The financial contribution from IMI2 JU is a maximum of EUR 3 140 000	Research and Innovation Action (RIA) Two-stage submission and evaluation process. Only the applicant consortium whose proposal is ranked first at the first stage is invited for the second stage.

The following general conditions shall apply to this IMI2 JU Call for Proposals. They are based on the General Annexes to the Horizon 2020 Work Programme 2018-2020[52].

LIST OF COUNTRIES AND APPLICABLE RULES FOR FUNDING

By way of derogation[53] 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 IMI2 JU provided their participation is deemed essential for carrying out the action by the IMI2 JU or when such funding is provided for under a bilateral scientific and technological agreement or any other arrangement between the Union and the country in which the legal entity is established[54].

STANDARD ADMISSIBILITY CONDITIONS, PAGES LIMITS AND SUPPORTING DOCUMENTS

Part B of the General Annexes to the Horizon 2020 Work Programme 2018-2020 shall apply *mutatis mutandis* for the actions covered by this Call for proposals.

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

- at stage 1 of a two-stage call, the limit for RIA/IA short proposals is 30 pages;
- at stage 2 of a two-stage call, the limit for RIA/IA full proposals is 70 pages.

STANDARD ELIGIBILITY CONDITIONS

Part C of the General Annexes to the Horizon 2020 Work Programme 2018-2020 shall *apply mutatis mutandis* for the actions covered by this Call for proposals.

[52] http://ec.europa.eu/research/participants/data/ref/h2020/other/wp/2018-2020/annexes/h2020-wp1820-annex-ga_en.pdf
[53] 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
[54] In accordance with Article 10(2) of the Regulation (EU) No 1290/2013 and Article 1 of Commission Delegated Regulation (EU) No 622/2014

In addition, under all two-stage submission procedures the following additional condition[55] applies:

The participants from EFPIA constituent entities and affiliated entities and 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 Associated Partners.

TYPES OF ACTION: SPECIFIC PROVISIONS AND FUNDING RATES

Part D of the General Annexes to the Horizon 2020 Work Programme 2018-2020 shall apply *mutatis mutandis* for the actions covered by this Call for proposals.

TECHNOLOGY READINESS LEVELS (TRL)

Part G of the General Annexes to Horizon 2020 Work Programme 2018-2020 shall apply *mutatis mutandis* for the actions covered by this Call for proposals.

EVALUATION RULES

Part H of the General Annexes to the Horizon 2020 Work Programme 2018-2020 shall apply *mutatis mutandis* for the actions covered by this Call for proposals with the following additions:

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:

[55] 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 *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 JU annual work plan:*	Impact *The following aspects will be taken into account:*	Quality and efficiency of the implementation *The following aspects will be taken into account:*

RIA
 	
1st stage
 	
Evaluation of two-stage evaluation
	▪ Level to which all the objectives of the Call topic text are addressed;
	
	▪ Soundness of the concept and credibility of the proposed methodology;
	
	▪ Extent that the proposed work is beyond the state of the art and demonstrates innovation potential;
	
	▪ Appropriate consideration of interdisciplinary approaches and use of stakeholder knowledge.
		▪ Demonstration of how the outputs of the project will contribute to each of the expected impacts mentioned in the relevant Call topic text;
		
		▪ Outline of how the project plans to leverage the public-private partnership model to achieve greater impact on innovation within research and development, regulatory, clinical and healthcare practices, as relevant;
		
		▪ Impacts on competitiveness and growth of companies including SMEs;
		
		▪ Quality of the proposed outline to:
		  ▪ Disseminate, exploit and sustain the project results;
		  ▪ Manage research data;
		  ▪ Communicate the project activities to relevant target audiences.
			▪ Quality and effectiveness of the work plan outline, including extent to which the resources assigned to work packages are in line with their objectives and deliverables;
			
			▪ Appropriateness of the outline management structures and procedures;
			
			▪ Appropriateness of the allocation of tasks, ensuring that all participants have a valid role and adequate resources in the project to fulfil that role;
			
			▪ Complementarity of the participants and extent to which the consortium as whole brings together the necessary expertise;
			
			▪ Strategy to create a successful partnership with the industry consortium as mentioned in the Call topic text.

Type of action	Excellence *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 JU annual work plan and, for two stage procedures, is consistent with the stage 1 proposal:*	Impact *The following aspects will be taken into account:*	Quality and efficiency of the implementation *The following aspects will be taken into account:*

RIA
 	
2nd stage of two-stage evaluation
	▪ Level to which all the objectives of the Call topic text are addressed;
	
	▪ Soundness of the concept and credibility of the proposed methodology;
	
	▪ Extent that the proposed work is beyond the state of the art and demonstrates innovation potential;
	
	▪ Appropriate consideration of interdisciplinary approaches and use of stakeholder knowledge.
		▪ Demonstration of how the outputs of the project will contribute to each of the expected impacts mentioned in the relevant Call topic text;
		
		▪ Demonstration of how the project plans to leverage the public-private partnership model to achieve greater impact on innovation within R&D, regulatory, clinical and healthcare practices, as relevant;
		
		▪ Impacts on competitiveness and growth of companies including SMEs;
		
		▪ Quality and effectiveness of the proposed measures to:
		  ▪ Disseminate, exploit and sustain the project results;
		  ▪ Manage research data;
		  ▪ Communicate the project activities to relevant target audiences.
			▪ Quality and effectiveness of the work plan, including extent to which the resources assigned to work packages are in line with their objectives and deliverables;
			
			▪ Appropriateness of the management structures and procedures, including management of risk and innovation;
			
			▪ Appropriateness of the allocation of tasks, ensuring that all participants have a valid role and adequate resources in the project to fulfil that role;
			
			▪ Complementarity of the participants and extent to which the consortium as whole brings together the necessary expertise;
			
			▪ Clearly defined contribution and effective integration of the industrial partners to the project.

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 proposals under a two-stage submission procedure, at both stages (Stage 1 and Stage 2):

- the threshold for individual criteria will be 3;
- the overall threshold, applying to the sum of the three individual scores, will be 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 Horizon 2020 Rules for Participation.[56]

Under the two-stage evaluation procedure, and on the basis of the outcome of the first stage evaluation, the applicant consortium of the highest ranked short proposal (first stage) for each topic[57] will be invited to discuss with the relevant industry consortium the feasibility of jointly developing a full proposal (second stage).

Under the stage 2 preparation process, the applicant consortia of the second and third-ranked short proposals (stage 1) for each topic may be invited by the IMI2 JU, in priority order, for preliminary discussions with the industry consortium if the preliminary discussions with the higher ranked proposal and the industry consortium fail. The IMI2 JU may explore this possibility if the first ranked applicant consortium and the industry consortium jointly notify the IMI2 JU that the preparation of a joint full proposal is not feasible. If this is the case, the first ranked consortium and the industry consortium shall notify IMI2 JU without delay, not later than within 30 days from the invitation to submit the stage 2 proposal. This notification must be accompanied by a joint report clearly stating the reasons why a stage 2 proposal is considered not feasible in order for the IMI2 JU to take the decision whether to invite the lower ranked consortium. In the absence of a joint notification within the deadline, it is deemed that the first ranked applicant consortium and the industry consortium are going to submit the joint stage 2 proposal. Accordingly, the second and third-ranked short proposals will be formally rejected.

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.

IMI2 JU evaluation procedure is confidential. The members of the applicant consortia shall avoid taking any actions that could jeopardise confidentiality.

[56] https://www.imi.europa.eu/sites/default/files/uploads/documents/apply-for-funding/call-documents/imi2/IMI2_ManualForSubmission_v1.7_November2018.pdf

[57] 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.

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
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 2018-2020 shall apply mutatis mutandis for the actions covered by this Call for proposals.

ACTIONS INVOLVING FINANCIAL SUPPORT TO THIRD PARTIES

Part K of the General Annexes to the Horizon 2020 Work Programme 2018-2020 shall apply mutatis mutandis for the actions selected under topics covered by this Call for proposals.

CONDITIONS RELATED TO OPEN ACCESS TO RESEARCH DATA

Part L of the General Annexes to the Horizon 2020 Work Programme 2018-2020 shall apply mutatis mutandis for the actions covered by this Call for proposals.

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 IMI2 JU website.

SUBMISSION TOOL

Proposals in response to a topic of the IMI2 JU Call for proposals must be submitted online, before the call deadline, by the coordinator via the Submission Service section of the relevant topic page available under Funding & tender opportunities - Single Electronic Data Interchange Area (SEDIA).

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: https://ec.europa.eu/research/participants/data/ref/h2020/other/legal/templ/h2020_tmpl-clinical-studies_2018-2020_en.pdf.

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 IMI2 JU Call for proposals shall not be selected[58].

In order to ensure excellence in data and knowledge management consortia will be requested to disseminate scientific publications on the basis of open access[59] (see 'Guidelines on Open Access to Scientific Publications and Research Data in Horizon 2020').

To ensure actions are implemented properly, at the time of the signature of the grant agreement, each selected consortia must have agreed upon a consortium agreement, i.e. the internal arrangements regarding their operation and co-ordination.

Two-stage full proposals must contain a draft plan for the exploitation and dissemination of the results.

Applicants intending to submit a proposal in response to this IMI2 JU Call should also read the topic text, the IMI2 JU Manual for submission, evaluation and grant award, and other relevant documents[60] (e.g. IMI2 JU model Grant Agreement).

[58] Article 19 of Horizon 2020 Framework Programme and Articles 13 and 14 of the Horizon 2020 Rules for Participation.
[59] 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
[60] http://www.imi.europa.eu/apply-funding/call-documents/imi2-call-documents

List of Acronyms

Acronym	Meaning
AAPS	American Association Of Pharmaceutical Scientists
ADR	Adverse Drug Reaction
AI	Artificial Intelligence
CASPAR	Classification Criteria For Psoriatic Arthritis
CEA	Cost-Effectiveness Analysis
CEN/TS	European Committee For Standardisation / Technical Specification
cfDNA	Circulating Free DNA
CHIM	Controlled Human Infection Model
Chromium	Single-Cell RNA Sequencing Platform (10xgenomics) – Reads 3' End Of
CMC	Chemistry, Manufacturing, And Control
CPTR	Critical Path To Tb Drug Regimens
CRO	Contract Research Organisation
CROSS	ChemoRadiotherapy for Oesophageal Cancer Followed by Surgery Study
CSTD	Closed System Drug Transfer Devices
CT	Computer Tomography
ctDNA	Circulating Tumour DNA
CUA	Cost-Utility Analysis
CyTOF	Mass cytometry by time-of-flight.
DMP	Data Management Plan
DP	Drug Product
DPH	Drug Product Handling
DSUR	Developmental Safety Update Report
DTPs	Drug Tolerant Persister Cells
DZIF	German Centre For Infection Research
EBA	Early Bactericidal Activity
EC	European Commission
EFPIA	European Federation Of Pharmaceutical Industries And Associations
EGFR	Epidermal Growth Factor Receptor
EMA	European Medicines Agency
EQAs	External Quality Assessment Schemes
EUR	Euros

Acronym	Meaning
ExPEC	Extra-Intestinal Pathogenic Escherichia Coli
FAIR	Findable, Accessible, Interoperable, Reusable
FDA	Food And Drug Administration
FTE	Full-Time Equivalents
Gates MRI	Gates Medical Research Institute
GCP	Good Clinical Practice
GDPR	General Data Protection Regulation
GEMM	Genetically Engineered Mouse Models
GLP	Good Laboratory Practice
GMP	Good Manufacturing Practice
GRAPPA	Group For Research And Assessment Of Psoriasis And Psoriatic Arthritis
GSK	Glaxosmithkline
HCA	Human Cell Atlas
HTA	Health Technology Assessment
ICH	International Conference On Harmonisation Of Technical Requirements For
ICI	Immune Checkpoint Inhibitor
IMI1 JU	Innovative Medicines Initiative Joint Undertaking
IMI2 JU	Innovative Medicines Initiative 2 Joint Undertaking
IMI2 JU AP	IMI2 JU Associated Partner
IMPD	Investigational Medicinal Product Dossier
iMRM	Immuno-Multiple Reaction Monitoring
IMRT	Intensity-Modulated Radiation Therapy
INDSR	Investigational New Drug Study Report
IPD	Individual Patient Data
iPS	Induced Pluripotent Stem
ISO	International Organisation For Standardisation
IT	Information Technology
KUM	Klinikum Of The University Of Munich
LAM	Lipoarabinomannan, A Component Of The Mycobacterium Tuberculosis Cell
MDR-TB	Multidrug Resistant-Tuberculosis
ML	Machine Learning
MRD	Minimal Residual Disease

Acronym	Meaning
MTB	Mycobacterium Tuberculosis
NCE	New Chemical Entity (A Candidate Medicine Or Drug)
NGS	Next Generation Sequencing
NSCLC	Non-Small Cell Lung Cancer
pCR	Pathological Complete Response
PCR	Polymerase Chain Reaction
PDO	Patient-Derived Organoid
PDX	Patient-Derived Xenograft
PET	Positron Emission Tomography
PIC	Patient Informed Consent
PKPD	Pharmacokinetic-Pharmacodynamic
PsA	Psoriatic Arthritis
PsO	Psoriasis
PSRI	Periodic Safety Reports For Investigators
PT	Proton Therapy
RECIST	Response Evaluation Criteria In Solid Tumours
RI	Research Infrastructure
RIA	Research and Innovation Action
RIs	Research Infrastructures
RNA	Ribonucleic Acid
RSV	Respiratory Syncytial Virus
RT	Radiotherapy with photons
RTOs	Research and Technology Organisations
scRNA-seq	Single-Cell RNA-Sequencing – Expression Of The Transcriptome Per Single
SGG	Strategic Governance Group
Smart-seq2	(Switching Mechanism At 5′ End Of RNA Template) Technology Which
SME	Small And Medium-Sized Enterprises
SOP	Standard Operating Procedure
SUSAR	Suspected Unexpected Serious Adverse Reaction
TB	Tuberculosis
TDTDC	Tuberculosis Drug Treatment Development Consortium
UK	United Kingdom Of Great Britain And Northern Ireland

Acronym	Meaning
US	United States Of America
USD	Us Dollar
VAF	Variant Allele Frequency
WP	Work Package
XDR-TB	Extensively Drug Resistant-Tuberculosis