

Third amended Annual Work Plan and Budget for 2018

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

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

**Annex to the Decision of the IMI2 JU Governing Board
No. IMI2-GB-DEC-2018-23 approved on 13.07.2018**

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Chronology and list of reviews

Version	Date of the adoption by the Governing Board	Items
Version 1.0	15.12.2017	Annual Work Plan and Budget for 2018
Version 2.0	09.03.2018	<p>First amended Annual Work Plan and Budget for 2018</p> <p>IMI2 States Representatives Group and Scientific Committee consultation carried out from 09 January to 30 January 2018</p> <p>Update of the following sections:</p> <ul style="list-style-type: none"> ▪ IMI2 Key Performance Indicators ▪ 2.2.2 Scientific priorities for 2018 <p>Insertion of Annex I</p>
Version 3.0	12.06.2018	<p>Second amended Annual Work Plan and Budget for 2018</p> <p>Update of the following sections:</p> <ul style="list-style-type: none"> ▪ 2.2.2 Scientific priorities for 2018 - Budget ▪ 4. Budget
Version 4.0	13.07.2018	<p>Third amended Annual Work Plan and Budget for 2018</p> <p>IMI2 States Representatives Group and Scientific Committee consultation carried out from 08 May to 04 June 2018</p> <p>Update of the following sections:</p> <ul style="list-style-type: none"> ▪ 3.2.2 Scientific priorities for 2018 ▪ 3.3 Call management rules ▪ 4. Budget <p>Insertion of Annexes II and III</p>

2 Introduction

The year 2018 will mark the 10th anniversary of the launch of the very first Innovative Medicines Initiative (IMI) Call for proposals. As such, it is an excellent opportunity for IMI2 JU to assess and communicate on how far it has come and stimulate a discussion on IMI2 JU's current activities and future direction.

IMI2 JU will continue to focus on its core activity of launching Calls for proposals for projects that address key challenges highlighted in the IMI Strategic Research Agenda in areas such as diabetes/metabolic disorders, neurodegeneration, immunology, infection control (including vaccines), translational safety, data and knowledge management, and oncology.

In addition, as the results of the interim review of the IMI2 programme have been made public in October 2017, in 2018 IMI2 JU will focus on reviewing and implementing the recommendations made by the reviewers.

We have already started putting in place systems to address these recommendations. For example, a new set of relevant, accepted, credible, easy and robust key performance indicators is being defined. We have also developed a strategy to attract more small and medium-sized enterprises (SMEs) to IMI2 JU. We are also putting greater efforts into identifying our projects' most important outputs and communicating on them to a wider audience.

To ensure that IMI2 JU projects include a broad range of stakeholders, IMI2 JU will continue to reach out to priority groups like SMEs, patients, and regulators. IMI2 JU will also engage proactively with potential Associated Partners from the philanthropic and public sectors as well as companies from other industry sectors (e.g. ICT, imaging, medical technology, animal health, nutrition, etc.).

Throughout the year, the IMI2 JU Programme Office will strive to deliver work of the highest quality, following strict ethical standards, adhering to the principle of sound financial management and using appropriate checks and balances.

In the long term, these activities will help IMI2 JU to achieve its goals of accelerating and improving medicines development and ensuring that new discoveries are rapidly transformed into benefits for both the wider medical research community, and healthcare systems and patients.

Pierre Meulien
Executive Director

3 Annual Work Plan Year 2018

3.1 Executive Summary

The main goals of IMI2 JU in 2018 are set out as follows:

- Launching two new Calls for proposals based on scientific priorities set out in section 2.2.2.
- Successfully manage and connect a growing portfolio of projects, under both the Seventh Framework Programme for Research (FP7) and Horizon 2020 (H2020).
- Expand the basis of external collaborations and partnerships to best meet the challenges of the biopharmaceutical environment and optimise the innovation framework.
- Implement an ambitious communication strategy to demonstrate, in a spirit of openness and transparency, the added value of the partnership to EU citizens. The results of the socio-economic impact study on completed IMI1 projects will also contribute to meeting this objective.
- Implement the recommendations of the interim evaluation of IMI2 JU (completed on 30 June 2017, with conclusions and observations published on 9 October 2017).
- Improve and upgrade various aspects of our operating systems, including implementation of the Call management process under Horizon 2020, effective transition to the Horizon 2020 IT tools, review of the risk assessment and internal control framework, and reorganisation of IMI2 JU Programme Office towards enhanced efficiency and cost effectiveness.
- Carry out and implement audits and controls over beneficiaries that receive of IMI2 JU funding and companies' in-kind contributions.

3.2 Operations

3.2.1 Objectives & indicators - risks & mitigations

The key objectives for IMI2 JU operations in 2018 are identified by the Governing Board in the Annual Work Plan and by the Management at operational level.

Key operational objectives for 2018 are as follows:

- Initiate competitive calls for proposals within the Strategic Research Agenda priorities bringing together the different stakeholders involved in drug development (including SMEs, regulators and patient organisations) and foster cross-project collaboration through proactive outreach strategies and conducive call design;
- Ensure sound budget implementation through the efficient management of calls for proposals, grant award process and close monitoring of ongoing projects, ensuring the completion and close-out;
- Demonstrate the EU added value of IMI2 JU through assertive communication to target audiences of the openness, transparency, relevance, effectiveness, efficiency and coherence of IMI2 JU activities;
- Involve industry from related sectors other than the pharmaceutical industry (diagnostics, medical technologies industry, imaging, digital industry, etc.) in IMI2 JU projects through proactive outreach strategies;
- Ensure IMI2 JU internationalisation and build productive linkages to major international efforts to address Global Challenges (AMR, Alzheimer's, autism, cancer, emerging infectious diseases, etc.).

IMI2 Key performance indicators (KPIs)

Reporting on measuring and outcomes on the ten following Key Performance Indicators will be provided yearly as part of the IMI2 JU Annual Activity Reports for year 2018 and beyond.

KPI	Definition	Comment	Relates to	Baseline	Target
1	Number of relevant priority areas in the WHO "Priority Medicines for Europe and the World 2013 Update" reflected in the IMI2 Strategic Research Agenda (SRA) and addressed by IMI2 projects.	Based on the SRA and including the WHO priority medicines therapeutic areas: - Expressed as a number of areas reflected in the IMI2 portfolio. - Complemented by the number and budget of grant agreements that delivered them.	IMI2 Regulation objective b1: b1: "increase the success rate in clinical trials of priority medicines identified by the WHO"	0	12
2	The number of project developed assets which complete a significant milestone during the course of an IMI2 project.	Assets are defined as new drug or diagnostic candidates, targets, biomarkers or other tools that can be shown to have reached a significant milestone or pass a significant stage gate.	IMI2 Regulation objective b1, b2, b4, b5 and b6: b1: "increase the success rate in clinical trials of priority medicines identified by the WHO" b2: "reduce the time to reach clinical proof of concept in medicine development..." b4: "develop diagnostic and treatment biomarkers for diseases clearly linked to clinical relevance and approved by regulators" b5: "reduce the failure rate of vaccine candidates in phase III of clinical trials through new biomarkers for initial efficacy and safety checks" b6: "improve the current drug development process by providing the support for the development of tools, standards and approaches to assess efficacy, safety and quality of regulated health products"	0	50

KPI	Definition	Comment	Relates to	Baseline	Target
3	<p>New or improved guidelines, methodologies, tools, technologies or solutions accepted by regulatory authorities for use in the context of R&D, specifically for:</p> <ul style="list-style-type: none"> - new tools for preclinical drug development, - biomarkers and tools developed to predict clinical outcomes, - improved protocols to design and process of clinical trials, - new biomarkers developed for the efficacy and safety of vaccine candidates. 	<ul style="list-style-type: none"> - Measured by the number of the formal qualification procedures completed (letters of support, qualification opinions received). - Complemented by number of qualification procedures launched. - Expressed as net figure. - Complemented by the number and budget of grant agreements that delivered them. 	<p>IMI2 Regulation objective b1, b2, b4, b5 and b6:</p> <ul style="list-style-type: none"> b1: "increase the success rate in clinical trials of priority medicines identified by the WHO" b2: "reduce the time to reach clinical proof of concept in medicine development..." b4: "develop diagnostic and treatment biomarkers for diseases clearly linked to clinical relevance and approved by regulators" b5: "reduce the failure rate of vaccine candidates in phase III of clinical trials through new biomarkers for initial efficacy and safety checks" b6: "improve the current drug development process by providing the support for the development of tools, standards and approaches to assess efficacy, safety and quality of regulated health products" 	0	10 (for completed procedures)

KPI	Definition	Comment	Relates to	Baseline	Target
4	New taxonomies of diseases and new stratifications (such as the definition of patient subpopulations, development, validation and use of new diagnostics) developed.	<ul style="list-style-type: none"> - Expressed as net figure. - As published and/or implemented by industrial partners and evidenced in annual reporting. - Complemented by the number and budget of grant agreements that delivered them. 	<p>IMI2 Regulation objective b3 and b4:</p> <p>b3: "develop new therapies for diseases for which there is a high unmet need..."</p> <p>b4: "develop diagnostic and treatment biomarkers for diseases clearly linked to clinical relevance and approved by regulators"</p>	0	30
5	Contribution (in-kind or in-cash) from non-pharma actors (e.g. non-pharma industries, foundations, charities, professional organisations).	Expressed as total amount in EUR.	<p>IMI2 Regulation objective a:</p> <p>a: "to support... the development and implementation of pre-competitive research and of innovation activities of strategic importance to the Union's competitiveness and industrial leadership...";</p> <p>and IMI2 Regulation recital 8:</p> <p>"The initiative should consequently seek to involve a broader range of partners, including mid-caps, from different sectors, such as biomedical imaging, medical information technology, diagnostic and animal health industries."</p>	0	EUR 300 Million

KPI	Definition	Comment	Relates to	Baseline	Target
6	Share of IMI projects whose resources/outputs are made accessible beyond the consortia partners (with or without fee), such as major databases, bio-banks, in silico tools, training materials, clinical trial networks, guidance etc.	<ul style="list-style-type: none"> - Complemented by the number and budget of grant agreements that delivered them. - Accessibility to be evidenced by online availability (with or without fee), and documented by project reports. 	<p>IMI2 Regulation objective a, b2 and b6:</p> <p>a: "to support... the development and implementation of pre-competitive research and of innovation activities of strategic importance to the Union's competitiveness and industrial leadership..."</p> <p>b2: "reduce the time to reach clinical proof of concept in medicine development"</p> <p>b6: "improve the current drug development process by providing the support for the development of tools, standards and approaches to assess efficacy, safety and quality of regulated health products"</p>	0	50%
7	Co-authorships and cross-sector publications between European researchers on IMI2 projects (sectors include academia, small and mid-sized companies, pharma, regulators, patient organisations, etc.).	<ul style="list-style-type: none"> - Expressed as net figure - Complemented by the number and budget of grant agreements that delivered them. 	<p>IMI2 Regulation objective a:</p> <p>a: "to support... the development and implementation of pre-competitive research and of innovation activities of strategic importance to the Union's competitiveness and industrial leadership..."</p>	0	1500

KPI	Definition	Comment	Relates to	Baseline	Target
8	New tools and processes generated by IMI2 projects that have been implemented by the industry participants of IMI projects.	<ul style="list-style-type: none"> - New tools and processes: e.g. animal models, standards, biomarkers, SOPs, use of screening platforms and clinical trial networks. - Expressed as net figure. - Complemented by the number and budget of grant agreements that delivered them. - Assessment based on yearly reporting by industrial partners until the project close-out meetings. 	<p>IMI2 Regulation objective a, b2 and b6:</p> <p>a: "to support... the development and implementation of pre-competitive research and of innovation activities of strategic importance to the Union's competitiveness and industrial leadership..."</p> <p>b2: "reduce the time to reach clinical proof of concept in medicine development"</p> <p>b6: "improve the current drug development process by providing the support for the development of tools, standards and approaches to assess efficacy, safety and quality of regulated health products"</p>	0	50
9	Share of projects involving patient organisations and healthcare professionals' associations (as consortium partners, members of advisory boards, members of stakeholder groups etc).	<ul style="list-style-type: none"> - Complemented by the number and budget of grant agreements that delivered them. 	<p>IMI2 Regulation objective a, and b1:</p> <p>a: "to support... the development and implementation of pre-competitive research and of innovation activities of strategic importance to the Union's competitiveness and industrial leadership..."</p> <p>b1: "increase the success rate in clinical trials of priority medicines identified by the WHO"</p>	Share of IMI 1 projects involving patient organisations: (participants /advisory boards etc. 40%)	80%

10	Support to SMEs: share of SMEs participating as formal IMI project beneficiaries.	- To be complemented by the number of SMEs benefitting from IMI project support in other ways.	<p>H2020 priority; IMI2 Regulation recital 9</p> <p>"(...) should seek to foster the capacity of smaller actors such as research organisations, universities and SMEs for participating in open innovation models and to promote the involvement of SMEs in its activities, in line with its objectives"</p>	Share of SMEs participating as formal IMI1 project beneficiaries: 15.96%	20%
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Risks & mitigations

Risks are a strategic element of planning activities as their identification enables management to customise their objectives and corresponding actions. That further enables the prioritisation of actions to reduce the risks to an acceptable level. This section gives an overview of the risks and corresponding mitigating actions identified by the IMI2 JU Programme Office to support the achievement of the strategic goals and objectives set out above.

The risk assessment on the objectives and actions planned for 2018 shows in particular that some strategic risks identified are associated with IMI2 JU mission and have therefore to be accepted as such thus the IMI2 JU has planned appropriate mitigating measures to control any possible adverse effects This is typically the case of:

- Insufficient participation of non-pharma industry and SMEs as well as limited leverage effect of private contributions.
 - Control measures planned aim at developing new partnerships and promoting IMI2 JU visibility at international level through targeted actions by area and in collaboration with projects. This will ensure that the IMI2 JU brand is enhanced by the international strategy and relationship. In addition, joint IMI-EFPIA events are planned at regional and national level involving industry and policymakers. Furthermore, the IMI website is promoting different ways of contributing to IMI projects as Associated Partners and Partners in Research. Finally, on the specific issue of SME participation IMI2 JU and EFPIA are exploring new initiatives (such as incubator models) and potential call topics targeting SMEs (focusing on areas of new technology where standardisation and interaction between SMEs and large pharma companies could accelerate the development of innovative solutions such as sensors or organ-on-a-chip platforms).
- In addition, the IMI2 JU programme may be affected adversely by factors such as delay in defining the annual scientific priorities and call topics, insufficient comprehensibility of the participation process, low budget execution and postponement of project conclusion. The risk is that IMI2 JU may be perceived as unable to meet the needs of patients and the scientific community losing scientific attractiveness and stakeholders' (especially SME) involvement, resulting in low participation to calls and unsatisfactory programme implementation.
 - In view of ensuring efficient management of the grant award process and optimal budget implementation on ongoing projects, the IMI2 JU Programme Office is reinforcing its monitoring activities in liaison with all project coordinators in order to:
 - reassess the project needs and the work plan;
 - thoroughly review the overall need for payments appropriations in 2018 as the basis for a revised forecast;
 - enhance interactions between science and finance operations;
 - closer monitoring of the high-risk projects.
 - Furthermore, IMI2 JU will continue i) to implement the reengineered Call topic definition process reinforcing the Strategic Governing Groups (SGG) as thematic platforms addressing defined areas under the umbrella of the IMI2 JU SRA and ii) to search the advice of patients through the Patient Advisory Committee (PAC).
- Unbalance – at the end of the programme – between the EU financial contribution and the in-kind contribution provided by industry.
 - Measures to control and mitigate this risk are the systematic monitoring of projects' financial management made by the IMI2 JU Programme Office on the periodic report received from coordinators associated with ex-post control of costs incurred in indirect actions by industry and associated partners planned according to a risk-based plan.

- Finally, the risks of negative external perception at political level due to inaccurate comments about IMI in the press and other public fora have been identified.
 - IMI is promoting an ambitious communication strategy to demonstrate, in a spirit of openness and transparency, the results achieved by the partnership. To that end, the IMI2 JU will be proactive in identifying and promoting stories that highlight IMI's successes. The Programme Office shall also maintain close relationships with key decision-makers to ensure they have an informed view of how IMI works and its successes.

Concerning risks related to the performance of the Programme Office and operations, particular attention will be given to the organisational structure and staff allocation, especially as regards project management activities, the efficiency of which is dependent upon a sound interaction between science and finance. This is considered crucial by the management in order to ensure that the structure and resources of the JU continue to meet evolving organisational objectives and needs. Moreover, management will ensure that annual targets and objectives as well as key performance indicators are updated and coordinated with responsibilities and tasks are also revised to reflect changing strategic priorities. In turn, continuous measures are to be taken to strengthen both IMI2 JU operational procedures, increasing the resources available in some specific areas, improving the approach used for topic development, project monitoring and reporting as well as for IT management.

Finally, as UK stakeholders have largely contributed to the IMI success and the consequences of Brexit remain unpredictable, the IMI2 Governing Board will continue to monitor within the EU's broader political agenda the potential impact of Brexit on its strategy and programme implementation.

3.2.2 Scientific priorities for 2018

The IMI2 JU activities for 2018 are fully in line with the objectives as set out in Article 2 of the IMI2 JU Regulation. In particular, they aim at the development and implementation of pre-competitive research and innovation activities of strategic importance to the EU's competitiveness and industrial leadership, and address specific H2020 societal challenges, in particular improving European citizens' health and well-being.

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

In order to achieve its objectives, IMI continues to seek the involvement of a broader range of partners from different sectors e.g. biomedical imaging, medical information technology, diagnostics and/or animal health industries among others. The actions resulting from the 2018 priorities will generate results that will have a high impact and facilitate the maximum number of stakeholders to join forces. The outcome and impact of these actions should bring great benefits to patients and society at large. There will also be engagement with regulatory agencies and other health bodies fostering the approval of research outcomes. Involving the wider community in this way should help to advance the development of new approaches and technologies for the prevention, diagnosis and treatment of diseases with an expected high impact on public health.

Small- and medium-sized enterprises (SMEs) have an important role in strengthening the competitiveness and industrial leadership in the European Union. In addition, SME involvement might offer a complementary perspective to industry and the academia, and help deliver the long-term impact of IMI2 JU. Thus IMI2 in 2018 will increase its efforts for engaging SMEs in all its activities and encouraging their involvement in applicant consortia.

IMI has identified four scientific priorities, broken down into several topics, for 2018, taking into account the advice provided by Strategic Governing Groups to the IMI2 JU Governing Board. As described in the following pages, each priority area will be implemented via the launch of one or more topics, which will generate multi-stakeholder actions, potentially including (or even driven by) Associated Partners. Further details regarding the expected multi-stakeholder actions are elaborated under the individual topics. Topics for 2018 have been prioritised based on criteria that include the highest impact on reducing attrition in drug development, speeding up patient access, improving health outcomes and enhancing the biomedical research ecosystem.

Additional topics for 2018 might also be considered at a later stage in the case of very urgent public health needs, such as rapid response to emerging diseases. The Annual Work Plan 2018 would then be updated accordingly.

To implement the 2018 priorities, IMI2 JU will initiate two competitive Calls for proposals, each covering several topics (see table at the end of this section), with launch dates in March and July 2018.¹

Topics launched on the basis of this Annual Work Plan 2018 will seek synergies with other ongoing initiatives especially those funded under Horizon 2020 and at the national level, and those identified by the European Strategy Forum on Research Infrastructures (ESFRI), to ensure the consistency of approaches, to leverage other funding initiatives and to avoid duplication of effort and funding.

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

A. Neurodegeneration and other Neuroscience Priorities

The priority area Neurodegeneration and other Neuroscience Priorities aims to address the high-unmet medical need for effective disease modifying and improved symptomatic interventions, as well as relevant companion diagnostics, for brain disorders in general and neurodegenerative disorders/Alzheimer's disease (AD) in particular. The priority area addresses the following themes: 1) increasing disease aetiology understanding for new drug target identification & validation as well as predictive animal models; 2) development of translational model systems and identification/validation of biomarkers; 4) improving clinical trial capabilities and methodologies including primary/secondary prevention.

Activities in 2018 will address the following topic:

- 1) **Development and validation of translational platforms in support of synaptopathy drug discovery.** The science linking alterations in synaptic function, genetics, and underlying pathways with Central Nervous System (CNS) disorders is emerging. What still needs to be addressed is how these alterations are causal in the development of brain disorders, if they represent a common pathophysiological mechanism across disorders, and, finally, if targeting such alterations is feasible for the development of new treatments. The topic supports activities for the development of predictable in-vivo models and predictive early translational clinical models or biomarkers, such as a physiological marker of synaptic dysfunction, which for example is altered in early Alzheimer's Disease (at very least in prodromal subjects, preferably in pre-symptomatic subjects), as well as in neurodevelopmental and psychiatric disorders. These should be sensitive enough to detect both abnormalities versus healthy controls and pharmacological intervention. An important aim of the topic is to demonstrate the value of these new tools and methods for supporting drug discovery and development efforts across a spectrum of therapeutic CNS indications, including neurodegenerative, neurodevelopmental and psychiatric disorders. Accordingly, the topic activities should address at least one of the four major brain disorders namely Alzheimer's, Parkinson's disease, major depression and schizophrenia, and ideally at least two, one in the neurodegenerative and one in the psychiatric/neurodevelopmental field.

Expected impact:

- Validation of tools and platforms for discovery of new biological insights into brain disease.
- Enabling of the development of more personalised treatments for patients with brain diseases.
- Enabling the development of new approaches to disease interception for brain diseases.

Type of actions:

Research and Innovation Actions

B. Immunology

Autoimmune diseases cover over 100 distinct diseases and syndromes, together affecting approximately 5% of the population of Europe, with two-thirds of the patients being female. The burden of autoimmune disease crosses medical and scientific boundaries, and requires cross-functional collaboration by scientists and physicians with interests in diseases of widely differing organ systems. In addition, there is an increased awareness that immune-mediated mechanisms play a key role in several, if not all, chronic diseases from cancer to metabolic disorders and therefore new immunology based approaches may be game changers for treatment of millions of patients affected by these conditions. Respiratory diseases in particular are relevant here. Within this remit, activities should seek progress towards novel diagnostic, monitoring and treatment paradigms for the mechanisms being involved in triggering the early onset, remission and progression of early lung diseases in particular, bronchiectasis, asthma, and chronic obstructive pulmonary disease (COPD).

The proposed work will focus on a key set of immune mediated diseases or on disease mechanisms where working in partnership will benefit the knowledge base and accelerate delivery of drug treatments to patients. The proposed work will build on the knowledge base and infrastructure present within the European Union and the H2020 Associated Countries. This include achievements from ongoing research-based initiatives which together have aggregated substantive information on disease phenotypes, biomarkers and other factors associated with disease progression in many autoimmune disorders in order to guide better patient treatments. This should aim to enable identification of potential targets for therapeutic intervention and early diagnosis of disease with predictive biomarkers, eHealth, digital or telemedicine tools, to allow the development of experimental medicine approaches to safe and efficacious treatments, considering also health system sustainability of treatment intervention.

Activities in 2018 will address the following topics:

- 2) **Targeted immune intervention for the management of non-response and relapse.** The aim of this topic is to identify novel biomarkers predictive of clinical disease behaviour and response. This should be achieved by applying state of the art molecular and immune technologies and sophisticated informatics approaches on highly annotated pre- and post-therapy bio-samples obtained from patients with Systemic Lupus Erythematosus (SLE), Rheumatoid Arthritis (RA), Multiple Sclerosis (MS), Ulcerative Colitis (UC), Crohn's Disease (CD), Asthma, and Chronic Obstructive Pulmonary Disease (COPD). A major aim beyond studying an individual disease is the discovery of cross-disease biomarkers with relevance to a group of immune-mediated inflammatory diseases.
- 3) **Non-invasive clinical molecular imaging of immune cells.** Current pharmacodynamic assessments of immune cells are based on peripheral blood biomarkers, or on biopsies acquired by invasive procedures, while current imaging tracers provide limited information on disease-relevant immune cell subtypes, or measures of direct engagement of immune targets. The topic objective is to study how immunotracers designed to bind specific immune cell biomarkers may enable the clinical imaging of immune cell subtypes and immune markers of disease. Activities supported are those that will provide in vivo insights into effects of immunomodulatory therapies at disease sites (organs/tissues), improve knowledge about the pathophysiology of various immune-mediated diseases, and enable patient stratification based on immune signatures. The overall objective is to develop and validate a quantitative, non-invasive, immune-cell-imaging platform, which includes (novel) molecular imaging agents, (hybrid) imaging modalities, and image processing algorithms. The final objective is to extend the current markers and validate them extensively for clinical use.
- 4) **Microenvironment imposed signatures in tissue and liquid biopsies in immune-mediated disease.** This topic focuses on the identification of key organ and disease specific signatures with correlates in body fluids that may predict disease, track progression and/or therapeutic response of immune diseases. The topic supports activities for the identification and optimisation of promising technologies and/or platforms suitable for interrogating both immune and non-immune cells in target tissues at single cell level, for better understanding of pathways regulating disease, and to define tissue/disease specific signatures, which can be correlated in peripheral blood. The technologies for the identified signature should be evaluated first in existing clinical retrospective cohorts as well as in samples from ongoing clinical trials, and finally verified in a bespoke clinical study. Thus the technologies for the identified signature need to be adaptable and of sufficient robustness for use in clinical trials.

- 5) **Emerging translational safety technologies and tools for interrogating human immunobiology.** The overall objective of the topic is to enhance translational safety assessment approaches for immunomodulatory therapeutics (spanning oncology and non-oncology indications) through development and validation of innovative non-clinical tools and technologies, supported by access to *in vitro*, *ex vivo* and *in vivo* model-derived immune cell and tissue resources, with an emphasis on evaluating human-relevance. To this purpose, the topic supports activities in two main areas. First, activities should focus on the development of innovative comparative (cross-species) *in situ* and *ex vivo* molecular, biochemical tools, the cellular profiling of immune cells and their association with functional/phenotypic endpoints for predictive safety assessment for immuno-modulatory drugs. Second, activities should lead to the establishment, refinement and validation of non-clinical tools and models to enable the development of novel classes of immunomodulatory medicines, supporting *in vitro-in vivo* and cross-species translation for recapitulating *in vivo* human immunobiology.

Expected Impact

- Generation of tools and capabilities required to support precision medicine.
- Increase the efficiency of the drug discovery and clinical development process.
- Improved methods for recognition and diagnosis of autoimmune and inflammatory disorders and a range of treatment options.
- Earlier availability of new, more cost effective therapies to patients most likely to benefit in different geographical regions.
- Expanding our current knowledge will give rise to more precise, targeted treatments yielding long-lived reductions in disease, improved patient quality of life and fulfilling unmet medical needs in patient care.
- Options for improved treatment of respiratory patients to decrease their risk for morbidity and mortality, via a better understanding of disease progression, remission and the identification of reliable markers for its diagnosis and risk.
- Facilitating the design and interpretation of rationally designed stratified clinical trials via the better understanding and scientific base of the early respiratory disease population.
- Potential high impact on future guidelines to treat patients with respiratory diseases.

Type of actions:

Research and Innovation Actions

C. Infection control including vaccines

Infection control including vaccines is a key priority of IMI. The aim is to support the development of new platforms that facilitate rapid deliveries of novel and improved diagnostics, vaccines and treatments for infections, including emerging and re-emerging ones.

Antimicrobial resistance (AMR) continues to be a major global public health threat. The clinical burden is associated with soaring treatment and societal costs with a cost of AMR being estimated at around 1.5 billion Euros per year only in Europe. Despite the recognised need for new antimicrobials the reality is that as a society we are faced with the potential situation where prescribers could have few, if any, therapeutic options to treat certain bacterial infections. Continued efforts will focus on overcoming the barriers to the discovery, development and delivery of effective antibiotics; furthermore work on novel, resistance-breaking antibiotics should be supported.

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

The discovery and development of new antimicrobials to address AMR is an undisputed European and global challenge that is compounded by a low return on investment (RoI). This has subsequently led to a reduction in resources applied across the pharmaceutical industry and decline in scientific discoveries. Overall, this situation has compromised the delivery of new options to treat and prevent resistant infections. The AMR Accelerator is a programmatic approach developed via different pillars that together should address the challenges we face and increase the overall investment in AMR research and the development of new treatment options. As indicated in the relevant call for proposals, several of the funded actions will be complementary to each other's, thus the relevant consortia will be required to conclude collaboration agreements to coordinate the work under the complementary grant agreements². The aim of the AMR Accelerator is to progress a pipeline of potential medicines to treat patients with resistant bacterial infections in Europe and across the globe. Specifically, if successful, projects in the Accelerator are expected to deliver up to, or more than, ten new preclinical candidates, and more than five 'Phase 2-ready' assets. In particular, the "Pillar C: Portfolio Building Networks (PBN) to advance the R&D pipeline of new and innovative agents to address AMR" includes multiple topics. The PBN initiative provides 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 selected cases tuberculosis (TB) and non-tubercular mycobacteria NTM.

Activities in 2018 will address the following topics:

- 6) **Pillar A: Capability Building Network to accelerate and validate scientific discoveries.** The Capability Building Network (CBN) will support activities to: 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 activities to further basic science and discoveries to enable future drug discovery and development in the prevention (vaccines, monoclonal antibodies, immunoprophylaxis) and treatment of multidrug resistant (MDR) bacterial infections including tuberculosis (TB), and non-tubercular mycobacteria (NTM). Although most research in the Accelerator related to TB is in the scope of the topic TB Drug Development Network (TBDDN), TB activities could be in the scope of the CBN topic, if the scientific concepts are of broader applicability (e.g. immunoprophylaxis).

² IMI 2 JU Model Grant Agreement Article 2, Article 31.6 and Article 41.4.

- 7) **Pillar B: Tuberculosis drug development network to accelerate and validate scientific discoveries and advance the R&D pipeline of new and innovative agents to address the global tuberculosis epidemic.** The TB Drug Development Network (TBDDN) topic supports activities 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 aim of the topic is to profile and progress anti-TB compounds from advanced lead through Phase 1 and the collection, sharing, and analysis of TB clinical trial data. Additionally, the topic supports activities for the development of new alternative anti-tubercular drugs (for example, based on host-defence or virulence approaches).
- 8) **Pillar C: Portfolio Building Networks (PBN) to advance the R&D pipeline of new and innovative agents to address AMR. Progress new assets (One pre New Molecular Entity (preNME) and One first-time-in-human (FTIH)) for tuberculosis that act synergistically with bedaquiline, cytochrome bc or cytochrome bd inhibitors.** The topic goal is to develop and advance a portfolio of anti-TB drugs that may be used in combination with bedaquiline and cytochrome bc inhibitors to shorten treatment regimens and improve safety and efficacy.
- 9) **Pillar C: Portfolio Building Networks (PBN) to advance the R&D pipeline of new and innovative agents to address AMR. Progress novel assets (One first-time-in-human (FTIH)) for non-tubercular mycobacteria (NTM) that may act synergistically with bedaquiline, and cytochrome bc drugs.** The topic goal is to develop and advance a portfolio of anti-NTM drugs that may be used in combination with bedaquiline and cytochrome bc inhibitors to shorten treatment regimens and improve safety and efficacy.
- 10) **Pillar C: Portfolio Building Networks (PBN) to advance the R&D pipeline of new and innovative agents to address AMR. Discover and progress novel assets with new mechanisms of action (1 pre-new molecular entity (NME) for tuberculosis (TB) and 1-pre- new molecular entity (NME) for non-tubercular mycobacteria (NTM)) and biomarkers for TB and NTM infection.** The topic supports activities to identify novel assets with new mechanisms of action through high throughput screening campaigns for TB and NTM, with special focus in *M. avium* complex. Novel screening platforms and tools are needed for this evaluation. The resulting hits should be profiled and further optimized in-vitro and in-vivo. In addition, a better understanding of the host-mycobacteria interaction and the impact of coexisting viral infections should be considered to provide insights about biomarkers and new targets for mycobacteria,
- 11) **Pillar C: Portfolio Building Networks (PBN) to advance the R&D pipeline of new and innovative agents to address AMR. Determination of gepotidacin levels in tonsils and prostatic tissue.** Gepotidacin (GSK2140944) is a novel antibiotic that selectively inhibits bacterial DNA gyrase and topoisomerase IV by a unique mechanism, which is not utilized by any currently approved human therapeutic agent. In presence of increasing antimicrobial resistance, there are fewer options to treat gonorrhoea, in particular at the pharyngeal site where tissue penetration is essential to activity, and extended spectrum β -lactamases (ESBLs) multidrug resistant (MDR) urological infections due to *E. coli*. The topic will support activities to assess penetration of gepotidacin 1) in tonsils following elective tonsillectomy in adults, age >18 years or adolescents, age 12-17 years, and 2) in prostatic tissue following elective prostate biopsy or transurethral resection of the prostate in adult males.
- 12) **Pillar C: Portfolio Building Networks (PBN) to advance the R&D pipeline of new and innovative agents to address AMR. Infection site targeting, antibiotic encapsulated nanoparticles for treating extracellular bacterial infections.** The topic support activities to achieve three main objectives. First, to identify a bacterium or infection site targeting ligand (small molecule preferred). Second, to incorporate such ligand into a nanoparticle system that can be retained selectively in infected tissues for long periods. Third, to encapsulate an appropriate antibiotic into the targeted

nanoparticle and confirm improved efficacy over free antibiotic and non-targeted encapsulated antibiotic, driven by higher local concentration at the infection site.

- 13) **Pillar C: Portfolio Building Networks (PBN) to advance the R&D pipeline of new and innovative agents to address AMR. Functional Ethionamide Boosters. A novel combination for tuberculosis therapy.** The topic goal is to generate a small molecule clinical candidate that can boost the activity of Ethionamide (ETH) and revert the existing resistance to this drug, by acting on bacterial transcriptional regulators. This topic supports activities aimed at identifying novel small molecules that are capable of: a) increasing the level of bioactivation of ETH reducing the levels required to achieve maximal efficacy both in vitro (>10-fold) and in vivo (>3-fold) and b) revert pre-existing ETH clinical resistance using a very low oral dose. This will allow opening the scope of ETH field of use to both drug sensitive and Multi-Drug-Resistant (MDR) patients. The topic activities intend to progress these new compounds from candidate selection stage to a proof of concept as ETH Booster in tuberculosis patients.
- 14) **Pillar C: Portfolio Building Networks (PBN) to advance the R&D pipeline of new and innovative agents to address AMR. Intravenous treatments of serious infections (urinary tract infections (UTI), intra-addominal infections (IAI) & hospital-acquired pneumonia/ventilator associated pneumonia (HAP/VAP)) caused by Gram(-) bacteria (Enterobacteriaceae +/- Pseudomonas and/or Acinetobacter.** In the various threats encompassed in the global AMR crisis, Gram(-) bacteria and especially Extended Spectrum beta-lactamases-producing and carbapenemases-producing Enterobacteriaceae consistently rank among the most problematic organisms for which novel ways of managing the infections they cause are lacking. The scope of this topic will be to progress novel lead compounds against these organisms, by performing medicinal chemistry optimization, in vitro and in vivo activity characterization, as well as pharmacokinetic, absorption, distribution, metabolism elimination and toxicology (ADMET), formulation and chemistry, manufacturing, and controls (CMC) studies. A particular focus will be on compounds identified from phenotypic screens of natural product extracts / libraries, and on compounds identified through non-traditional phenotypic screens (i.e. screens in non-traditional rich media and/or screens where a proxy for bacterial cell death is employed).

Expected impact of the topics:

- A pipeline of promising new agents for tackling antibiotic-resistant bacterial infections, including AMR tuberculosis.
- A significant contribution to the development of a vibrant AMR research environment in the EU and to the strengthening of its competitiveness and industrial leadership.
- Major impact on the improvement of public health.

Type of actions:

Research and Innovation Actions

D. Digital health and patient-centric evidence generation

This area of priority will address key areas that have the potential to be game changers for delivering access to innovative treatments for large patients populations. These are several. The challenge and opportunities of The increasing digitalisation in health research and technology, including the need for developing and implementing regulatory strategies and policies for digital health technologies creates both challenges and opportunities. There is both a challenge and a real opportunity in fully leveraging new technologies, digitisation, and telehealth. There is a need to fully revisit the current concept of running clinical trials, how patients are recruited, how they are followed, how data are monitored and reported. In this context pioneering multi-company platform trials such as I-SPY2 (breast cancer), IMI EPAD (prevention of Alzheimer's Disease), and GBM AGILE (glioblastoma multiforme) are already demonstrating the potential benefits of this approach. Finally, new capabilities to utilise real world data (RWD) offer powerful opportunities to complement the evidence obtained from clinical trials and this concept needs further development.

Activities in 2018 will address the following topics:

- 15) **Development of a platform for federated and privacy-preserving machine learning in support of drug discovery.** This topic will support activities towards the development of a federated privacy-preserving machine learning platform that is demonstrably safe and scalable enough to be deployed to a significant representation (at least half of the data) of the actual preclinical warehouses of at least 6 major pharmaceutical companies in yearly evaluation runs. The platform should be then used in an industrial setting and evaluated to establish proof-of-concept. The scope is the prediction of the activity of chemical compounds across an extensive set of biological assays. The resulting models will be evaluated on predictive performance gains in terms of accuracy and chemical and biological applicability domain, and on their impact in actual discovery projects, (e.g. how many lab experiments can be replaced by in silico predictions).
- 16) **Centre of excellence – remote decentralised clinical trials.** Recruitment and retention of patients are known to be one of the most challenging aspects in completion of clinical trials. The three main barriers commonly reported that discourage patients from participating in a clinical trial are: geography -distance to the clinical site, awareness and trust. Telemedicine is viewed as the central capability needed for distributing meaningful parts of clinical trial activities out to community settings. The topic aims on disaggregating the current model of running clinical trials, defining building blocks and mapping new technologies (e.g. telemedicine, mobile health, e.g. e-consent) to support the new decentralised clinical trial (DCT) approach. Activities might include among others: 1) review of experience to date to define and share challenges, obstacles, minimal requirements, solutions in DCT/home monitoring in a secured manner and assessment of data integrity and quality; 2) definition of the decentralised ecosystem and stakeholders; 3) recommendations on the creation of a Centre of Excellence on decentralised clinical trials; 4) define an intermediary model: hybrid studies mixing DCT approach with classical models, alleviating the burden for patients (e.g. rare diseases) and ensuring more real-life assessment; 5) setting up of initial pilot studies; 6) generate evidence for updating Good Clinical Practice (GCP) and International Conference on Harmonisation (ICH) guidelines.
- 17) **Digital endpoints in neurodegenerative and immune-mediated diseases.** The IMI2 program “Digital transformation of clinical trials endpoints” seeks to develop objective, continuous or high frequency digital measures of clinical efficacy and disability experienced by patients. In this topic, this will be implemented for patients with immune mediated and neurodegenerative progressive illnesses, for example rheumatoid arthritis (RA), systemic lupus erythematosus (SLE) inflammatory bowel disease (IBD), Huntington disease (HD) and Parkinson's disease (PD). The digital measures for each disease area should be correlated with validated clinical scales of disease severity and with the disabilities considered meaningful by patients & care-givers. This should provide information acceptable to payers in assessing changes in burden and disability caused by these diseases, while providing useful data for development and qualification of certain digital measures as primary and secondary endpoints of clinical efficacy.

- 18) **Integrated research platforms enabling patient-centric drug development.** The topic overall objective is to design and prepare for implementation of a “patient-centric” and highly efficient approach for medical research, through a collaborative public private partnership and integration of Real World Data (RWD) with clinical platform trials. The aim is the establishment of Integrated Research Platforms (IRPs) in diseases of high-unmet need such as e.g. major depressive disorder (MDD), tuberculosis (TB), non-alcoholic steato-hepatitis (NASH), and neurofibromatosis (NF). The topic will support activities for the establishment of common foundational elements to address key elements applicable to integrated research platforms (IRPs) in all disease areas, including regulatory aspects, a clinical operations framework, quantitative design and statistical methods and the legal and intellectual properties framework. In addition, the proposed new trial paradigm should create and maintain for each IRP a sustainable network of hospitals, healthcare providers and investigators who will leverage rather than duplicate efforts in the preparation of and for execution of platform trials. When fully implemented, these networks will have two main components, both with common-foundational and disease-specific dimensions.
- 19) **Blockchain Enabled Healthcare.** The overall objective of this topic is to establish a common blockchain ecosystem for pharmaceutical development, manufacturing, and distribution that provides an incentive and serves as the basis for all participants to engage, adopt, and benefit. The topic supports activities that should initially establish an effective governance organisation and approach to enable continuous improvement and open competition among service providers while ensuring that critical factors such as data integrity, privacy, regulatory compliance and efficiency are built into a “Healthcare Foundation”. Such foundation should serve as an integration layer between underlying blockchain technologies and business application layer. The results should be applied to the delivery of use cases prioritized by clearly defined business value, benefits, return on investment (RoI) and feasibility.

Expected impact of the topics:

- Expand and democratise clinical trial participation globally and expand use of telemedicine in areas of current low uptake, potentially improving health outcomes.
- Accelerate patient access to innovative medical treatments.
- Reduce patient burden while participating in clinical trials.
- Provide benefit to society by expanding access to healthcare via telemedicine.
- Enable more efficient and cost-effective clinical trials and real world studies.
- Create business opportunities and economic growth by bringing technology companies and sensor developers into medically regulated space and drive new developments in data standards and privacy safeguards.

Type of actions:

Research and Innovation Actions

Calls for Proposals

Call number and topics	Call launch timing	IMI2 JU funding (in EUR) ^{3,4}	In-kind contribution (in EUR) from EFPIA entities and Associated Partners
<u>IMI2 Call 14</u>	15 March 2018	82 357 000	84 920 360
<p>Immunology</p> <ul style="list-style-type: none"> ▪ Targeted immune intervention for the management of non-response and relapse (RIA)⁵ ▪ Non-invasive clinical molecular imaging of immune cells (RIA)⁶ 			
<p>Digital health and patient centric evidence generation</p> <ul style="list-style-type: none"> ▪ Development of a platform for federated and privacy-preserving machine learning in support of drug discovery (RIA)⁷ ▪ Centre of excellence – remote decentralised clinical trials (RIA)⁸ 			
IMI2 Call 14 process			
<p>Two-stage call with predefined submission deadline. Indicative Call deadline for Short proposals: 14 June 2018 Indicative Call deadline for Full Proposals: 11 December 2018 Research and Innovation Actions (RIA)</p>			

³ Based on total operational commitment appropriations available in 2018. This is without prejudice to commitment appropriations to be carried over from 2017 to 2018 (to be approved during 2018).

⁴ The maximum possible rate of co-financing is 100 %.

⁵ Potential applicants must be aware that this topic, if exceptionally needed, may be subject to a restricted follow-up Call for proposals to be launched by IMI 2 JU at a later stage. This follow-up Call for proposals may be restricted to the consortium already selected under such topic, in order to enhance its results and achievements. The consortium will be entitled to open to other beneficiaries as appropriate. The detailed scope of the restricted Call shall be described in the relevant Annual Work Plan.

⁶ Potential applicants must be aware that this topic, if exceptionally needed, may be subject to a restricted follow-up Call for proposals to be launched by IMI 2 JU at a later stage. This follow-up Call for proposals may be restricted to the consortium already selected under such topic, in order to enhance its results and achievements. The consortium will be entitled to open to other beneficiaries as appropriate. The detailed scope of the restricted Call shall be described in the relevant Annual Work Plan.

⁷ Potential applicants must be aware that this topic, if exceptionally needed, may be subject to a restricted follow-up Call for proposals to be launched by IMI 2 JU at a later stage. This follow-up Call for proposals may be restricted to the consortium already selected under such topic, in order to enhance its results and achievements. The consortium will be entitled to open to other beneficiaries as appropriate. The detailed scope of the restricted Call shall be described in the relevant Annual Work Plan.

⁸ Potential applicants must be aware that this topic, if exceptionally needed, may be subject to a restricted follow-up Call for proposals to be launched by IMI 2 JU at a later stage. This follow-up Call for proposals may be restricted to the consortium already selected under such topic, in order to enhance its results and achievements. The consortium will be entitled to open to other beneficiaries as appropriate. The detailed scope of the restricted Call shall be described in the relevant Annual Work Plan.

Call number and indicative topics	Call launch timing	IMI2 JU funding (in EUR) ^{9, 10}	In-kind contribution (in EUR) from EFPIA entities and Associated Partners
<p style="text-align: center;">IMI2 Call 15</p> <p>Neurodegeneration and other Neuroscience Priorities</p> <ul style="list-style-type: none"> ▪ Development and validation of translational platforms in support of synaptopathy drug discovery (RIA) <p>Immunology</p> <ul style="list-style-type: none"> ▪ Microenvironment imposed signatures in tissue and liquid biopsies in immune-mediated diseases (RIA)¹¹ ▪ Emerging translational safety technologies and tools for interrogating human immuno-biology (RIA) <p>Infection control including vaccines</p> <ul style="list-style-type: none"> ▪ AMR Accelerator programme Pillar A: Capability Building Network to accelerate and validate scientific discoveries (RIA)¹² ▪ AMR Accelerator programme Pillar B: Tuberculosis drug development network to accelerate and validate scientific discoveries and advance the R&D pipeline of new and innovative agents to address the global tuberculosis epidemic (RIA) <p>Digital health and patient centric evidence generation</p> <ul style="list-style-type: none"> ▪ Digital endpoints in neurodegenerative and immune-mediated diseases (RIA) ▪ Integrated research platforms enabling patient-centric drug development (RIA) ▪ Blockchain Enabled Healthcare (RIA)¹³ 	18 July 2018	171 875 862	214 847 000
IMI2 Call 15 process			
<p>Two-stage call with predefined submission deadline. Indicative Call deadline for Short proposals: 24 October 2018 Indicative Call deadline for Full Proposals: 15 May 2019 Research and Innovation Actions (RIA)</p>			

⁹ Based on estimate of total operational commitment appropriations available in 2018. This is without prejudice to commitment appropriations to be carried over from 2017 to 2018 (to be determined early 2018).

¹⁰ The maximum possible rate of co-financing is 100 %.

¹¹ Potential applicants must be aware that this topic, if exceptionally needed, may be subject to a restricted follow-up Call for proposals to be launched by IMI 2 JU at a later stage. This follow-up Call for proposals may be restricted to the consortium already selected under such topic, in order to enhance its results and achievements. The consortium will be entitled to open to other beneficiaries as appropriate. The detailed scope of the restricted Call shall be described in the relevant Annual Work Plan.

¹² Potential applicants must be aware that this topic, if exceptionally needed, may be subject to a restricted follow-up Call for proposals to be launched by IMI 2 JU at a later stage. This follow-up Call for proposals may be restricted to the consortium already selected under such topic, in order to enhance its results and achievements. The consortium will be entitled to open to other beneficiaries as appropriate. The detailed scope of the restricted Call shall be described in the relevant Annual Work Plan.

¹³ Potential applicants must be aware that this topic, if exceptionally needed, may be subject to a restricted follow-up Call for proposals to be launched by IMI 2 JU at a later stage. This follow-up Call for proposals may be restricted to the consortium already selected under such topic, in order to enhance its results and achievements. The consortium will be entitled to open to other beneficiaries as appropriate. The detailed scope of the restricted Call shall be described in the relevant Annual Work Plan.

Call number and indicative topics	Call launch timing	IMI2 JU funding (in EUR) ^{9, 10}	In-kind contribution (in EUR) from EFPIA entities and Associated Partners
<p style="text-align: center;">IMI2 Call 16</p> <p>Infection control including vaccines</p> <ul style="list-style-type: none"> ▪ AMR Accelerator programme Pillar C: Portfolio Building Networks (PBN) to advance the R&D pipeline of new and innovative agents to address AMR. Progress new assets (one pre-new molecular entity (preNME) and one first-time-in-human (FTIH) start) for tuberculosis(TB) that act synergistically with bedaquiline, cytochrome bc or cytochrome bd inhibitors (RIA)¹⁴ ▪ AMR Accelerator programme Pillar C: Portfolio Building Networks (PBN) to advance the R&D pipeline of new and innovative agents to address AMR. Progress novel assets (one FTIH start) for non-tubercular mycobacteria (NTM) that may act synergistically with bedaquiline, and cytochrome bc drugs. (RIA)¹⁵ ▪ AMR Accelerator programme Pillar C: Portfolio Building Networks (PBN) to advance the R&D pipeline of new and innovative agents to address AMR. Discover and progress novel assets with new mechanisms of action (one preNME for TB and one pre NME for NTM) and biomarkers for TB and NTM infection. (RIA)¹⁶ ▪ AMR Accelerator programme Pillar C: Portfolio Building Networks (PBN) to advance the R&D pipeline of new and innovative agents to address AMR. Determination of gepotidacin levels in tonsils and prostatic tissue. (RIA) ▪ AMR Accelerator programme Pillar C: Portfolio Building Networks (PBN) to advance the R&D pipeline of new and innovative agents to address AMR. Infection site targeting, antibiotic encapsulated in nanoparticles for treating extracellular bacterial infections. (RIA) 	18 July 2018	46 900 000	0

¹⁴ Potential applicants must be aware that this topic, if exceptionally needed, may be subject to a restricted follow-up Call for proposals to be launched by IMI 2 JU at a later stage. This follow-up Call for proposals may be restricted to the consortium already selected under such topic, in order to enhance its results and achievements. The consortium will be entitled to open to other beneficiaries as appropriate. The detailed scope of the restricted Call shall be described in the relevant Annual Work Plan.

¹⁵ Potential applicants must be aware that this topic, if exceptionally needed, may be subject to a restricted follow-up Call for proposals to be launched by IMI 2 JU at a later stage. This follow-up Call for proposals may be restricted to the consortium already selected under such topic, in order to enhance its results and achievements. The consortium will be entitled to open to other beneficiaries as appropriate. The detailed scope of the restricted Call shall be described in the relevant Annual Work Plan.

¹⁶ Potential applicants must be aware that this topic, if exceptionally needed, may be subject to a restricted follow-up Call for proposals to be launched by IMI 2 JU at a later stage. This follow-up Call for proposals may be restricted to the consortium already selected under such topic, in order to enhance its results and achievements. The consortium will be entitled to open to other beneficiaries as appropriate. The detailed scope of the restricted Call shall be described in the relevant Annual Work Plan.

Call number and indicative topics	Call launch timing	IMI2 JU funding (in EUR) ^{9, 10}	In-kind contribution (in EUR) from EFPIA entities and Associated Partners
<ul style="list-style-type: none"> ▪ AMR Accelerator programme Pillar C: Portfolio Building Networks (PBN) to advance the R&D pipeline of new and innovative agents to address AMR. Functional Ethionamide boosters, a novel combination for TB therapy. <i>(RIA)</i> <hr style="border: 1px solid #ccc; margin: 10px 0;"/> <ul style="list-style-type: none"> ▪ AMR Accelerator programme Pillar C: Portfolio Building Networks (PBN) to advance the R&D pipeline of new and innovative agents to address AMR. Intravenous treatments of serious infections (urinary tract infections (UTI), intra-addominal infections (IAI) & hospital-acquired pneumonia/ventilator associated pneumonia (HAP/VAP)) caused by Gram(-) bacteria (Enterobacteriaceae +/- Pseudomonas and/or Acinetobacter. <i>(RIA)</i> 			
IMI2 Call 16 process			
Single-stage call with predefined submission deadline. Indicative Call deadline for proposals: 24 October 2018 Research and Innovation Actions (RIA)			

Overall total	301 132 862	299 767 360
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Budget

A table overview of the operational budget for 2018 is set out below.

	Heading Title 3	Budget 2018.0		Budget 2018 Amendment 2		Amended Budget 2018.2		Comments
Chapter		Commitment Appropriation (CA)	Payment Appropriation (PA)	Commitment Appropriation (CA)	Payment Appropriation (PA)	Commitment Appropriation (CA)	Payment Appropriation (PA)	
30	Implementing the research agenda of IMI JU	265,331,457	205,596,167			265,331,457	205,596,167	Grant agreements - Payments
C2	Appropriations carried over from previous years			209,724,074	54,709,354	209,724,074	54,709,354	
	Total operational costs Title 3	265,331,457	205,596,167	209,724,074	54,709,354	475,055,531	260,305,521	

The difference between the total budget available for Title 3 (EUR 475,055,531) and the budget available for fresh Calls in 2018 (EUR 265,331,457) is EUR 209,724,074. This amount represents the unused commitment appropriations carried over to the 2018 budget, to conclude Grant Agreements for IMI2 - Call 10 (EUR 173,890,000), IMI1 amounts recovered from beneficiaries in 2017 carried over to the 2018 budget (EUR 25,669), amount carried over to the 2018 budget for IMI2 projects (EUR 35,801,405) and amount for IMI2 projects late payment interests (EUR 7,000).

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

Description	Commitment Appropriation (CA)	Payment Appropriation (PA)
unused operational appropriations IMI2 (H2020) (2017, 2018)	7,000	54,709,354
unused operational appropriations IMI2 (H2020) Call 10 EUR 173,890,000 (2017) carried over for Grant Agreements IMI2 Call 10	173,890,000	
unused operational appropriations carried over for new Calls to be launched in 2018	35,801,405	
<i>IMI2 (H2020) Call 13 (2017)</i>	<i>8,074,331</i>	
<i>IMI2 (H2020) Call 9 (2017)</i>	<i>722,479</i>	
<i>IMI2 (H2020) Call 8 (2018)</i>	<i>22,531,012</i>	
<i>IMI2 (H2020) Call 11 (2018)</i>	<i>1,716,007</i>	
<i>IMI2 (H2020) Call 13 (2018)</i>	<i>2,080,000</i>	
<i>50 % unused running costs (2017) carried over for new Calls to be launched in 2018</i>	<i>677,576</i>	
IMI1 (FP7) amounts recovered in 2017 from beneficiaries (to be carried over for IMI1)¹⁷	25,669	
TOTAL	209,724,074	54,709,354

A table overview of the 2018 Budget is set out in Chapter 4 to this Annual Work Plan.

¹⁷ Recoveries could be used only with respect to IMI'1' related appropriations

3.2.3 Call management (planning, evaluation, selection)

Activities related to proposals evaluation and grant preparation

Key activities in 2018 will comprise the launch of two competitive Calls for proposals implementing the 2018 scientific priorities with indicative launch dates on 15 March 2018 and 18 July 2018. In a single-stage submission evaluation procedure, from the initial publication of the Call for proposals the submission deadline will be approximately three months from the publication of the calls for proposals. IMI2 JU will utilise the H2020 Participant Portal and Horizon 2020 IT infrastructure.

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

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

In addition, the evaluation of short proposals and full proposals submitted to Calls launched under the AWP in 2018 will be held according to the predefined timelines established in the relevant Call for proposals.

Timelines for completion of the evaluation process and of preparation will be kept as lean as possible with the aim of completing signature of the Grant Agreements within applicable time to grant (TTG), in compliance with the Horizon 2020 framework, i.e. a maximum of eight months from the final date of submission of the full proposals.¹⁸

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

3.2.4 Activities to support and monitor ongoing projects

58 ongoing projects will be running at different stages of their life cycle in 2018 with additional projects coming online during the year when Call 8 Ebola+ (4th and 5th cut-off), Call 10 (launched in 2016) and two calls launched in 2017 (Calls 11 and 12) complete their evaluation cycles (as indicated in the second column on the below table– “ongoing in 2018”). All projects will submit to IMI2 JU a periodic report for the previous year summarising their progress and costs incurred. These reports form the basis for the Programme Office’s ex-ante controls.

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

Given the current planning and project durations, it is expected that IMI2 JU will organise 14 reviews for projects launched under IMI1 JU (Calls 6, 9 and 11) and IMI2 JU (Calls 1, 2, 3, 5, 6 and 7).

¹⁸ Article 20 of the Regulation (EU) No 1290/2013 of the European Parliament and of the Council of 11 December 2013 laying down the rules for participation and dissemination in “Horizon 2020”

The following table presents a forecast of the reporting expected for 2018.

IMI Calls	ongoing in 2018	Project periodic report due in 2018						Of which	
		1st RP	2nd RP	3rd RP	4th RP	5th to 7th RP	Total	finishing in 2018	Final report due 2018
1	0	0	0	0	0	0	0	0	0
2	0	0	0	0	0	1	1	0	1
3	3	0	0	0	0	4	4	2	3
4	3	0	0	0	0	3	3	3	2
5	1	0	0	0	0	1	1	1	1
6	1	0	0	0	0	2	2	0	1
7	1	0	0	0	0	1	1	1	1
8	3	0	0	0	4	0	4	1	2
9	2	0	0	3	1	0	4	0	2
10	1	0	0	1	0	0	1	0	0
11	8	0	1	7	0	0	8	1	1
IMI2 C1	1	0	0	1	0	0	1	0	0
IMI2 C2	4	0	1	6	0	0	7	2	5
IMI2 C3	5	0	5	0	0	0	5	0	0
IMI2 C4	0	0	1	0	0	0	1	0	1
IMI2 C5	6	1	5	0	0	0	6	0	0
IMI2 C6	4	3	1	0	0	0	4	1	1
IMI2 C7	7	7	0	0	0	0	7	0	0
IMI2 C8	3	1	1	0	0	0	2	0	0
IMI2 C9	6	6	0	0	0	0	6	0	0
IMI2 C10	8	0	0	0	0	0	0	0	0
IMI2 C11	7*	0	0	0	0	0	0	0	0
IMI2 C12	7	0	0	0	0	0	0	0	0
Total	81	18	15	18	5	12	68	12	21

* The estimated number is based on the number of key project results identified in the call text (7 projects)

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

3.2.5 Monitoring and analysis of projects' results

68 project periodic reports will be submitted in 2018 (for ongoing and finalised in 2017 IMI projects – see column 8 in the above table– “Project periodic report due in 2018 – Total”). These reports will be used to track progress against their stated objectives and deliverables as laid out in the relevant description of the action.

This reporting will also allow an assessment of project achievements and the impact of results. In addition to the usual ex-ante controls, a combination of internal management information systems, external databases, independent evaluations and, if necessary, commissioned studies and surveys will be used to measure the progress and identify significant achievements of IMI projects. For projects resulting from IMI2 JU calls launched from December 2016 onwards, this monitoring will be done using the functionalities of the Horizon 2020 IT infrastructures.

In 2018 the analysis of the IMI2 JU project scientific outputs in terms of publications and collaboration among IMI researchers will be continued. Where feasible, monitoring and analysis approaches will be refined in line with observations from the European Court of Auditors (ECA) to ensure the highest possible standards.

3.2.6 Stakeholders' engagement and external collaborations

In 2018 IMI2 JU will continue to develop its relationships and engagement with key stakeholders such as patients, small and medium-sized enterprises, regulators, payers and healthcare professions to ensure that its outputs are aligned with and address the needs of society.

IMI2 JU's goal is to champion a patient centric-approach at all levels and encourage all the projects that it funds to work in partnership with patients wherever possible. IMI2 JU has listened to the needs expressed by patients and will create an IMI2 JU Patient Community which will give the patient voice a more prominent position in IMI both strategically and operationally. In addition, IMI2 JU aims to recruit a Seconded National Expert (SNE) to help drive the creation of the IMI2 JU Patient Community (IMI PC) as well as, coordinate and implement the patient engagement strategy of IMI2 JU.

Given their importance in driving employment and innovation in the European Union and the H2020 Associated Countries, the IMI2 JU will increase its engagement with SMEs and encourage their participation in IMI2 JU projects. In 2018, the IMI2 JU will continue to highlight SME opportunities in all topic texts and also embed SME participation at the earliest stages of topic development through collaboration with the Strategic Governance Groups and through exploring call designs more appealing to SMEs.

The IMI2 JU will also continue to develop and disseminate targeted materials for SMEs and continue the SME outreach programme outlined in the IMI2 JU SME strategy. This includes partnering with other European, national and regional clusters to participate in events aimed at encouraging SMEs to apply and participate in IMI2 JU projects.

The regulatory environment is key to ensuring that safe and effective medicines reach the market for the benefit of patients. To date, IMI2 JU has been able to use its unique platform to create an interface between science and regulation. IMI2 JU will continue to develop this framework to engage with all relevant regulatory agencies. In particular, IMI2 JU will support optimising the scientific engagement of the European Medicines Agency (EMA) in IMI2 JU, expected to operate at three levels: strategic science-based recommendation, topics of interest definition within a specific research area, and engagement with research projects. IMI2 JU will also continue to foster engagement with competent national authorities as well as relevant HTA bodies in order to progress the goal of end-to-end integration in medicine development.

One important strategic objective for IMI2 JU is the involvement of other than the pharmaceutical sectors. For example, IMI2 JU has successfully brought together the major European diagnostics companies in 2017, an effort that will continue to be strengthened and supported throughout 2018. Likewise, important steps to engage the major players in the food and nutrition sector in discussions around a potential programme dedicated to the microbiome, started in 2017, and will be further facilitated in 2018.

IMI2 JU and ECSEL JU (www.ecsel.eu) initiated in 2017 the first discussions to explore possibilities for cooperation between both JU's in the domain of smart health along three thematic areas: sensors and diagnostics, imaging, and patient monitoring platforms. For 2018, dedicated workshops between sensor and diagnostics projects of the respective JU's are planned to explore synergies and potential collaborations, as well as follow-up discussions to identify gaps and a roadmap of common strategic priorities.

As the healthcare challenges faced by society are global, IMI2 JU will explore interactions and seek synergies with non-EU organisations when appropriate, for example in the area of antimicrobial resistance and biopreparedness. In an effort to align strategies and ensure complementarities, IMI2 JU and the Coalition for Epidemic Preparedness Innovations (CEPI) have agreed in 2017 to refer to each other's activities on their websites. In 2018, IMI2 JU will continue to exchange with CEPI and explore potential collaboration.

IMI2 JU and the Critical Path Institute (C-Path) are aligned in many of their scientific priorities, formalised by a Memorandum of Understanding (MoU) signed in 2011. IMI2 JU will continue to interact with C-PATH in 2018 and adapt the relationship as needed. IMI2 JU will also continue to sit on the Scientific Advisory Committee of C-FAST, an initiative formed in June 2012 by CDISC (Clinical Data Interchange Standards Consortium) and C-Path to accelerate clinical research and medical product development by creating and maintaining data standards, tools and methods for conducting research in therapeutic areas that are important to public health.

In order to share best practice between projects and develop potential synergies, IMI2 JU will encourage its projects to organise cross-project meetings for both IMI2-JU-funded and other initiatives. This is particularly important in helping disseminate information about IMI2 JU and ensuring harmonisation of approaches at both a European and global level. For example, for Q4 2018, a cross project meeting in the area of Mental Health involving IMI2-JU- funded projects as well as projects currently funded under H2020 and collaborating/synergistic initiatives funded by NIMH/NIH (examples are <https://www.nimh.nih.gov/about/organization/dtr/index.shtml>; <https://www.nimh.nih.gov/research-priorities/research-initiatives/fast-fast-fail-trials.shtml>; <https://www.nimh.nih.gov/research-priorities/rdoc/index.shtml>) and SFARI (<https://www.sfari.org/>) is envisaged. The meeting will allow cross-fertilisation between the projects with a focus on the aspects of digital technology applications in this research area.

3.2.7 Dissemination and information about projects results

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

The IMI Programme Office identifies results and successes in a variety of ways, including through formal routes (project periodic reports, interim reviews) and informal routes (direct contacts with project participants, monitoring of project websites and social media, etc.). IMI2 JU will continue to support and supplement the dissemination of projects' public deliverables via a variety of channels, including the IMI2 JU and projects' websites, newsletter, social media (Twitter and LinkedIn), the press and events. In addition, IMI will continue to explore how to make better use of EU specific dissemination channels for the promotion of projects and their results. In addition, following on from a pilot study performed in 2016 on the impact of IMI2 JU projects on the 3Rs (i.e. the replacement, reduction and refinement of animal use in research), IMI2 JU will undertake a more detailed analysis in 2018 on the contribution of project results to this specific area.

In 2018, the IMI2 JU expects to receive 21 final project reports. These reports will come from projects finishing in 2017 but reporting in 2018 (11 projects) and those finishing and reporting in 2018 (10 projects). In addition, 2 projects reaching their end date in 2018 will report in 2019. Capturing the outcomes and impacts of these projects presents IMI with a continuing challenge of ensuring that project results are disseminated widely and taken up by researchers in the field.

It is expected that at least 20 close-out meetings will be organised around the time of the final report submission. The close out meeting provides an opportunity for the consortium to present to the IMI2 JU how the project has reached its objectives, to highlight tangible results and to put the achievements of the project into context and to discuss the potential impact and legacy management. Members of EFPIA, the EC, IMI2 JU Scientific Committee and relevant SGG will be invited to attend the close out meetings to share not only in the results but also in the learnings and experiences of the project consortia. The IMI2 JU will prepare specific communication materials for each project based upon information provided in the respective final report and close out meeting.

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

3.2.8 Socio-economic impact study

The second phase of the socio-economic impact study begun in 2017 will continue in 2018. The study utilises the previously developed methodology and applies it to the next wave of IMI1 projects that have completed or are drawing to a close. As with the original study this new evaluation looks at short-term outcomes (2-3 years) such as improved scientific quality, enhanced knowledge production, network-based R&D capacity building, and human resources development. It also considers mid-term impacts (4-5 years) and longer term outcomes, known as 'wealth and health' benefits. Mid-term impacts indicators include concrete results on biomarker validation/toxicology test, big data and shared IT infrastructures, improved knowledge transfer and communication. This study is necessary in order to enhance our performance evaluation framework which is currently under review.

The final report will be ready for publication by the end of 2018 and will be disseminated to all stakeholders, including policy makers at the European level. It is expected that this study will cost approximately 20.000 EUR.

3.3 Call management rules

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

The following general conditions shall apply to the IMI2 JU Calls for Proposals. They are based on the General Annexes to the Horizon 2020 Work Programme 2018-2020¹⁹.

LIST OF COUNTRIES AND APPLICABLE RULES FOR FUNDING

By way of derogation²⁰ from Article 10(1) of Regulation (EU) No 1290/2013, only the following participants shall be eligible for funding from the Innovative Medicines Initiative 2 Joint Undertaking:

- (a) legal entities established in a Member State or an associated country, or created under Union law; and
- (b) which fall within one of the following categories:
 - (i) micro, small and medium-sized enterprises and other companies with an annual turnover of EUR 500 million or less, the latter not being affiliated entities of companies with an annual turnover of more than 500 million; the definition of 'affiliated entities' within the meaning of Article 2(1)(2) of Regulation (EU) No 1290/2013 shall apply *mutatis mutandis*;
 - (ii) secondary and higher education establishments;
 - (iii) non-profit organisations, including those carrying out research or technological development as one of their main objectives or those that are patient organisations.
- (c) the Joint Research Centre;
- (d) international European interest organisations.

Participating legal entities listed in (b) above established in a third country may receive funding from the IMI 2 JU provided their participation is deemed essential for carrying out the action by the IMI 2 JU or when such funding is provided for under a bilateral scientific and technological agreement or any other arrangement between the Union and the country in which the legal entity is established²¹.

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 Work Plan.

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

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

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

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 Work Plan.

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

¹⁹ http://ec.europa.eu/research/participants/data/ref/h2020/other/wp/2018-2020/annexes/h2020-wp1820-annex-ga_en.pdf

²⁰ 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

²¹ In accordance with Article 10(2) of the Regulation (EU) No 1290/2013 and Article 1 of Commission Delegated Regulation (EU) No 622/2014

The participants from EFPIA constituent entities and affiliated entities and other Associated Partners which are pre-defined in the topics - under the section 'Industry consortium' - of a call for proposals do not apply at the stage 1 of the call. The applicant consortium selected from the stage 1 of the Call for Proposals is merged at the stage 2 with the EFPIA constituent entities or their affiliated entities and other Associated Partners.²²

Furthermore, in the context of the IMI2 JU 16 Call for proposals, (single-stage calls for proposals) under the scientific priority 'Infection control including vaccines', the following conditions apply

- The additional condition for participation²³ that each applicant consortium must include at least one EFPIA constituent or affiliated entity. This requirement is justified by the particular interest in establishing a mechanism for dedicated partnerships between EFPIA constituent or affiliated entities, and SMEs and/or academic teams, for the discovery and development of new antibacterial assets to address antimicrobial resistance (AMR). AMR is a major European and global challenge and a major public health concern. One of the goals of the European One Health Action Plan against AMR is "to increase the development and availability of new effective antimicrobials inside and outside the EU". EFPIA constituent entities or affiliated entities are uniquely placed to have the capability to ensure that during the rapid progression of new compounds and candidate drugs and vaccines in the projects to be selected under IMI2 JU Call 16 all the relevant regulatory and other requirements from jurisdictions around the world are appropriately considered, so that the generated data can be used when regulatory filings will be made;
- In derogation²⁴ to the eligibility conditions for participation established under Part C of the General Annexes to the Horizon 2020 – Work Programme 2018 – 2020, the minimum conditions for applicant consortia for Research & Innovation Actions (RIA) under Call 16 shall be of at least two legal entities, independent from each other, established in different EU Member States or countries associated to Horizon 2020. The limited size of the applicant consortia is justified by the specificity of the AMR research space where small consortia operate to rapidly progress towards the development of new compounds while maintaining operation agility.

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 Work Plan.

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 Work Plan.

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 Work Plan with the following additions:

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

Award criteria and scores:

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

²² 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"

²³ 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".

²⁴ Article 9(5) of the Regulation (EU) No 1290/2013 of the European Parliament and of the Council of 11 December 2013 laying down the rules for participation and dissemination in "Horizon 2020".

Type of action	Excellence	Impact	Quality and efficiency of the implementation
RIA and IA 1st stage evaluation	<p>The following aspects will be taken into account, to the extent that the proposed work corresponds to the topic description in the call for proposals and referred to in the IMI2 annual work plan:</p> <p>Clarity and pertinence of the proposal to meet all key objectives of the topic;</p> <p>Credibility of the proposed approach;</p> <p>Soundness of the concept, including trans-disciplinary considerations, where relevant;</p> <p>Extent that proposed work is ambitious, has innovation potential, and is beyond the state of the art;</p> <p>Mobilisation of the necessary expertise to achieve the objectives of the topic, ensure engagement of all relevant key stakeholders</p>	<p>The following aspects will be taken into account, to the extent to which the outputs of the project should contribute at the European and/or International level:</p> <p>The expected impacts of the proposed approach as mentioned in the call for proposals</p> <p>Added value from the public private partnership approach on R&D, regulatory, clinical and healthcare practice as relevant;</p> <p>Strengthening the competitiveness and industrial leadership and/or addressing specific societal challenges;</p> <p>Improving European citizens' health and wellbeing and contribute to the IMI2 objectives²⁵.</p>	<p>The following aspects will be taken into account:</p> <p>Coherence and effectiveness of the outline of the project work plan, including appropriateness of the roles and allocation of tasks, resources, timelines and approximate budget;</p> <p>Complementarity of the participants within the consortium (where relevant) and strategy to create a successful partnership with the industry consortium as mentioned in the topic description in the Call for proposal;</p> <p>Appropriateness of the proposed management structures and procedures, including manageability of the consortium.</p>
RIA and IA Single stage, and 2nd stage evaluation	<p>The following aspects will be taken into account, to the extent that the proposed work corresponds to the topic description in the call for proposals and referred to in the IMI2 annual work plan and is consistent with the stage 1 proposal:</p> <p>Clarity and pertinence of the proposal to meet all key objectives of the topic;</p>	<p>The following aspects will be taken into account, to the extent to which the outputs of the project should contribute at the European and/or International level:</p> <p>The expected impacts of the proposed approach as mentioned in the call for proposals;</p> <p>Added value from the public private partnership approach on R&D, regulatory, clinical and healthcare practice as relevant;</p>	<p>The following aspects will be taken into account:</p> <p>Coherence and effectiveness of the project work plan, including appropriateness of the roles and allocation of tasks, resources, timelines and budget;</p> <p>Complementarity of the participants within the consortium (where relevant);</p>

²⁵ Article 2 of the Council Regulation (EU) No 557/2014 of 6 May 2014 establishing the Innovative Medicines Initiative 2 Joint Undertaking (O.J. L169 of 7.6.2014)

Type of action	Excellence	Impact	Quality and efficiency of the implementation
	<p>Credibility of the proposed approach;</p> <p>Soundness of the concept, including trans-disciplinary considerations, where relevant;</p> <p>Extent that proposed work is ambitious, has innovation potential, and is beyond the state of the art;</p> <p>Mobilisation of the necessary expertise to achieve the objectives of the topic, ensure engagement of all relevant key stakeholders.</p>	<p>Enhancing innovation capacity and integration of new knowledge;</p> <p>Strengthening the competitiveness and industrial leadership and/or addressing specific societal challenges;</p> <p>Improving European citizens' health and wellbeing and contribute to the IMI2 objectives;²⁵</p> <p>Any other environmental and socially important impacts;</p> <p>Effectiveness of the proposed measures to exploit and disseminate the project results (including management of IPR), to communicate the project, and to manage research data where relevant.</p>	<p>Clearly defined contribution to the project plan of the industrial partners (where relevant);</p> <p>Appropriateness of the management structures and procedures, including manageability of the consortium, risk and innovation management and sustainability plan.</p>
Type of action	Excellence	Impact	Quality and efficiency of the implementation
<p>CSA</p> <p>1st stage</p> <p>evaluation</p>	<p>The following aspects will be taken into account, to the extent that the proposed work corresponds to the topic description in the Call for proposal and referred to in the IMI2 annual work plan:</p> <p>Clarity and pertinence of the proposal to meet all key objectives of the topic</p> <p>Credibility of the proposed approach;</p> <p>Soundness of the concept, including trans-disciplinary considerations, where relevant;</p> <p>Quality of the proposed coordination and/or support measures.</p> <p>Mobilisation of the necessary expertise to achieve the objectives of the topic, ensure</p>	<p>The following aspects will be taken into account, to the extent to which the outputs of the project should contribute at the European and/or International level:</p> <p>The expected impacts of the proposed approach as mentioned in the Call for proposal;</p> <p>Added value from the public private partnership approach on R&D, regulatory, clinical and healthcare practice as relevant.</p> <p>Strengthening the competitiveness and industrial leadership and/or addressing specific societal challenges;</p> <p>Improving European citizens' health and wellbeing and</p>	<p>The following aspects will be taken into account:</p> <p>Coherence and effectiveness of the outline of the project work plan, including appropriateness of the roles and allocation of tasks, resources, timelines and approximate budget;</p> <p>Complementarity of the participants within the consortium (where relevant) and strategy to create a successful partnership with the industry consortium as mentioned in the topic description in the Call for proposal.</p> <p>Appropriateness of the proposed management structures and procedures, including</p>

Type of action	Excellence	Impact	Quality and efficiency of the implementation
	engagement of all relevant key stakeholders.	contribute to the IMI2 objectives ²⁶ .	manageability of the consortium.
CSA Single stage and 2nd stage evaluation	<p>The following aspects will be taken into account, to the extent that the proposed work corresponds to the topic description in the Call for proposal and referred to in the IMI2 annual work plan and is consistent with the stage 1 proposal:</p> <p>Clarity and pertinence of the proposal to meet all key objectives of the topic;</p> <p>Credibility of the proposed approach;</p> <p>Soundness of the concept, including trans-disciplinary considerations, where relevant;</p> <p>Quality of the proposed coordination and/or support measures.</p> <p>Mobilisation of the necessary expertise to achieve the objectives of the topic and to ensure engagement of all relevant key stakeholders.</p>	<p>The following aspects will be taken into account, to the extent to which the outputs of the project should contribute at the European and/or International level:</p> <p>The expected impacts of the proposed approach as mentioned in the Call for proposal;</p> <p>Added value from the public private partnership approach on R&D, regulatory, clinical and health care practice as relevant</p> <p>Strengthening the competitiveness and industrial leadership and/or addressing specific societal challenges;</p> <p>Improving European citizens' health and wellbeing and contribute to the IMI2 objectives²⁷.</p> <p>Effectiveness of the proposed measures to exploit and disseminate the project results (including management of IPR), to communicate the project, and to manage research data where relevant.</p>	<p>The following aspects will be taken into account:</p> <p>Coherence and effectiveness of the project work plan, including appropriateness of the roles and allocation of tasks, resources, timelines and budget;</p> <p>Complementarity of the participants within the consortium (where relevant);</p> <p>Clearly defined contribution to the project plan of the industrial partners (where relevant);</p> <p>Appropriateness of the management structures and procedures, including manageability of the consortium, risk and innovation management and sustainability plan.</p>

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

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

²⁶ Article 2 of the Council Regulation (EU) No 557/2014 of 6 May 2014 establishing the Innovative Medicines Initiative 2 Joint Undertaking (O.J. L169 of 7.6.2014)

²⁷ Article 2 of the Council Regulation (EU) No 557/2014 of 6 May 2014 establishing the Innovative Medicines Initiative 2 Joint Undertaking (O.J. L169 of 7.6.2014)

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

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

The full evaluation procedure is described in the IMI2 JU Manual for submission, evaluation and grant award in line with the H2020 Rules for Participation.²⁸

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

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

Under the two-stage evaluation procedure, and on the basis of the outcome of the first stage evaluation, the applicant consortium of the highest ranked short proposal (first stage) for each topic²⁹ will be invited to discuss with the relevant industry consortium the feasibility of jointly developing a full proposal (second stage). The applicant consortia of the second and third-ranked short proposals (first stage) for each topic may be invited for preliminary discussions with the industry consortium if the preliminary discussions with the first ranked proposal and the industry consortium fail. In such a case, the first applicant consortium and the industry consortium shall be responsible for jointly notifying the IMI2 JU if the preparation of a joint full proposal is not feasible. This notification must be accompanied by a joint report clearly stating the reasons why a joint full proposal is considered not feasible. Upon acknowledgement and after consideration of the specific circumstances, the IMI2 JU may decide to invite the next-ranked applicant consortium in priority order, i.e. the second ranked proposal is contacted only after failure of preliminary discussions with the first ranked, and the third ranked after the second ranked.

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

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

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

²⁸ http://www.imi.europa.eu/sites/default/files/uploads/documents/apply-for-funding/call-documents/imi2/IMI2_ManualForSubmission_v1.6_October2017.pdf

²⁹ 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
Single-stage	Maximum 5 months from the submission deadline at the single stage.	N/A	Maximum 8 months from the submission deadline.
Two-stages	Maximum 5 months from the submission deadline at the first stage.	Maximum 5 months from the submission deadline at the second stage.	Maximum 8 months from the submission deadline at the second stage.

BUDGET FLEXIBILITY

Part I of the General Annexes to the Horizon 2020 - Work Programme 2018–2020 shall apply *mutatis mutandis* for the actions covered by this Work Plan.

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 Work Plan.

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 Work Plan.

However, should a project “opt-out” of these provisions, a Data Management Plan must still be prepared. A template for the Data Management Plan is available on the [IMI2 JU website](#).

SUBMISSION TOOL

Proposals in response to a topic of the IMI2 JU Call for proposals must be submitted on-line, before the call deadline, by the coordinator via the Electronic Submission Service of the Participant Portal: <http://ec.europa.eu/research/participants/portal/desktop/en/home.html>

No other means of submission will be accepted.

OTHERS

For proposals including clinical trials/studies/investigations, a specific template to help applicants to provide essential information on clinical studies in a standardised format is available under: <http://www.imi.europa.eu/apply-funding/call-documents/imi2-call-documents#imi2-call-documents-collapsible-1>.

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.³⁰

In order to ensure excellence in data and knowledge management consortia will be requested to Disseminate scientific publications on the basis of open access³¹ (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.

Single-stage proposals and 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 the IMI2 JU Calls should also read the topic text, the IMI2 JU Manual for submission, evaluation and grant award, and other relevant documents³² (e.g. IMI2 JU model Grant Agreement).

³⁰ Article 19 of Horizon 2020 Framework Programme and Articles 13 and 14 of the Horizon 2020 Rules for Participation.

³¹ 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

³² <http://www.imi.europa.eu/apply-funding/call-documents/imi2-call-documents>

3.4 Support to Operations

3.4.1 Communication and events

Communication objectives

The overarching objectives of IMI2 JU's communications efforts are:

- to raise awareness and perception of IMI2 JU among all target groups;
- to encourage experts from all relevant groups to apply for funding under IMI2 JU Calls for proposals (with a particular focus on groups such as patients and SMEs).

The year 2018 marks the 10th anniversary of the very first IMI Call for proposals and this will represent an excellent opportunity to both showcase what IMI has achieved and discuss its future direction. In addition, IMI2 JU is now gathering growing numbers of success stories from both ongoing and closed projects, and this will help to support the message that IMI is a successful initiative, delivering scientifically excellent results and offering value for money to taxpayers.

IMI's 10th anniversary

In 2018, IMI will celebrate its 10th anniversary, and this is an excellent hook for communications. IMI2 JU will therefore plan a year-long programme of events and activities across its communications channels to promote IMI's successes and encourage discussion on its future plans. Highlights of the year will include:

- a scientific symposium featuring IMI2 JU-funded research;
- a book of IMI projects;
- a series of short video interviews.

Development of the IMI2 JU website

The IMI2 JU website is undergoing a redesign that will be completed in late 2017. In 2018, IMI2 JU will focus on refining the content, and on building on the dedicated sections for core stakeholder groups, namely universities, patients, SMEs, regulatory bodies, HTA, payers, and industry.

Further develop success stories

IMI2 JU now holds meetings with the representatives of projects that have finished, learning about what the projects have achieved and their legacy. With a large number of projects scheduled to finish in 2017 and 2018, these meetings will provide IMI2 JU with a wealth of success stories that can be adapted for different audiences and channels and back up IMI2 JU's key messages. IMI2 JU will also continue to maintain close contacts with ongoing projects to gather and promote their latest news and results.

Media outreach

The coverage of IMI2 JU in both the general and specialist press tends to be either neutral or positive in tone. In 2018, IMI2 JU will work to ensure that this trend continues by building and maintaining links with journalists, issuing regular press releases, organising press interviews, and inviting journalists to IMI2 JU events.

At the same time, IMI2 JU will remain alert to issues that could damage IMI2 JU's reputation and respond accordingly, for example by preparing briefings or sets of questions and answers.

Communication channels

IMI2 JU will continue to develop the following channels:

- events (both IMI2 JU and external)
- website
- newsletter
- social media (LinkedIn, Twitter)
- multipliers (e.g. European Commission & EFPIA, States Representatives Group, Scientific Committee, National Contact Points, relevant scientific associations, patient organisations, etc.)
- media (general and specialist, mainly in Europe but also elsewhere)
- direct mailings
- publications
- videos
- direct contacts with opinion leaders.

Key events in 2018

Event	Timeline
Promote IMI2 JU projects	Ongoing
IMI2 JU presence in the European Parliament	Ongoing
IMI2 JU presence at relevant external events, e.g. BIO, BIO-Europe, ESOF, BioFIT	Throughout year
Event with and for patients	Q2
Promote IMI2 JU Calls for proposals (webinars, info days, website, etc.)	Q2, Q4
IMI2 JU scientific symposium (10 years)	Q4
IMI2 JU Stakeholder Forum 2018	Q4

3.4.2 Procurement and contracts

In order to reach its objectives and adequately support its operations and infrastructures, IMI2 JU will allocate funds to procure the necessary services and supplies. To make tender and contract management as effective and cost-efficient as possible, IMI2 JU makes as much use as possible of multi-annual framework contracts, several of which are inter-institutional in nature.

In 2018, IMI2 JU intends to implement one such framework contract by concluding a specific contract for the provision of external audit services for its 2018 and 2019 accounts. Most essential framework contracts are already in place or and will be running beyond 2018. The framework contract for the provision of IT services (for all Joint Undertakings occupying the White Atrium building) will come to an end in 2018. An open procedure will have to be launched in Q1 2018 to ensure seamless service continuity. The estimated budget for this tender is approximately 4,500,000 EUR, covering the needs of all contracting Joint Undertakings over a four-year period.

Furthermore, the IMI2 JU will launch an open call for tender for the conclusion of a communication services contract, for which the estimated value is 250,000 EUR, designed to cover the tenth anniversary events and activities mentioned in Section 2.4.1.

Finally, the framework contract for the provision of Ex-Post Audits for the Framework Programme 7 (for all EC services, DG RTD being the lead contractor) came to an end in 2017. An open call for tender will be launched in Q1 2018 for a cascade type framework contract with other Joint Undertakings (FCH JU and Clean Sky JU), with IMI2 JU as lead contractor, to ensure seamless service continuity. The estimated budget is 1,600,000 EUR, covering the needs of all contracting Joint Undertakings over a four-year period.

3.4.3 IT and logistics

IMI2 JU information and communications technologies (ICT) strategic objective is to deliver value to the business and to be a key enabler of new business initiatives with the goal of supporting and shaping the present and future of IMI. Operations and administration information systems and infrastructure aim at making all IMI processes simpler and more efficient.

In order to achieve the afore-mentioned goal IMI2 JU IT will focus its 2018 activities on three areas:

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

2.4.3.1 Business operations information systems

In 2017, IMI2 JU's business operations started utilising the full suite of H2020 IT tools for the management of IMI2 calls, applications, evaluations and grants.

With the full transition expected to be completed by the end of 2017, IT will monitor satisfactory functioning for all end-users, in close liaison with EC services.

IMI1 projects remain in IMI's in-house developed application SOFIA.

The reporting needs of various IMI's stakeholders are supported by Qlikview, which is a reporting tool with a variety of tailor-made dashboards, enabling the analysis of scientific and financial data regarding IMI calls and projects.

Since IMI1 projects continue running until at least 2020 the following developments are foreseen for SOFIA application:

- Maintenance (continuous) of the application with helpdesk support, bug fixes and implementation of service requests (Q1 – Q4 2018)

Moreover, the following developments are foreseen for Qlikview:

- Addition of reports based on the needs of external, for example EFPIA Office, SRG, and internal stakeholders, and improvement of currently available dashboards (Q1 – Q4 2018)

2.4.3.2 Collaboration, communication and administration management information systems

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

Furthermore, a number of web-based applications, related to human resources management, time management, mission management, document management, incident management and internal communications are available to IMI2 JU staff.

Last but not least, a new website was implemented in 2017, replacing the look and feel but also the back-end web content management system.

The following developments are foreseen in 2018 in order to safeguard the continuous improvement and increase of scope of the afore-mentioned systems:

- Enhancement of the applications regarding performance, usability and user interface in order to improve the end-user experience and facilitate IMI2 JU staff work (Q1 – Q4 2018)
- Maintenance (continuous) of the applications with helpdesk support, bug fixes and implementation of service requests (Q1 – Q4 2018)
- Implementation of the paperless office concepts based on the assessment of the practicality of current document repository application to support the automation of IMI2 JU's administrative processes compared to commercial off-the-shelf products with applied workflows, which is taking place in 2017 (Q2-Q4 2018).

Furthermore, in 2017 IMI2 JU considered the possibility of using the EC application SYSPER II for personnel time management. In 2018, IMI2 JU should move to SYSPER II, therefore all the necessary IT changes will have to take place in order to support this transition (Q3-Q4 2018).

2.4.3.3 Infrastructure, security and office automation support

IMI2 JU shares IT infrastructure, related IT operations and office automation support with other JUs that are also located in the same premises. In the context of the common infrastructure the following activities are foreseen for 2018, which are expected to provide with efficiency gains in the operation of the organisation:

- Maintenance (continuous) of the common infrastructure and networks and end-user office-automation support covering incidents, service requests and improvements (Q1 – Q4 2018)

- A new call for tenders for the provision of IT services (office support, IT infrastructure maintenance, etc.) that will lead to the signature of a new framework contract. (Q3- Q4 2018)

Moreover, IMI2 JU utilises an online infrastructure in order to host its business operations information systems, and the collaboration, communication and administration information systems mentioned above. The following activities are anticipated to take place in 2018 in the context of the dedicated infrastructure:

- Maintenance (continuous) of the online infrastructure (Q1 – Q4 2018).

3.4.4 Human Resources

The 2018 objective for HR shall be: recruit, train, assess, motivate and retain highly qualified staff with a view to ensure effective and efficient operation of the JU as well as ensuring equal opportunities. This objective will be implemented through the following four main themes:

Staffing

The staffing needs of IMI2 JU will be the same as in 2017. The total number of staff remains to 54 temporary and contract agents as well as 2 additional seconded national experts.

In accordance with the Staff Regulations, technical adaptations have been made to the Staff Establishment Plan in order to create margin for reclassification (promotions) of staff. Those adaptations do not affect the total number of staff, 54 (39 temporary agents and 15 contract agents).

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

Organisation development

Human resources will advise management on means and actions to enhance operational efficiency and effectiveness. The main action shall be the oversight of duties and responsibilities that has been assigned to best achieve fulfilment of objectives and tasks.

HR management

Human Resources will deal with core functions such as day-to-day management of administrative workflows and process, performance management and assessment, safety and wellbeing at work, salary, compensation and benefits, employee motivation, communication, and training.

In addition, during the second semester of 2018, IMI2 JU is expected to move to SYSPER II, which will help in the personnel administration.

Inter-JU cooperation

The efficiency and cost effective management of IMI2 JU resources is also based on a close collaboration with other Joint Undertakings through arrangements and mechanisms of pooling expertise for specific time-bound tasks. In 2018, the JUs will continue to share human resources IT tools where necessary, common calls for tender as well as a common approach to implementing rules of the EU Staff regulation.

3.4.5 Administrative budget and finance

Budget 2018

A table overview of the administrative budget for the financial year 2018 is set out below.

Chapter	Heading Title 1	Budget 2018.0		Budget 2018 Amendment 2		Amended Budget 2018.2	
		Commitment Appropriation (CA)	Payment Appropriation (PA)	Commitment Appropriation (CA)	Payment Appropriation (PA)	Commitment Appropriation (CA)	Payment Appropriation (PA)
11	Staff in active employment	5,425,000	5,425,000			5,425,000	5,425,000
12	Staff recruitments - miscellaneous expenditure	20,000	20,000		13,975	20,000	33,975
13	Missions and duty travels	190,000	190,000		36,906	190,000	226,906
14	Socio-medical structure	360,000	360,000		22,517	360,000	382,517
17	Representation	20,000	20,000		431	20,000	20,431
	Title 1 - Total	6,015,000	6,015,000	0	73,830	6,015,000	6,088,830

Chapter	Heading Title 2	Budget 2018.0		Budget 2018 Amendment 2		Amended Budget 2018.2	
		Commitment Appropriation (CA)	Payment Appropriation (PA)	Commitment Appropriation (CA)	Payment Appropriation (PA)	Commitment Appropriation (CA)	Payment Appropriation (PA)
20	Office building and associated costs	729,000	729,000		168,355	729,000	897,355
21	Information technology purchases	712,000	712,000		603,585	712,000	1,315,585
22	Office equipment (movable property and associated costs)	153,000	153,000			153,000	153,000
23	Current administrative expenditure	123,000	123,000		7,744	123,000	130,744
24	Telecommunication and postal expenses	68,000	68,000		42,956	68,000	110,956
25	Expenditure on formal meetings	158,000	158,000		28,401	158,000	186,401
26	Running costs in connection with operational activities	300,000	300,000		74,138	300,000	374,138

	Heading Title 2	Budget 2018.0		Budget 2018 Amendment 2	Amended Budget 2018.2		
27	External communication, information and publicity	625,000	625,000		100,617	625,000	725,617
28	Service contracts	730,000	730,000		308,686	730,000	1,038,686
29	Expert contracts and cost of evaluations	700,000	700,000		41,216	700,000	741,216
	Title 2 - Total	4,298,000	4,298,000		1,375,697	4,298,000	5,673,697
	Total running costs Title 1 + Title 2	10,313,000	10,313,000		1,449,527	10,313,000	11,762,527

The payment appropriations carried over to the 2018 budget are related to the commitments carried forward from 2017 to 2018.

The operational budget is covered under section 3.2.2. Calls for proposals.

A table overview of the 2018 budget is set out in Chapter 4 of this Annual Work Plan.

Financial Management

During 2018, the finance team will continue with its day to day activities of initiation, verification and payments of invoices and cost claims, creation of commitments, recovery orders, and analysis of periodic reports and negotiations of financial and administrative parts of projects. These activities will be conducted in a timely manner that will be monitored through corporate KPIs, in particular payment times and budget execution.

Best practice and highest quality standards will be ensured through the availability of a Manual of Financial Procedures that is under regular revision. In addition, knowledge dissemination will be further developed through the development of further guidance and the tenure of several financial workshops, in particular targeting beneficiaries, with the aim to reduce errors in financial reporting.

3.4.6 Data protection

Objectives	<p>To implement the Data Protection reform following the adoption of the General Data Protection Regulation [Regulation (EU) 2016/679 of 27 April 2016] which enters into application on 25 May 2018 after a two-year transition period.</p> <p>To continue to promote a culture of data protection at IMI2 JU.</p> <p>To support processes and projects in establishing common minimum requirements for protecting and sharing personal data.</p>
Planned Activities	<p>To implement the data protection reform following the adoption of the General Data Protection Regulation and in particular:</p> <ul style="list-style-type: none"> ▪ <u>increased accountability</u>: advise and support controller and data processors on their responsibility and liability for further processing; ▪ <u>higher data handling standards</u>: reinforce the Data Protection Officer role (e.g. performance of data protection impact assessments, further recording of processing activities and collection of evidence for obtaining consent); ▪ <u>data security</u>: establish internal procedures in relation to the use of technologies; ▪ <u>transparency</u>: implement changes in consent and take into account the shifting of the burden of proof for compliance. <p>To continue to promote a culture of data protection at IMI2 JU:</p> <ul style="list-style-type: none"> ▪ training and advising; ▪ implement the revised procedure for handling notifications; ▪ participate in the EU network for Data Protection Officers and implement best practices; ▪ follow-up progress on implementation and potential impact of the new EU framework for data protection. <p>To support processes and projects in establishing common minimum requirements for protecting and sharing data:</p> <ul style="list-style-type: none"> ▪ advising; ▪ follow-up on recommendations addressed to IMI2 JU by the European Data Protection Supervisor.
Expected results	<p>To ensure that personal data is protected, that the General Data Protection Regulation is complied with and that the implementation of the related legal requirements for EU agencies and bodies is handled smoothly.</p> <p>Actions:</p> <ul style="list-style-type: none"> ▪ train newcomers; ▪ inform IMI2 JU staff on data protection matters during internal meetings; ▪ provide advice upon request; ▪ support the preparation of internal notifications; ▪ prepare prior-checking notifications and/or their updates; ▪ attend EDPS and Data Protection Officers meetings; ▪ prepare standard operating procedures.

Access to documents

IMI2 JU will continue to address requests for access to IMI2 JU documents according to Regulation (EC) No 1049/2001, in a spirit of openness and transparency in order to bring its activities and output closer to the public. In this context, the programme office will further develop a transparency policy on activities of its governance bodies in accordance with the Council Regulation setting up IMI2 JU.

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

- Improving public awareness of IMI2 JU activities and processes;
- Stimulating the interaction on key issues.

3.5 Governance

Key objectives

- Further develop an IMI2 JU strategic orientation and related objectives.
- Ensure that activities are in line with and support IMI2 JU strategic orientation.
- Further improve the efficiency and effectiveness of the IMI2 JU's governance activities.
- Promote and maintain a positive reputation among stakeholders and partners as a key facilitator of healthcare research.

Planned activities

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

IMI2 JU will continue to provide support to the Governing Board, the Scientific Committee, the States Representatives Group, and the Stakeholders' Forum and their working groups.

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

The **Scientific Committee** will continue in its advisory role to the Governing Board of the IMI2 JU and will notably be consulted on the scientific priorities to be addressed in Annual Work Plans and on the scientific achievements to be described in the Annual Activity Report.

At least two meetings of the Scientific Committee are planned for 2018.

The term of the current Scientific Committee members will come to end in 2018, and a new Committee will be appointed in 2nd half of 2018.

The Chair will participate in Governing Board meetings as observer. Information can be found at: <http://www.imi.europa.eu/about-imi/governance/scientific-committee>

The **States Representatives Group** will be consulted on the Annual Work Plans and will receive information on Calls outcomes and evaluation process. At least two meetings of the States Representatives Group are planned for 2018. With the end of the current mandate of the SRG Chair and Vice-Chair, an election process will be held. The Chair will participate in Governing Board meetings as observer. Information can be found at: <http://www.imi.europa.eu/about-imi/governance/states-representatives-group>

In addition, a joint meeting between the IMI2 Scientific Committee and the States Representatives Group is planned in order to strengthen the synergies between the two advisory bodies and exchange on topics of common interest.

In order to cover all areas of life science research and innovation of public health interest and to further develop the IMI2 JU objectives, IMI2 JU will pursue its action to attract a wide range of legal entities, notably promoting the possibility to become **Associated Partners** at programme or topic level. Practical information can be found at: <http://www.imi.europa.eu/get-involved>,

The **Strategic Governing Groups** (SGGs) continue to ensure the coordination of IMI2 JU's work in seven strategic areas and work to make the development of new topics more transparent and effective. The SGGs are made up of representatives from companies active or interested in the area covered by the scope of the SGG as well as representatives from the European Commission, the IMI Programme Office and the IMI2 JU Scientific Committee. Currently, the seven established SGGs focus on the following areas: immunology; diabetes / metabolic disorders; neurodegeneration; translational safety; digital health and patient-centric evidence generation; infections control, and oncology. In early 2018, the Digital Health and Patient-Centric Evidence Generation SGG evolved from the former SGG "Data and Knowledge Management" (DKM), and received a new mandate focused on digital health and evidence generation, building on the achievements and the initial mandate of the SGG DKM.

In 2018 the SGGs will continue to develop comprehensive strategies for future projects for their specific areas.

Each SGG will meet at least 2 to 3 times a year to discuss their portfolio of projects and ensure synergies with ongoing projects, both projects within IMI2 JU and those outside. They may engage with external parties to consult on topic development or key challenges in specific areas as required. Efforts will be made to enhance communication with these bodies as well as seek feedback on any significant IMI activities and developments.

An objective in 2018 will also be to facilitate better cross SGG coordination and interactions by putting in place an updated IT platform and organising dedicated cross-SGG meetings. These improved efficiency mechanisms will facilitate the increased flow of information not only within a given SGG, but also with IMI2 governance bodies (GB, SC, SRG). Therefore, the SGG meeting agendas, publishable minutes and attendance lists will be more readily available. In addition, they will be called upon to advise on how best to exploit IMI2 JU projects' outputs, enhance cross-projects' collaboration as well as explore synergies with similar or complementary activities at national and global level.

In line with article 13.3 (b) of IMI2 JU Regulation, costs of activities related to allowing the SGGs perform these tasks and achieve their objectives are considered as eligible in-kind contributions under the conditions set out in the SGG charter.³³

Expected results

- Streamlined governance activities

Actions:

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

³³ http://www.imi.europa.eu/sites/default/files/uploads/documents/reference-documents/IMI2_GB_DEC_2016_21_Decision_on_new_SGGs_Charter_SIGNED_30SEP2016.pdf

3.6 Internal Control framework

Internal control

The IMI2 JU is aligning its Internal Control Framework (ICF) to the revised control framework adopted by the European Commission on 19 April 2017³⁴. The new ICF moves away from a compliance-based to a principle-based system and provides the necessary flexibility to adapt to specific characteristics and circumstances while ensuring a robust internal control with a consistent assessment throughout the IMI2 JU. This approach aims at helping the organisation to achieve its objectives and sustain operational and financial performance³⁵. In that context, the activities foreseen for 2018 will essentially aim at maintaining throughout the JU Office the achieved level of effectiveness and efficiency of the internal control framework while in parallel setting up the tools, functions and methodologies needed for the implementation of the new approach.

Financial procedures

Financial procedures guide IMI2 JU operations and lay out how the JU uses and manages its funds and resources.

In 2018 focus will be put on the following:

- periodic revision of the operating financial procedures and in particular of the Manual of Procedure for financial Operations (MoP);
- follow up and implementation of the results of the validation performed during 2017 by DG BUDG on the accounting management system of the IMI2 JU.

Ex-ante and ex-post controls

Ex-ante controls

In accordance with Article 18 of IMI 2 JU Financial Rules “each operation shall be subject at least to an ex ante control based on a desk review of documents and on the available results of controls already carried out relating to the operational and financial aspects of the operation”. In that view, ex-ante controls are essential to prevent errors and avoid the need for ex-post corrective actions. Those controls are performed by the IMI2 JU in the form of a desk and mid-term review and definitely assure the implementation of the principle of sound financial management throughout the IMI2 JU operations.

In 2018 the IMI2 JU will continue to assess and update the procedures defining the controls to be performed by project and finance officers for every cost claim, invoice, commitment and payment taking into account risk based and cost-effectiveness considerations. Specific attention will be placed on the:

- continued implementation of the joint guidance on H2020 ex-ante controls for interim and final payments adopted by the Commission Common Support Centre;
- financial checks during the Grant Agreement Preparation (GAP) phase;
- information and communication campaigns for IMI2 JU beneficiaries on H2020 rules and how to avoid errors in cost reporting.

Ex-post controls

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

³⁴ Communication on the revision of the Internal Control Framework (ICF) – C(2017)2373.

³⁵ Effectiveness, efficiency and economy of operations; reliability of reporting; safeguarding of assets and information; prevention, detection, correction and follow-up of fraud and irregularities; and adequate management of the risks relating to the legality and regularity of the underlying transactions, taking into account the multiannual character of programmes as well as the nature of the payments (IMI2 JU Financial Rules, Art 12.2).

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

As regards the IMI2 JU programme, IMI's ex-ante and ex-post controls of grants are both aligned with the harmonised strategies adopted for the entire H2020 Programme. The IMI programme office will carry out the ex-ante checks as prescribed in the H2020 Control strategy. As for ex-post controls, the Commission Common Audit Service (CAS) will carry out the H2020 audits in accordance with the common H2020 audit strategy. IMI2 JU contributes to the implementation of the audit strategy in close cooperation with the CAS. The harmonised legal framework will enable IMI2 JU to draw an additional element of assurance from extension of audit results on shared beneficiaries across the H2020 programme.

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

Internal and external audits

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

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

The IAS will continue performing the internal audit function. IAS will perform an in-depth risk assessment in IMI2 JU in the course of 2018, which will result in a new Strategic Internal Audit Plan for the period 2019-2021.

In 2018, the Audit manager will contribute to the overall corporate objective of receiving an unqualified ('clean') ECA audit opinion and positive statement of assurance.

ECA will audit and issue opinions on the legality and regularity of the underlying transactions. In accordance with the IMI2 Financial rules, IMI2 JU's 2017 annual accounts will be audited by an external audit company while the Court will draw an opinion on the basis of their work.

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

Anti-fraud strategy

Anti-fraud measures are an essential part of sound financial management required under the EU Financial Regulation, safeguards to financial interests of the Joint Undertaking and contribute to its reputation.

In 2018 IMI2 JU will make an assessment of the first three years of implementation of its anti-fraud Action Plan.

Additional actions will focus on:

- awareness about fraud risk across the JU as well as among partners and beneficiaries;
- fraud risk analysis and reviews especially in areas considered vulnerable;
- training of staff disseminating relevant reports within the JU as appropriate and maintaining operational contacts with the European Anti-fraud Office (OLAF).

4 Budget 2018

An overview of the 2018 budget per chapters is set out below.

STATEMENT OF REVENUE								
	Heading Revenue	Budget 2018.0		Budget 2018 Amendment 2		Amended Budget 2018.2		Comments
Chapter		Commitment Appropriation (CA)	Payment Appropriation (PA)	Commitment Appropriation (CA)	Payment Appropriation (PA)	Commitment Appropriation (CA)	Payment Appropriation (PA)	
10	European Commission contribution (including EFTA contribution)	270,487,957	208,398,667			270,487,957	208,398,667	Commitment appropriations include EUR 5,156,500 for running costs and EUR 265,331,457 for operational costs. Payment appropriations include running costs of EUR 5,156,500 and operational costs of EUR 203,242,167.
C2	Appropriations carried over			209,724,074	56,158,881	209,724,074	56,158,881	The amount carried over from previous years. Administrative expenditure - payment appropriation. Operational expenditure - commitment and payment appropriation.
	Title 1 - Total	270,487,957	208,398,667	209,724,074	56,158,881	480,212,031	264,557,548	
20	EFPIA contribution	5,156,500	5,156,500			5,156,500	5,156,500	EFPIA contribution to IMI JU running costs.
21	EFPIA constituent entities or their affiliated entities contributions	-	1,000,000			0	1,000,000	EFPIA companies contributions to operational payment appropriations
	Title 2 - Total	5,156,500	6,156,500	0	0	5,156,500	6,156,500	
30	Associated Partners contributions	-	1,354,000			0	1,354,000	Bill and Melinda Gates Foundation contribution to operational payment appropriations
	Title 3 - Total		1,354,000	0	0	0	1,354,000	
	Total contributions	275,644,457	215,909,167	209,724,074	56,158,881	485,368,531	272,068,048	

STATEMENT OF EXPENDITURE

Chapter	Heading Title 1	Budget 2018.0		Budget 2018 Amendment 2		Amended Budget 2018.2		Comments
		Commitment Appropriation (CA)	Payment Appropriation (PA)	Commitment Appropriation (CA)	47	Commitment Appropriation (CA)	Payment Appropriation (PA)	
11	Staff in active employment	5,425,000	5,425,000			5,425,000	5,425,000	Salaries
12	Staff recruitments - miscellaneous expenditure	20,000	20,000		13,975	20,000	33,975	Miscellaneous expenditure on staff recruitment: travel expenses, etc.
13	Missions and duty travels	190,000	190,000		36,906	190,000	226,906	Mission expenses
14	Socio-medical structure	360,000	360,000		22,517	360,000	382,517	Other staff costs: training, language classes, medical service, interim staff
17	Representation	20,000	20,000		431	20,000	20,431	Representation, receptions and internal meetings
	Title 1 - Total	6,015,000	6,015,000	0	73,830	6,015,000	6,088,830	

	Heading Title 2	Budget 2018.0		Budget 2018 Amendment 2		Amended Budget 2018.2		Comments
Chapter		Commitment Appropriation (CA)	Payment Appropriation (PA)	Commitment Appropriation (CA)	Payment Appropriation (PA)	Commitment Appropriation (CA)	Payment Appropriation (PA)	
20	Office building and associated costs	729,000	729,000		168,355	729,000	897,355	Rent, works, common/IMI charges and parking. Additional costs: indexation, insurance, water/gas, electricity, heating, maintenance + repairs, security and surveillance.
21	Information technology purchases	712,000	712,000		603,585	712,000	1,315,585	IT purchases, software licences, software development, IMI website.
22	Office equipment (movable property and associated costs)	153,000	153,000			153,000	153,000	Purchases and rental of office equipment, maintenance and repair.
23	Current administrative expenditure	123,000	123,000		7,744	123,000	130,744	Office supply. Literature, subscriptions, translation services, bank charges and miscellaneous office expenditure.
24	Telecommunication and postal expenses	68,000	68,000		42,956	68,000	110,956	Data communication such as telephone, video conferences and postal services.
25	Expenditure on formal meetings	158,000	158,000		28,401	158,000	186,401	Official meetings such as SRG, Scientific committee, Governing Board and working groups created by GB.
26	Running costs in connection with operational activities	300,000	300,000		74,138	300,000	374,138	Expenditure in connection with research activities and objectives of IMI (workshops, meetings and events targeting IMI projects).
27	External communication, information and publicity	625,000	625,000		100,617	625,000	725,617	External communication and events such as Info Days, stakeholder forums.
28	Service contracts	730,000	730,000		308,686	730,000	1,038,686	Studies, audits.
29	Expert contracts and cost of evaluations	700,000	700,000		41,216	700,000	741,216	Costs linked to evaluations, expert contracts.
	Title 2 - Total	4,298,000	4,298,000	-	1,375,697	4,298,000	5,673,697	
	Total administrative costs Title 1 + Title 2	10,313,000	10,313,000	-	1,449,527	10,313,000	11,762,527	

	Heading Title 3	Budget 2018.0		Budget 2018 Amendment 2		Amended Budget 2018.2		Comments
Chapter		Commitment Appropriation (CA)	Payment Appropriation (PA)	Commitment Appropriation (CA)	Payment Appropriation (PA)	Commitment Appropriation (CA)	Payment Appropriation (PA)	
30	Implementing the research agenda of IMI JU	265,331,457	205,596,167			265,331,457	205,596,167	Grant agreements - Payments
C2	Appropriations carried over from previous years			209,724,074	54,709,354	209,724,074	54,709,354	
	Total operational costs Title 3	265,331,457	205,596,167	209,724,074	54,709,354	475,055,531	260,305,521	
	Total contributions	275,644,457	215,909,167	209,724,074	56,158,881	485,368,531	272,068,048	

An overview of the 2018 budget and structure per budget lines is set out in the table below:

Expense budget line	Description	Commitment appropriations (CA)	Payment appropriations (PA)	C2 - Payment Appropriation (PA)
A01100	Staff in active employment and costs linked to employment	3,644,000	3,644,000	
A01101	Family Allowances	374,000	374,000	
A01102	Transfer and expatriation allowance	405,000	405,000	
A01110	Contract Agents	636,000	636,000	
A01111	Seconded National Experts	0	0	
A01130	Insurance against sickness	98,000	98,000	
A01131	Insurance against accidents and occupational diseases	15,000	15,000	
A01132	Unemployment insurance for temporary staff	39,000	39,000	
A01133	Pension	0	0	
A01140	Birth and death allowance	10,000	10,000	
A01141	Annual travel costs from the place of employment to place of origins	59,000	59,000	
A01144	Fixed local travel allowances	3,000	3,000	
A01149	Other allowances	0	0	
A01172	Cost of organizing traineeships within IMI	32,000	32,000	
A01175	Translation and typing services and work to be contracted	0	0	
A01177	Other services rendered	5,000	5,000	
A01178	PMO fees	45,000	45,000	
A01180	Sundry recruitment expenses	0	0	
A01181	Travelling expenses (taking up duty)	5,000	5,000	
A01182	Installation allowance	43,000	43,000	
A01183	Moving expenses	0	0	
A01184	Temporary daily allowance	10,000	10,000	
A01190	Weightings (correction coefficient)	2,000	2,000	
A01191	Salaries adaptation	0	0	
11	Staff in active employment	5,425,000	5,425,000	-
A01200	Miscellaneous expenditure on staff recruitment	20,000	20,000	13,975
12	Staff recruitments - miscellaneous expenditure	20,000	20,000	13,975
A01300	Mission expenses	190,000	190,000	36,906

Expense budget line	Description	Commitment appropriations (CA)	Payment appropriations (PA)	C2 - Payment Appropriation (PA)
13	Missions and duty travels	190,000	190,000	36,906
A01401	Socio-medical structure, EU school	80,000	80,000	
A01410	Other trainings	110,000	110,000	122
A01430	Medical service	5,000	5,000	
A01440	Trainings covered by the SLA	6,000	6,000	12,675
A01490	Other interventions	159,000	159,000	9,720
14	Socio-medical structure	360,000	360,000	22,517
A01700	Representation expenses	20,000	20,000	431
17	Representation	20,000	20,000	431
	Title 1 - Total	6,015,000	6,015,000	73,830
A02000	Rentals	569,000	569,000	105,869
A02001	Guarantees	0	0	
A02002	Contributions	0	0	
A02010	Insurance	0	0	
A02020	Water gas electricity and charges	131,000	131,000	912
A02030	Cleaning and maintenance	0	0	
A02040	Furnishing of premises (works)	10,000	10,000	61,574
A02050	Security and surveillance	19,000	19,000	
A02090	Other expenditure on buildings	0	0	
20	Office building and associated costs	729,000	729,000	168,355
A02101	Hardware, infrastructure and related services	218,000	218,000	275,917
A02102	Software development, licenses and related services	494,000	494,000	327,667
A02103	Other expenses maintenance and repair	0	0	
21	Information technology purchases	712,000	712,000	603,585
A02200	Purchase	123,000	123,000	
A02201	Rentals	10,000	10,000	
A02202	Maintenance utilisation and repair	20,000	20,000	
A02203	Other office equipment	0	0	
22	Office equipment (movable property and associated costs)	153,000	153,000	-
A02300	Stationery and office supply	40,000	40,000	1,872
A02320	Bank charges	0	0	
A02321	Exchange rate losses	0	0	
A02329	Other financial charges	0	0	

Expense budget line	Description	Commitment appropriations (CA)	Payment appropriations (PA)	C2 - Payment Appropriation (PA)
A02330	Legal expenses	0	0	
A02350	Other operating expenditure	13,000	13,000	5,872
A02351	Petty expenses	0	0	
A02360	Library stocks purchase of books and subscriptions	44,000	44,000	
A02370	Translation interpretation	26,000	26,000	
23	Current administrative expenditure	123,000	123,000	7,744
A02400	Correspondence and communication expenses	68,000	68,000	42,956
24	Telecommunication and postal expenses	68,000	68,000	42,956
A02500	Formal meetings	158,000	158,000	28,401
25	Expenditure on formal meetings	158,000	158,000	28,401
A02600	Running costs in connection with operational activities	24,000	24,000	13,276
A02601	Events	0	0	
A02602	Workshops	270,000	270,000	56,862
A02603	Knowledge Management	6,000	6,000	4,000
26	Running costs in connection with operational activities	300,000	300,000	74,138
A02700	External communication	225,000	225,000	74,958
A02701	Events	300,000	300,000	19,519
A02702	Material	100,000	100,000	6,140
27	External communication, information and publicity	625,000	625,000	100,617
A02800	Ex-post Audits	536,000	536,000	277,153
A02801	Studies, consultancy, services	114,000	114,000	
A02802	Audit services	80,000	80,000	31,533
28	Service contracts	730,000	730,000	308,686
A02900	Evaluation Experts meetings	600,000	600,000	40,309
A02901	Evaluation Facilities	100,000	100,000	907
A02902	Evaluations ENSO	0	0	
29	Expert contracts and cost of evaluations	700,000	700,000	41,216
	Title 2 - Total	4,298,000	4,298,000	1,375,697
B03000	Implementing the research agenda of IMI1 JU	0		
B03001	Call 1	0	57,000	
B03002	Call 2	0	700,000	
B03003	Call 3	0	6,086,573	
B03004	Call 4	0	2,630,148	

Expense budget line	Description	Commitment appropriations (CA)	Payment appropriations (PA)	C2 - Payment Appropriation (PA)
B03005	Call 5	0	0	
B03006	Call 6	0	7,500,000	
B03007	Call 7	0	54,426	
B03008	Call 8	0	9,206,582	
B03009	Call 9	0	6,927,000	
B03010	Call 10	0	1,200,000	
B03011	Call 11	0	21,523,399	
B03012	ENSO 2012	0	0	
B03013	ENSO 2013	0	0	
B03020	Implementing the research agenda of IMI2 JU	0		
B03021	IMI2 Call 1	0	2,900,000	
B03022	IMI2 Call 2	0	16,784,857	
B03023	IMI2 Call 3	0	7,679,759	
B03024	IMI2 Call 4	0	113,000	
B03025	IMI2 Call 5	0	7,001,500	
B03026	IMI2 Call 6	0	8,060,000	
B03027	IMI2 Call 7	0	4,147,984	
B03028	IMI2 Call 8	0	19,592,850	
B03029	IMI2 Call 9	0	1,000,000	
B03030	IMI2 Call 10	0	58,008,218	
B03031	IMI2 Call 11	0	2,627,194	
B03032	IMI2 Call 12	0	21,795,677	
B03033	IMI2 Call 13	0	0	
B03034	IMI2 Call 14	82,357,000	0	
B03035	IMI2 Call 15	136,074,457	0	
B03036	IMI2 Call 16	46,900,000	0	
B03037	IMI2 Call 17	0	0	
30 – C1	Implementing the research agenda of IMI JU	265,331,457	205,596,167	
B03020 - C2	Implementing the research agenda of IMI2 JU	7,000		54,683,685
B03030 - C2	IMI2 Call 10	173,890,000		
B03035 - C2	IMI2 Call 15	35,801,405		
B03000 - C2	*Implementing the research agenda of IMI1 JU	25,669		25,669
30 - C2	Implementing the research agenda of IMI JU	209,724,074	-	54,709,354
	Title 3 - Total	475,055,531	205,596,167	54,709,354
	Total expenditures	485,368,531	215,909,167	56,158,881

* amounts recovered from beneficiaries during 2017 carried over to 2018

4.1 Staff Establishment Plan 2018

Grade	Establishment Plan 2017			Year 2018											
				Posts evolution						Organisational evolution			Establishment Plan 2018		
	PERM			Promotion / Career advancement			Turn-over (departures/arrivals)			New posts (per grade)			Requested (Budget)		
				Officials	TA - LT	TA - ST	Officials	TA - LT	TA - ST	Perm	TA - LT	TA - ST	PERM	TA	TOTAL
AD16															
AD15															
AD14		1	1											1	1
AD13															
AD12		2	2											2	2
AD11		2	2											2	2
AD10															
AD9		3	3		+ 2									5	5
AD8		7	7		- 2									7	7
AD7		6	6		+ 2									4	4
AD6					- 2									2	2
AD5		12	12		+ 2									10	10
Total AD		33	33		- 2									33	33
AST11															
AST10															
AST9															
AST8		1	1											1	1
AST7															
AST6															
AST5															
AST4					+ 2									2	2
AST3		4	4		- 2									2	2
AST2															
AST1		1	1											1	1
Total AST		6	6											6	6
SC6															
SC5															
SC4															
SC3															
SC2															
SC1															
Total SC		0	0											0	0
Overall Total		39	39											39	39

Contract Agents Grade	2017	2018
FG IV	2	2
FG III	12	12
FG II	1	1
FG I	0	0
Total CA	15	15

Seconded National Experts	2017	2018
	2	2

Annex I - IMI2 Call 14 topics text

Introduction

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

The Innovative Medicines Initiative 2 Joint Undertaking (IMI2 JU) has been created³⁶ 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 World³⁷.

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 companies³⁸, 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)³⁹ is the main reference for the implementation of research priorities for IMI2 JU. The scientific priorities for 2018 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.

³⁶ Council Regulation (EU) No 557/2014 of 6 May 2014 establishing the Innovative Medicines Initiative 2 Joint Undertaking (IMI2 JU).

³⁷ http://www.who.int/medicines/areas/priority_medicines/en/

³⁸ Under IMI2 JU, mid-sized companies having an annual turnover of EUR 500 million or less not being affiliated entities of companies with an annual turnover of more than 500 million; the definition of 'affiliated entities' within the meaning of Article 2(1)(2) of Regulation (EU) No 1290/2013 applies mutatis mutandis. Where established in an EU Member State or an associated country, are eligible for funding.

³⁹ 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) 2016/679⁴⁰ and Clinical Trial Regulation (EU) 536/2014⁴¹ (and/or Directive 2001/20/EC⁴²) and any relevant legislation⁴³.

Before submitting a proposal, applicant consortia should familiarise themselves with all Call documents such as the IMI2 JU Manual for evaluation, submission and grant award⁴⁴, 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).

⁴⁰ 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.

⁴¹ 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.

⁴² 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.

⁴³ Directive 95/46/EC on the protection of individuals with regard to the processing of personal data and the free movement of such data and implementing national laws: <http://eur-lex.europa.eu/legal-content/EN/TXT/?uri=celex:31995L0046>

⁴⁴ http://www.imi.europa.eu/sites/default/files/uploads/documents/apply-for-funding/call-documents/imi2/IMI2_ManualForSubmission_v1.6_October2017.pdf

Topic 1: Targeted immune intervention for the management of non-response and relapse

Topic details

Topic code	IMI2-2018-14-01
Action type	Research and Innovation Action (RIA)
Submission and evaluation process	2 stages

Specific challenges to be addressed

A large number of patients suffering from immune-mediated diseases fail to respond well or at all to current standard-of-care treatments or quickly relapse while on, or following, treatment. Currently, one of the most challenging questions in human immunology is to understand whether it is possible to accurately predict which patients will fail to respond to treatment, which patients will sustain a longer term treatment response, or which patients will suddenly flare up during periods of disease control. At present, there is a lack of a mechanistic understanding of non-response combined with an absence of biomarkers to predict clinical responses. Detailed analysis of clinical samples before and during treatment would enable breakthrough discoveries on the mechanisms, the clinical management of non-response, and the identification of patients prone to relapse. The topic focuses on the application of state-of-the-art molecular and immune technologies and sophisticated informatics approaches to highly annotated pre- and post-therapy bio-samples obtained from patients with systemic lupus erythematosus (SLE), rheumatoid arthritis (RA), multiple sclerosis (MS), ulcerative colitis (UC), Crohn's disease (CD), asthma, and chronic obstructive pulmonary disease (COPD), in order to identify novel biomarkers that are predictive of clinical disease behaviour and response. In addition, this topic provides an opportunity for the discovery of cross-disease biomarkers with relevance to a group of immune-mediated inflammatory diseases. Biomarkers of treatment or therapeutic response to a given therapy across multiple diseases may provide key insights.

We have a poor understanding of the immune factors driving chronic progressive diseases, triggers of immune-mediated exacerbations and relapses and their underlying molecular signals. These episodes are highly clinically relevant, yet are often poorly controlled. The topic, through the study of patients who respond or do not respond to treatment, as well as placebo patients, aims to identify molecular mechanisms that can be targeted to control immune-mediated exacerbation and relapse. The topic represents a great opportunity for the use of patient-centric monitoring/sampling devices in order to obtain correlated data from patient reported outcomes/symptoms and associated bio-samples (e.g. tissue biopsies from skin, kidney, mucosal and lung, sputum, stool, blood and urine). Patient bio-resources should be ideally matched with high dimensional profiling of patients' signs and symptoms including patient reported outcomes, and the use of digital tools to capture patient outcomes and environment.

The topic addresses the challenge of translating insights from treatment non-response and disease exacerbation into new treatment paradigms at the individual patient level.

Subtopics and the Call process

To ensure that the topic attracts high-level clinical and scientific expertise for the indications selected, and to provide in-depth technical knowledge for the profiling and informatics of bio-samples, the topic is divided into the following four subtopics:

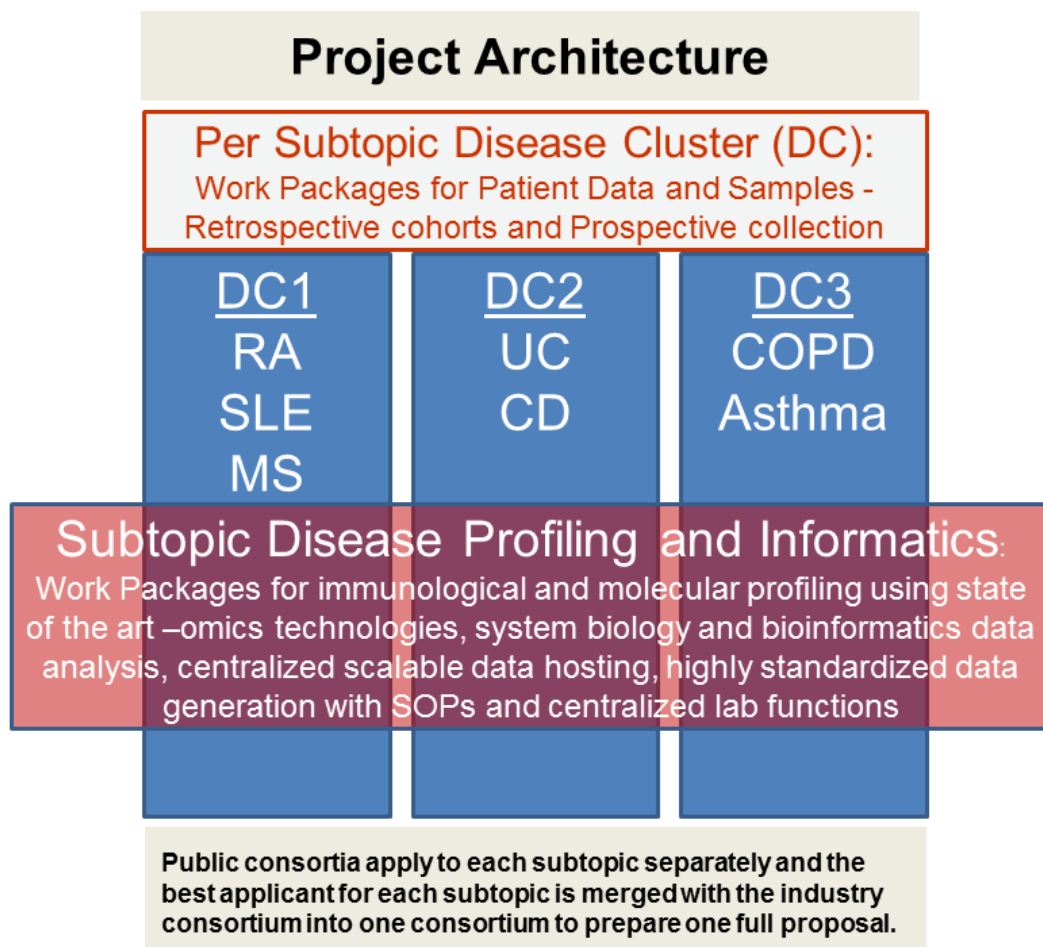
Subtopic 1: Disease profiling and informatics: state-of-the-art molecular and immune technologies in combination with cutting edge systems biology approaches to identify biomarkers predictive of treatment non-response, relapse and flare-up;

Subtopic 2: Disease cluster 1 (DC1): SLE, RA, and MS;

Subtopic 3: Disease cluster 2 (DC2): UC and CD;

Subtopic 4: Disease cluster 3 (DC3): Asthma and COPD.

Subtopics 2-4 focus on specific disease clusters. Applicant consortia will comprise disease-specific experts in clinical, scientific, biostatistics and regulatory affairs who have access to retrospective and prospective patient cohorts, bio-samples and data. These disease cluster teams will collaborate with each other and with the ‘Disease profiling and informatics’ subtopic 1 team in order to establish novel biomarkers and algorithms predictive of clinical disease behaviour and response.



Two-stage Call process: at stage 1, sub-consortia will be formed for each subtopic 1-4. At stage 2, the selected sub-consortia will be combined with the industry consortium into a single consortium.

At Stage 1, applicant consortia should submit short proposals to only one of the four subtopics 1-4.

Applicants can submit short proposals to any of the subtopics and to more than one, provided a separate short proposal is submitted for each subtopic.

A key objective of this topic is to create a research and technology platform for all the disease clusters to discover and validate novel biomarkers predictive of treatment response or non-response. To maximise cross-learning and to enable data sharing, it is envisioned 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.

Thus, at stage 2 the full proposal will be submitted by the consortium composed of the winning applicant sub-consortia of all four subtopics and the industry consortium.

An overall coordinator (selected from the winning consortium of the subtopic 1 Disease profiling and informatics) 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 of no short proposal being over the threshold for one or two disease cluster subtopics, the second stage of the Call will still be initiated by the merger of the remaining consortia and the industry consortium, but the net IMI2 funding and the EFPIA in-kind contributions will be adapted accordingly.

Considering the essential role of subtopic 1 for the preparation of the full proposal and implementation of the funded action, potential applicants must be aware that the whole topic may be discontinued and the stage 2 evaluation may not take place if no short proposal is selected under this subtopic.

Need and opportunity for public-private collaborative research

In a field of medicine where the diseases and underlying science are so complex, no critical mass exists to make significant progress. In order to develop a better understanding of human immune-mediated diseases, only a large international scientific collaborative project that includes excellence in academia, the pharmaceutical industry, SMEs and regulatory authorities, coupled with a critical amount of high quality data, can be successful. Hence, translating basic science into the clinic cannot be achieved by a single entity but requires the definition of common strategies, setting new standards and the necessary critical mass created by all key stakeholders both from the private and public sectors. The proposed work will focus on seven prominent immune-mediated diseases where a public-private partnership will advance our understanding and help accelerate the development of personalised drug treatments for patients.

In addition, to achieve significant impact and drive a timely change in the field for the benefit of patients, it is necessary to kick-start the process by building on all available assets and learnings, and, via a combination of key resources globally, mobilising stakeholders in EU Member States and H2020 Associated Countries and potentially beyond.

Scope

The action generated by this topic aims to provide better control of immune-mediated diseases.

In particular, the topic aims to identify new approaches to:

- characterise human immune-mediated diseases;
- profile and analyse immune cells obtained from non-blood tissues;
- discover individual disease and cross-disease biomarkers predictive of treatment response, non-response, relapse and flare-up;
- perform early phase clinical trials (e.g. enriched study populations for certain molecular pathways; adaptive and basket trial designs etc.) and identify potential novel patient-centric treatment approaches. The focus will be on patients from well-characterised immune-mediated diseases (SLE, RA, MS, UC, CD, Asthma and COPD).

The ultimate goal is to develop a translational research platform that will improve patient management and personalised treatment by identification/validation of predictive biomarkers for non-response, rapid progression and remission. This would lead to an increased likelihood of treatment success with decreased costs for:

- patients and society, due to fewer side effects and a reduction in the treatment of patients who are unlikely to respond;
- pharmaceutical companies, due to decreased development costs as a function of being able to demonstrate efficacy and safety in smaller, more targeted patient populations that are likely to show greater or earlier response rates.

Expected key deliverables

Subtopic: Disease profiling and informatics

- Molecular profiling of non-responders that will lead to a better understanding of the pathways regulating the response to treatment in seven different diseases (RA, SLE, MS, UC, CD, COPD and asthma), and reveal drug targets for therapeutic intervention.
- Discovery of biomarkers predictive of clinical responses (e.g. non-response, depth of remission, duration of response, rebound effects, frequency and severity of flares).
- Establishment of technology platforms, including transcriptomics (e.g. single cell-, BCR-, TCR-, RNA-Seq), genomics (e.g. SNP, Immunochip, exome sequencing), microbiomics, metabolomics, epigenetics (e.g. DNA methylation, ATAC-Seq, ChIP-Seq), immunophenotyping (flow cytometry/CyTOF), proteomics and exosome profiling.
- Utilise a core set (scRNA-Seq, genetics, microbiomics (stool)) of state-of-the-art and emerging molecular and immune technologies and cutting-edge systems biology approaches to profile and analyse non-blood affected disease tissue samples to identify biomarkers predictive of treatment non-response, relapse and flare-up.
- Single cell RNA-Seq of non-blood tissue samples to determine the role of different cell types and identify distinct cell sub-populations that contribute to clinical response and disease progression and correlate with peripheral markers/signatures.
- Analysis of -omics datasets leading to the generation of novel methods and models to predictively identify and stratify responder, non-responder and relapse-prone patients aligned with specific therapies.
- Generation and hosting of an integrated large-scale data storage and computing platform to collect, store, analyse and integrate data to allow data mining for new targets and pathways.
- Establishment of a sustainable repository of well-annotated bio-samples to allow for the identification, tracking, storage and retrieval for subsequent profiling and analysis.

For each of the subtopics DC1, DC2 and DC3

- Analysis of retrospective and prospective clinical and biomarker cohorts with access to patient data and bio-samples.
- Patient bio-resources that should be ideally matched with high dimensional profiling of patients' signs and symptoms including patient reported outcomes and the use of digital tools to capture patient outcomes and environment.
- Establishment of an interface with the Disease profiling and informatics subtopic 1 to efficiently receive, send, track and store data and bio-samples, and establish necessary processes for high dimensional data analysis.
- Functional and clinical validation of biomarkers using human-based disease models (e.g. organoids / organ on a chip).
- Development of best practice for emerging biomarker validation and clinical application in immune-mediated diseases with early engagement of the European Medicines Agency (EMA) / Food and Drug Administration (FDA) (e.g. scientific advice, see <http://www.imi.europa.eu/sites/default/files/uploads/documents/apply-for-funding/call-documents/imi2/RegulatoryRequirementsGuide.pdf>)

Expected impact

Currently patients are treated as a 'statistical mean' due to our limited molecular insight into individual patients' disease biology and treatment response. This approach fails to appreciate the underlying heterogeneity in disease mechanisms that leads to indistinguishable clinical phenotypes. Better understanding of the link between the molecular characteristics of disease and non-response to targeted drug treatments will increase the likelihood of treatment success and thus decrease costs to patients (side effects) and society.

Similarly, the establishment of early markers of response will allow the identification of disease endotypes that may be responsive to different therapies.

The proposed precision-immunology approach is expected to achieve a reduction in failure rates in early clinical trials and to provide access for novel therapeutics to the most appropriate patient populations. Insights gained from this study will inform the design of platform trials for single indications with multiple mechanisms, further supporting precision medicine approaches. In addition, a more accurate definition of subcategories of auto-immune disorders and their responses to particular therapies on an individual patient level will fuel novel target discovery, decrease phase 2 proof of concept (POC) attrition, and decrease the costs of development to achieve regulatory approval and appropriate reimbursement.

To this end, the action generated by this topic would be a powerful and unique instrument, with the capability to significantly move forward the development of a consensus on the best treatment options for defined subgroups of patients with high unmet medical needs, such as patients suffering from immune-mediated diseases. Such an instrument currently does not exist within Europe or elsewhere. Furthermore, beyond advancing our understanding of the disease, informing personalised approaches to patient care, and delivering potential novel treatments, the topic has the potential to establish Europe in a leadership position in this field of biology and medicine.

Small and medium-sized enterprises (SMEs) can be of great benefit to IMI2 JU projects. Their involvement in the action might offer a complementary perspective to industry and academia, and help deliver the long-term impact of the project. Therefore applicants should indicate how their proposals will impact and strengthen the competitiveness and industrial leadership of Europe by, for example, engaging suitable SMEs.

Potential synergies with existing consortia

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

In particular, the action generated from this topic should, among others, consider:

- IMI projects:
 - BTCURE** (<http://btcure.eu/>)
 - RTCURE** (http://cordis.europa.eu/project/rcn/211964_en.html)
 - PRECISESADS** (<http://www.precisesads.eu/>)
 - U-Biopred** (<http://www.europeanlung.org/projects-and-research/projects/u-biopred/home>)
 - INNODIA** (<https://innodia.eu/>)
 - European Lead Factory** (<https://www.europeanleadfactory.eu/>)
- Human Immunology Project Consortium (**HIPC**) (<https://www.immuneprofiling.org/hipc/page/show>)
- CD and UC: Inflammatory Bowel Disease Biomarkers Programme (**IBD-BIOM**) (<http://www.ibdbiom.eu/>), Inflammatory Bowel Disease Characterization by a multimodal integrated biomarker study (**IBD-CHARACTER**) (<http://www.ibdcharacter.eu/>), A System Medicine Approach to Chronic Inflammatory Disease (**SYSCID**) (<http://syscid.eu/>), Biological Therapy Cycles Towards Tailored, Needs-driven, Safer and Cost-effective Management of Crohn's Disease (**BIOCYCLE**) (<https://biocycle-project.eu/>), the next generation epigenetic medicine for inflammation (**EPIMAC**) (http://cordis.europa.eu/project/rcn/193846_en.html), Harnessing Targeted Nanotheranostics to Reprogram Activated Leukocytes in Inflammatory Bowel Disease (**LeukoTheranostics**) (http://cordis.europa.eu/project/rcn/198445_en.html), Identifying microbial triggers of inflammatory

bowel disease through the lens of the immune system (**IMMUNOBIOME**) (http://cordis.europa.eu/project/rcn/197878_en.html)

- MS: **MultipleMS** (<http://www.multiplems.eu/>) and **EUReMS** (<http://www.emsp.org/projects/eurems/>)
- RA and SLE: Accelerating Medicines Partnership (**AMP**) (<https://www.nih.gov/research-training/accelerating-medicines-partnership-amp>), Mechanisms to Attack Steering Effectors of Rheumatoid Syndromes with Innovated Therapy Choices (**Masterswitch**) (http://cordis.europa.eu/project/rcn/89367_en.html), Towards Early diagnosis and biomarker validation in Arthritis Management (**Euro-TEAM**) (http://cordis.europa.eu/project/rcn/105516_en.html), Monitoring innate immunity in arthritis and mucosal inflammation (**MIAMI**) (<http://miamiproject.eu/>), Relapses prevention in chronic autoimmune disease: common mechanisms and co-morbidities (**RELENT**) (<https://www.relent.eu/>), **SYSCID** (<http://syscid.eu/>)
- SLE: **SYSCID** (<http://syscid.eu/>) and **Lupus Europe** (<http://www.lupus-europe.org/>)
- Asthma and COPD: **Ga2Len** (<http://www.ga2len.net/>), **synergy-COPD** (<http://www.synergy-copd.eu/>) and **EvA** (http://cordis.europa.eu/project/rcn/87739_en.html)
- MS, RA, SLE: Immune Tolerance Network (**ITN**) (<https://www.immunetolerance.org/>)

Industry consortium

The industry consortium is composed of the following EFPIA companies:

- Sanofi (overall lead; disease profiling and informatics subtopic lead; DC1 subtopic lead)
- Roche (overall co-lead)
- Takeda (DC2 subtopic lead)
- AstraZeneca (DC3 subtopic lead)
- GlaxoSmithKline
- Janssen
- Novartis
- Pfizer

The industry consortium will provide bio-samples (e.g. blood, stool, sputum, urine, tissue biopsies, DNA, RNA) and patient characterised datasets (deep-clinical phenotyping) from various prospective clinical trials (baseline, active comparator and/or placebo) for SLE, RA, MS, UC, CD, asthma, and COPD. Note that there will be a difference in design of these clinical trials, and the specificities of the available bio-samples will be confirmed during the full proposal preparation. In addition, the availability and disease type of the bio-samples obtained from future prospective clinical trials performed by the industry consortium carries some attrition risk due to discontinuation of development activities, incompatibility of informed consent for certain profiling and analyses and/or legal considerations.

The industry consortium will contribute with technology platforms for bio-sample analysis to complement technologies provided by the public participants.

The industry consortium will include informatics and systems biology experts and clinical statisticians. Immunology expertise to contribute to functional validation of pathways and targets will be made available, as well as biomarker expertise to support validation activities and assay development.

Indicative duration of the action

The indicative duration of the action is 84 months.

Future project expansion

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

A consensus is emerging that common immune-mediated diseases share common pathways, with molecular support provided by analysis of transcriptomics, HLA haplotypes and GWAS studies. One of the goals of this topic is to identify single and multi-parameter biomarker sets in individual diseases and across multiple diseases to assist in determining responder versus non-responder patients. However, this profile will be derived from a limited number of patients, so it cannot be assumed that the profile defining these categories is exclusive in determining response. For example, there may be some patients with a non-responder profile who actually may benefit from the treatment. Thus, the candidate responder versus non-responder profile uncovered by this topic will be exploratory and not definitive, and will need to be followed up by future validation studies that include large numbers of patients and novel endpoints. Also, it is critical to maintain long-term follow up of the patients in these studies to validate which candidate biomarkers can accurately predict the depth of remission.

Future follow up studies will also be necessary as some patients may be non-responsive to therapy by virtue of being placed on an initial inappropriate treatment or having generated anti-drug antibody responses with initial or subsequent loss of efficacy. Thus, anti-drug responses may need to be assessed in patients on clinical trials of therapeutic proteins for incidence, titer, neutralising activity, and duration, as well as to generation of hypersensitivity responses. The generation of such anti-drug antibody responses and clinical responses may identify a distinct population of patients and provide a profile of those most prone to generate anti-drug antibody responses. This may lead to the development of tolerance induction protocols for such patients.

Indicative budget

The indicative EFPIA in-kind contribution is EUR 40 320 000.

The EFPIA in-kind contribution for each subtopic is:

Subtopic 1 (Profiling & informatics): EUR 16 128 000

Subtopic 2 (DC1 – SLE, RA, and MS): EUR 12 096 000

Subtopic 3 (DC2 – UC and CD): EUR 8 064 000

Subtopic 4 (DC3 – Asthma and COPD): EUR 4 032 000.

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

The financial contribution from IMI2 JU for each subtopic is:

Subtopic 1 (Profiling & informatics): a maximum of EUR 16 128 000

Subtopic 2 (DC1 – SLE, RA, and MS): a maximum of EUR 12 096 000

Subtopic 3 (DC2 – UC and CD): a maximum of EUR 8 064 000

Subtopic 4 (DC3 – Asthma and COPD): a maximum of EUR 4 032 000.

For all subtopics: in light of the fact that a single full proposal will be created at stage 2, where a common governance, management and other transversal activities will have to be agreed and developed, applicants have to be aware there might be a need for some slight modifications in the budgets from the stage 1 submissions.

Applicant consortium

One applicant consortium per subtopic will be selected on the basis of the short proposals submitted.

The first-ranked applicant consortium for each subtopic is expected to address all the research objectives of a particular subtopic and to make key contributions to the defined deliverables in synergy with the proposed industry consortium contributions (stage 1).

Applicants should summarise their know-how and expertise to demonstrate their ability to make critical contributions to the expected key deliverables within the duration of the action.

All first ranked applicant consortia of each subtopic are expected to work collaboratively with the industry consortium to develop a full proposal combining the key objectives of each individual subtopic (stage 2).

This may require mobilising, as appropriate, the following expertise and resources.

Expertise and resources required for subtopic on disease profiling and informatics

The expertise and resources required are as follows:

- experience in the establishment of a bio-sample repository to allow for the identification, tracking, and storage for subsequent profiling and analysis;
- expertise in standardised isolation, storage, processing and –omics analysis;
- centralised lab functions for state–of-the-art and emerging technologies for –omics analysis (e.g. single cell transcriptome analysis, spatial transcriptomics, genomics, epigenetics, microbiome, metabolomics, flow cytometry/CyTOF, proteomics, and exosome profiling) in clinical sample types (e.g. tissue biopsies, sputum, stool, blood, plasma, urine) across the selected diseases;
- expertise in the generation and hosting of an integrated, large-scale data platform and informatics pipeline to collect, store and analyse these data;
- expertise in data integration and/or harmonisation techniques and cutting-edge systems biology approaches to model multiple –omics datasets from multiple diseases to identify biomarkers that predict treatment non-responders or relapse-prone patient populations;
- expertise in informatics analysis and modelling to support patient stratification, future clinical trial design and precision medicine approaches;
- experience in collaborative functional validation of novel pathways, drug targets and biomarker candidates; proven expertise in efficiently managing and maintaining timelines for large, multi-institutional scientific projects, and proven expertise in project management including resources for project administration, management and communication;
- expertise in regulatory science and inclusion of regulatory experts.

Expertise and resources required for Subtopics DC1, DC2 and DC3

The expertise and resources required are as follows:

- access to pre-existing bio-samples (non-blood tissues required and matching blood samples desired) and patient data from retrospective biomarker and clinical trials suitable (e.g. tissue frozen, not fixed) for profiling using state–of-the-art and/or emerging technologies;
- ability to design and conduct interventional prospective clinically relevant and actionable biomarker trials to obtain high quality clinical data and well-annotated bio-samples;
- expertise in the development of human-based disease models based on novel insights from the –omics studies (e.g. organoids) - note mouse models are not applicable;
- the inclusion of patients and patient organisations in the consortia applying to the disease cluster subtopics (DC1, DC2, DC3) is actively encouraged;
- ability to anticipate the early integration of health economic evaluation and health technology assessment (HTA) where applicable;
- ability to contribute insights on patient reported outcomes and quality of life (QoL) elements for the definition of clinical response.

Partners providing medical record-based information (e.g. data from registries, bio-samples) as project background must be mindful that they, as background contributor, should have sufficient title to said

background to authorise its use within the project pursuant to the IMI2 JU intellectual property (IP) and legal framework. Consideration should also be given to any additional information that may be introduced after the start of the project but is not listed as project background at the start date. The applicants need also to take into consideration that the sharing of data and samples within the consortium should be allowed and be in conformity with the applicable data privacy laws and laws regarding ethical matters.

In addition to academic groups, relevant small and medium-sized enterprises (SMEs) with relevant proven expertise are encouraged to participate in the applicant consortium. SMEs can be of great benefit to IMI projects and, among other things, strengthen the competitiveness and industrial leadership of Europe. Their involvement might offer a complementary perspective to industry and the academia, and strengthen the long-term impact of the project. For these reasons, applicants should consider engaging SMEs throughout the proposal. Under this topic, the contribution of SMEs would be considered especially beneficial for the establishment of a bio-sample repository, the generation and hosting of an integrated large scale data platform, and the specialty profiling of bio-samples, using state-of-the-art and/or emerging technologies. In addition, SMEs would be considered beneficial for the project management and administration capabilities required of the applicant consortium, which is expected to include resources for project administration, management and communication.

The size of the applicant consortia should reflect the expertise needed to achieve the proposed objectives of the subtopic and to be in line with the proposed budget, while ensuring the manageability of the final consortium to allow efficient and effective team work. Therefore, the size of the applicant consortium needs to be justified in the proposal.

Suggested architecture of the full proposal

Each applicant consortium should include suggestions for creating the full proposal architecture in their short proposal, taking into consideration the industry contribution, existing technology platforms, and the clinical and scientific expertise needed for the immune-mediated diseases being studied.

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.

Governance of the overall project will be assured by the project coordinator and the scientific project lead.

The coordinator will be agreed upon by the full consortium created by the merger of the winning subtopic consortia at the start of the preparation of the full proposal and it will be nominated from the winning disease profiling and informatics subtopic 1.

This may require slight adjustment of the disease profiling and informatics subtopic work package 1 to accommodate any new structure changes. This topic consists of four subtopics, each with several distinct and common work packages, which in combination will deliver the objectives of the project. In the full proposal, the subtopic-specific governance structures will be maintained and guaranteed for each sub-topic by a partnership among the leading members of the respective applicant consortium together with one leading member designated by the industry consortium (see above, industry consortium section).

Particular attention will be given to implementing the scientific exchange of the specialist experts within and across the four subtopics, ensuring the integration of learnings, synergies and cross-fertilisation, and thereby maximising the outcome of this action.

The consortium is expected to have a strategy on the translation of the relevant project outputs into regulatory practices, clinical and healthcare practice. A plan for interactions with regulatory agencies/health technology assessment bodies, with relevant milestones and resources allocated, should be proposed to ensure this e.g.

qualification advice on the proposed methods for novel methodologies for drug development and qualification opinion.

Sustainability

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

The architecture outlined below for the full proposal and for the short proposals submitted to each subtopic is a suggestion; different innovative project designs are welcome, if properly justified.

All subtopics

Common work package: Project management, communication, dissemination and sustainability

This work package should be described by each submitting applicant consortium, and should include the elements necessary to ensure the proper functioning of each subtopic, bearing in mind that some modifications will be necessary at the stage 2 full proposal to adapt for an overall governance and integration, and that several activities will be shared among all participants of the full consortium to insure integration and avoid redundancy.

The goals of this work package will be as follows:

- overall coordination of the scientific work packages;
- budget administration;
- dissemination of scientific results and research data;
- development of a sustainability plan to facilitate continuation of the project beyond its anticipated duration;
- communication within the consortium and with external collaborators.

Expected applicant consortium contribution: coordination of work packages, budget administration, dissemination of scientific results, and development of a sustainability plan.

EFPIA consortium contribution: communication, dissemination of results, and development of sustainability plan.

Subtopic disease profiling and informatics

Work package 1 – Profiling

The goals of this work package will be as follows:

- coordinate the receipt, curation, storage and retrieval of bio-samples;
- reduce technical variability introduced during sample processing;
- minimise batch effects via centralised profiling on the same platforms\instruments.

Expected applicant consortium contribution:

- molecular profiling of non-blood tissue samples from DC1, DC2 and DC3 patients using RNA-Seq, single cell RNA-Seq, genetics (all three required), and flow cytometry/CyTOF (desired);
- profiling of DC1, DC2 and DC3 patient stool samples using microbiome and metabolome (required for DC2 and desired for DC1 and DC3);
- epigenetic, metabolomics, microbiomic (lung, skin), proteomic and exosome profiling on patient bio-samples from DC1, DC2 and DC3 (desired);
- to limit batch effects and to ensure comparable results across these diverse sets of bio-samples the profiling of DC1, DC2 and DC3 bio-samples should be performed at the fewest sites possible, on the

same instruments, and utilise a common core set of standard operating procedures for sample isolation, preparation and labelling. In addition, development of a quality control plan that includes control steps, control samples, blinding operators and randomisation of samples is desired;

- develop a bio-repository platform for the receipt, curation, tracking, storage and retrieval of bio-samples received from DC1, DC2 and DC3;
- transfer of profiling datasets to a centralised scalable data hosting and computing platform.

EFPIA consortium contribution:

- EFPIA partners may, if relevant, provide molecular profiling of bio-samples from DC1, DC2 and DC3 patients using RNA-Seq, single cell RNA-Seq, genetics (all required), and flow cytometry/CyTOF (desired);
- profiling of DC1, DC2 and DC3 patient stool samples using microbiomics and metabolome (required for DC2 and desired for DC1 and DC3);
- epigenetic, metabolomic, microbiomic (lung, skin), proteomic and exosome profiling of non-stool bio-samples obtained from DC1, DC2 and DC3 patients (desired);
- transfer of profiling datasets to a centralized scalable data hosting and computing platform generated and maintained by the disease profiling and informatics subtopic;
- provide informatics support to the disease profiling and informatics subtopic.

Work package 2 – Informatics

The goals of this work package will be as follows:

- characterise variations in –omics datasets generated at high resolution;
- establish a centralised, scalable data hosting and computing platform;
- identify novel biomarkers predictive of clinical disease behaviour and response;
- develop disease and clinical response-specific data that can be used to identify biological targets for drug development and biomarkers for patient stratification.

Expected applicant consortium contribution:

- analysis of –omics datasets of treatment non-responders to discover novel biomarkers predictive of clinical responses;
- use sophisticated data integration and harmonisation techniques and apply cutting-edge systems biology approaches to model multiple –omics datasets from multiple diseases to identify biomarkers or clusters of biomarkers that predict non-response. Inclusion in the project plan of data sets from other consortia (such as those mentioned in the Synergies section) via proposed collaborations could be considered;
- molecular profiling of non-responders that will lead to a better understanding of the pathways regulating the response to treatment in the seven different immune-mediated diseases and reveal drug targets for therapeutic intervention;
- analysis of –omics and clinical datasets to provide a better understanding of human immune-mediated diseases;
- integration of historic and prospective data for the identification of biomarkers and generation of models that predict treatment non-responders and/or relapse-prone patient populations in the seven indicated diseases. Determine whether commonalities exist (e.g. biomarkers) across the seven different diseases for identifying treatment non-responder and relapse-prone patients. Opportunities to integrate biomarker data of disease non-response from other disease could be considered if relevant;
- provide analysis and models to support patient stratification, future clinical trial design and precision medicine approaches;
- establishment of a centralised scalable data hosting and computing platform to enable data storing, sharing and data mining.

EFPIA consortium contribution:

- EFPIA partners will, where applicable, transfer prospective –omics and clinical datasets to the disease profiling and informatics subtopic for data hosting, mining and analysis;
- provision of scientific, clinical, profiling and informatics expertise for patient data and -omics datasets;
- provision of informatics expertise for discovery and confirmation of potential biomarkers predictive of clinical responses.

Subtopic DC1 – SLE, RA, and MS

Work package 1 – DC1 diseases, patients, cohorts, validation

The goals of this work package will be as follows:

- provide longitudinal bio-samples, including non-blood tissue samples from DC1 patients suitable for profiling by multiple –omics and emerging technologies;
- interface with the disease profiling and informatics teams to integrate the required clinical and scientific DC1 expertise and ensure appropriate design and interpretation of the data analysis;
- develop confirmation and validation assays using human models and primary cells.

Expected applicant consortium contribution:

- access to pre-existing DC1 patient cohorts, clinical data and a minimum of three longitudinal bio-samples for each patient, obtained pre-treatment, early post-treatment (2-4 weeks), and at the time of peak clinical response for the specific treatment and disease being studied from retrospective studies. For at least one of these time points, a non-blood affected disease tissue sample, such as RA synovium, lupus skin and/or kidney, or MS cerebrospinal fluid is required; and other matching tissue samples, such as joint fluid, blood, plasma, stool and urine samples are desired. Additional bio-samples are highly desired including follow-up samples taken during the remission and/or relapse phase or after treatment is withdrawn;
- interventional (approved standard-of-care therapies only) prospective biomarker trials to obtain clinical data and at least three longitudinal bio-samples for each patient, obtained pre-treatment, early post-treatment (2-4 weeks), and at the time of peak clinical response for the specific treatment and disease being studied. For at least one of these time points, a non-blood affected disease tissue sample, such as RA synovium, lupus skin and/or kidney, or MS cerebrospinal fluid is required; and other matching tissue samples, such as joint fluid, blood, plasma, stool and urine samples are desired. Additional bio-samples are highly desired including follow-up samples taken during the remission and/or relapse phase or after treatment is withdrawn;
- retrospective and prospective DC1 patient cohort immune interventions should ideally be an EMA/FDA approved targeted immune-therapy (biologic or small molecule therapeutic) which includes anti-TNFs: infliximab, adalimumab, certolizumab, golimumab, etanercept and biosimilars; BAFF inhibitor, benlysta (belimumab); hydroxychloroquine. Broad immunosuppressants such as azathioprine and non-immune therapy such as antibiotics are to be excluded from the study. Non-approved and off-label used drugs are not recommended;
- provide non-blood tissue samples suitable (e.g. frozen, not fixed) for single cell RNA-Seq and genetics (required) and other –omics, such as epigenetics, metabolomics, flow cytometry/CyTOF, proteomics and exosome profiling (desired). Note, for samples in which single cell RNA-Seq is performed it is desired that bulk RNA-Seq also be performed in parallel or duplicate sample aliquots be stored for future sequencing; however, bulk RNA-Seq should not be performed in lieu of single cell RNA-Seq;
- longitudinal stool samples from DC1 patient cohorts suitable for microbiome and metabolome are desired;
- breath analysis for volatile organic compounds (VOCs) on DC1 patients is desired;
- provide bio-samples, clinical data and any relevant datasets to the disease profiling and informatics subtopic for profiling and data analysis;

- interface with the disease profiling and informatics subtopic to ensure that clinical and scientific expertise in DC1 diseases is fully integrated into the design and interpretation of the data analysis being performed by the informatics teams;
- develop confirmation and validation assays using human models such as organoids and 'skin and/or kidney on a chip' type assays that focus on primary cells or induced pluripotent stem (IPS) cell derivatives are desired. Note mouse models are not applicable.

EFPIA consortium contribution:

- provide highly annotated clinical data and three or more longitudinal bio-samples for each patient with SLE, RA, or MS obtained pre-treatment, early post-treatment (2-4 weeks) and at the time of peak clinical response from the standard of care/active comparator arm of prospective clinical trials;
- provide samples and/or profiled –omics datasets to the Disease Profiling and Informatics subtopic for profiling, storage, data hosting and data analysis;
- provide scientific, clinical and developmental expertise to the DC1 and Disease Profiling and Informatics teams;
- interface with the Disease Profiling and Informatics subtopic to ensure that clinical and scientific expertise in DC1 diseases is fully integrated into the design and interpretation of the data analysis being performed by the informatics teams;
- provide scientific expertise necessary to develop human based models for confirmation and validation studies.

Subtopic DC2 – UC and CD

Work package 1 – DC2 diseases, patients, cohorts, validation

The goals of this work package will be as follows:

- provide longitudinal bio-samples, including non-blood tissue samples from DC2 patients suitable for profiling by multiple –omics and emerging technologies;
- interface with the Disease Profiling and Informatics teams to integrate the required clinical and scientific DC2 expertise and ensure appropriate design and interpretation of the data analysis;
- develop confirmation and validation assays using human models and primary cells.

Expected applicant consortium contribution:

- access to Crohn's disease (CD) cohorts including inflammatory disease, fibrostenosis and fistulising sub-groups, with and without active peri-anal disease. Other considerations would be early onset disease vs. late onset disease, post-operative Crohn's disease, and patients with extra intestinal manifestations. Overlap with autoimmune disease would be of special interest;
- access to ulcerative colitis (UC) cohorts based on disease distribution, extent of ulcerative colitis (E1-E3); it would be of special interest to study hospitalised acute, severe UC responsive vs. non-responsive to anti-TNF. UC with extra-intestinal manifestations, risk of deep venous thrombosis and overlap with psoriasis would be special populations of interest. Early onset disease vs. late onset disease analysis is desired;
- access to pre-existing DC2 patient cohorts, clinical data and a minimum of three longitudinal bio-samples for each patient, obtained pre-treatment, early post-treatment (2-4 weeks), and at the time of peak clinical response for the specific treatment and disease being studied from retrospective studies. For at least one of these time points, an affected disease mucosal tissue sample is required and other matching tissue samples, such as blood, plasma and urine samples are desired. Additional bio-samples are highly desired, including follow-up samples taken during the remission and/or relapse phase or after treatment is withdrawn;
- interventional (approved standard-of-care therapies only) prospective biomarker trials to obtain clinical data and at least three longitudinal bio-samples for each patient, obtained pre-treatment, early post-treatment (2-4 weeks), and at the time of peak clinical response for the specific treatment and disease being studied. For at least one of these time points, an affected disease mucosal tissue sample is required and other matching tissue samples, such as blood, plasma and urine samples are desired.

Additional bio-samples are highly desired including follow-up samples taken during the remission and/or relapse phase or after treatment is withdrawn;

- provide a minimum of three longitudinal stool samples per patient suitable for microbiome and metabolome (both required). Samples where 16S data is available are desired. Metabolomic platforms that assay microbial and host bio-actives and IgA sequencing are desired;
- retrospective and prospective DC2 patient cohort immune interventions should ideally be an EMA/FDA approved targeted immune-therapy (biologic or small molecule therapeutic) which includes anti-TNFs: Infliximab, adalimumab, certolizumab, golimumab, and biosimilars; anti-integrin: vedolizumab and natalizumab, and anti-p40: ustekinumab. Broad immunosuppressants such as azathioprine and non-immune therapy such as antibiotics are to be excluded from the study. Non-approved and off-label use is not recommended; however, faecal microbiota transplantation (FMT) intervention(s) may be considered;
- for DC2 immune intervention endpoints, the clinical phenotype of primary non-response should be distinguished from secondary loss of response. In the latter subgroup, inclusion of secondary loss of response in patients without anti-drug antibody is desired. Responders should have a clear 6-12 month response to the drug. Other notable sub-groups include long-term treatment responders (>5 years ideally on mono-therapy). While it is understood that clinical studies in patients with IBD use a variety of endpoints to define response and remission (including PRO and endoscopy/histology as per draft guidance from EMA and FDA), the present IMI2 collaboration uses for consistency the classical clinical endpoints;
- Crohn's Disease Activity Index (CDAI): response defined as $\Delta_{\text{baseline}} \geq 100$, remission absolute CDAI < 150;
- Mayo Clinic Score (MCS): response defined as $\Delta_{\text{baseline}} \geq 3$, remission absolute MCS < 2 with bleeding subscore 0 or 1; partial MCS, i.e., without endoscopy, is also acceptable;
- provide non-blood tissue samples (required) and matching blood samples (desired) suitable (e.g. frozen not fixed) for single cell RNA-Seq and genetics (required) and other –omics, such as epigenetics, metabolomics, flow cytometry/CyTOF, proteomics and exosome profiling (desired). Note that for samples in which single cell RNA-Seq is performed, it is desired that bulk RNA-Seq also be performed in parallel or duplicate sample aliquots be stored for future sequencing; however, bulk RNA-Seq should not be performed in lieu of single cell RNA-Seq;
- breath analysis for volatile organic compounds (VOCs) on DC2 patients is desired;
- provide bio-samples, clinical data and any relevant datasets to the disease profiling and informatics subtopic for profiling and data analysis;
- interface with the disease profiling and informatics subtopic to ensure that clinical and scientific expertise in DC2 diseases is fully integrated into the design and interpretation of the data analysis being performed by the informatics teams;
- develop validation assays using host epithelial cell – immune cell, host immune cell and microbe, host epithelial cell and microbe as examples of host microbial interactions. Organoid and 'gut on a chip' type assays that focus on primary cells or IPS cell derivatives are desired. Note that mouse models are not applicable.

EFPIA consortium contribution:

- provide highly annotated clinical data and three or more longitudinal bio-samples for each patient with UC or CD obtained pre-treatment, early post-treatment (2-4 weeks) and at the time of peak clinical response from the standard of care/active comparator arm of prospective clinical trials;
- provide samples and/or profiled –omics datasets to the disease profiling and informatics subtopic for profiling, storage, data hosting and data analysis;
- provide scientific, clinical and developmental expertise to the DC2 and disease profiling and informatics teams;
- interface with the disease profiling and informatics subtopic to ensure that clinical and scientific expertise in DC2 diseases is fully integrated into the design and interpretation of the data analysis being performed by the informatics teams;

- provide scientific expertise necessary to develop human based models for confirmation and validation studies.

Subtopic DC3 – Asthma and COPD

Work package 1 – DC3 diseases, patients, cohorts, validation

The goals of this work package will be as follows:

- provide longitudinal bio-samples, including non-blood tissue samples from DC3 patients suitable for profiling by multiple –omics and emerging technologies;
- interface with the disease profiling and informatics teams to integrate the required clinical and scientific DC3 expertise and ensure appropriate design and interpretation of the data analysis;
- develop confirmation and validation assays using human models and primary cells.

Expected applicant consortium contribution:

- retrospective and prospective DC3 patient cohort immune interventions should ideally be approved drugs such as Omalizumab, Mepolizumab, bronchodilators (LABA, SABA, LAMA), anti-inflammatory agents (ICS, oral steroid, Roflumilast), antibiotics and placebo arm (with or without standard of care treatment);
- DC3 patient immune intervention trial endpoints should include FEV1, EXACT for respiratory symptoms and St George's respiratory questionnaire for quality of life assessment for COPD patients, asthma control questionnaire, asthma symptom score, rate of exacerbations, time to next exacerbations;
- access to pre-existing DC3 patient cohorts, clinical data and a minimum of three longitudinal bio-samples obtained pre-treatment, early post-treatment (2-4 weeks), and at the time of peak clinical response for the specific treatment and disease being studied from retrospective studies. For at least one of these time points a non-blood affected disease tissue, such as sputum, lung biopsy, or bronchoalveolar lavage (BAL) fluid is required; and other matching tissue samples, such as blood, plasma, stool and urine are desired. Additional bio-samples are highly desired including follow-up samples taken during the remission and/or relapse phase (exacerbation) or after treatment is withdrawn;
- interventional (approved standard-of-care therapies only) prospective biomarker trials on DC3 patient cohorts to obtain clinical data and at least three longitudinal bio-samples obtained pre-treatment, early post-treatment (2-4 weeks), and at the time of peak clinical response for the specific treatment and disease being studied. For at least one of these time points a non-blood affected disease tissue, such as sputum, lung biopsy, or bronchoalveolar lavage (BAL) fluid is required; and other matching tissue samples, such as blood, plasma, stool and urine are desired. Additional bio-samples are highly desired including follow-up samples taken during the remission and/or relapse phase (exacerbation) or after treatment is withdrawn;
- provide non-blood tissue samples suitable (e.g. frozen not fixed) for single cell RNA-Seq and genetics (required) and other –omics, such as epigenetics, metabolomics, flow cytometry/CyTOF, proteomics and exosome profiling (desired). Note, for samples in which single cell RNA-Seq is performed it is desired that bulk RNA-Seq also be performed in parallel or duplicate sample aliquots be stored for future sequencing; however, bulk RNA-Seq should not be performed in lieu of single cell RNA-Seq;
- provide sputum or BAL fluid suitable for lung microbiome (required) and stool samples suitable for microbiome and metabolomics (desired);
- analysis of exhaled breath volatile organic compounds (VOC) for patient stratification and as an endpoint is desired for retrospective studies and required for prospective studies;
- transfer bio-samples, clinical data and any relevant datasets, to the disease profiling and informatics subtopic teams for profiling and data analysis;
- interface with the disease profiling and informatics subtopic to ensure that clinical, developmental and scientific expertise in DC3 diseases is fully integrated into the design and interpretation of the data analysis being performed by the informatics teams;

- develop validation assays using host epithelial cell – immune cell, host immune cell and microbe. Organoid and ‘lung on a chip’ type assays that focus on primary cells or IPS cell derivatives and originating from stratified patients are desired. Note that mouse models are not applicable.

EFPIA consortium contribution:

- provide highly annotated clinical data and three or more longitudinal bio-samples for each patient with asthma or COPD obtained pre-treatment, early post-treatment (2-4 weeks) and at the time of peak clinical response from the standard of care/active comparator arm of prospective clinical trials;
- provide samples and/or profiled –omics datasets to the disease profiling and informatics subtopic for profiling, storage, data hosting and data analysis;
- provide scientific, clinical and developmental expertise to the DC3 and disease profiling and informatics teams;
- provide informatics, scientific, clinical, and developmental expertise to identify respiratory phenotypes that steer away from asthma and COPD and are more aligned to ‘treatable traits’ and their response to standard of care;
- interface with the disease profiling and informatics subtopic to ensure that clinical and scientific expertise in DC3 diseases is fully integrated into the design and interpretation of the data analysis being performed by the informatics teams;
- provide scientific expertise necessary to develop human based models for confirmation and validation studies.

Topic 2: Non-invasive clinical molecular imaging of immune cells

Topic details

Topic code	IMI2-2018-14-02
Action type	Research and Innovation Action (RIA)
Submission and evaluation process	2 stages

Specific challenges to be addressed

Current pharmacodynamic (PD) assessments of immune cells are based on peripheral blood biomarkers, or from biopsy samples which are acquired by invasive procedures. Some existing medical imaging modalities provide a quantifiable, non-invasive, repeatable and localised measure of biological processes in the living body. However, current methodology and technology provides limited information on time-dependent and disease-specific relevant immune cell subpopulations and compartments types, or measures of direct engagement of immune targets.

Imaging tracers designed to bind specific immune cells ('immunotracers') or targets within immune-mediated pathways would enable the clinical imaging of the target immune cell subtypes and immune markers of disease in a clinical setting, which in turn would provide *in vivo* insights into effects of immunomodulatory therapies at disease sites (organs/tissues) and improve knowledge about the pathophysiology of various immune-mediated diseases. The ultimate ambition of clinical imaging with immunotracers is to enable tailored immunotherapy by allowing for:

- patient stratification based on immune status (personalised medicine);
- prediction of response or long-term outcome of therapeutic interventions;
- dose selection including personalised dosing;
- target engagement within the tissue of interest both regionally and focally.

Molecular imaging agents, (hybrid) imaging modalities, and image processing algorithms to image immune cells *in vivo* are advancing within the imaging field and can provide an immediate, non-invasive read-out of target expression over time. However, further novel imaging agents and technologies will need to be developed in order to extend the applicability of immune cell imaging to additional disease areas, additional tissue sites, and/or immune cell subpopulations especially by increasing the specificity of imaging agents. Therefore there remains a need to better understand the currently available markers and validate them extensively for clinical use. Thus, a strategic consortium that can connect innovative immunology research, imaging technology, and translational development to implement transformational immunotracers in the clinic is a requirement for the successful execution of this topic.

Need and opportunity for public-private collaborative research

This topic focuses on a set of immune cells of key importance in various disease areas involving widely differing organ/tissue systems, with the ultimate goal to develop a transformational set of clinical imaging agents and non-invasive methods that are capable of monitoring immune cell phenotype and function. A large number of potential therapies acting upon these immune cells exist or are being developed, and successful methods established within this topic will be broadly applicable in many indications across many different organisations and research groups. Even though, the field of (semi-)quantitative clinical imaging of defined immune cell subsets is advancing and moving from qualitative to quantitative measures, it would still require a very broad spectrum of diverse technical and biological expertise to move forward efficiently. This combination is unlikely to be within the scope of investment and capabilities for any one company or organisation, but collaborative efforts in a public-private partnership are most likely to harness all the skills and expertise required.

The topic provides a unique platform for leading experts from industry, academia and regulators. This platform is needed not only to define and create new and target-specific probes, but also for the testing/validation of imaging technologies and novel imaging algorithms, the generation of reagent packages, and ultimately for the clinical validation of the immunotracers and imaging technology in clinical trials. Generation and validation of a clinical immune-cell imaging platform that provides a non-invasive early indicator to detect immune cells of different phenotypes, correlations with efficacy, and benefit of a therapeutic intervention for various disorders will require collaboration between a diverse set of stakeholders with expertise in immunology, imaging technologies, data management, analytics and regulatory sciences.

Scope

This topic aims to establish a consortium that can develop and validate a quantitative, non-invasive, immune cell imaging platform, which includes novel and target-specific molecular imaging agents, (hybrid) imaging modalities, and image processing algorithms. The topic aligns with the IMI2 Strategic Research Agenda, as it aims to validate immune cell targets based on human biology and to facilitate precision medicine by identification and stratification of patients and prediction of therapeutic outcomes. In addition, it is expected that these agents will facilitate early diagnosis of the disease and/or classification of disease based on the immune phenotype.

The following objectives are within the scope of the proposal:

- clinical validation of existing imaging agents (e.g. agents targeting CD8⁺ T-cells and immune pathways);
- development and characterisation of novel molecular imaging agents to be used for imaging CD4⁺ T-cells, CD8⁺ T-cells, regulatory T-cells, B-cells, macrophages, and NK-cells, reflecting the presence of these cells in tissues/organs/tumours, or denoting markers of the activation status of these immune cells. The new imaging agents should be highly specific for these targets in order to improve their detection;
- establishing molecular imaging platforms in disease areas for which biopsies for validation of the imaging platform can be obtained (e.g. cancer, chronic obstructive pulmonary disease (COPD)/asthma, atopic dermatitis, vasculitis, psoriasis, Sjögren's syndrome, inflammatory bowel disease (IBD), rheumatoid arthritis (RA), and transplant). The platform is initially to be validated in a small number of diseases (identified as common denominator of all participating companies), and could subsequently be used for other disease areas e.g. should brain penetrant tracers be identified/developed neurodegenerative diseases and multiple sclerosis could also be considered;
- optimisation of the quality of immunotracers to ensure appropriate specificity of binding as well as pharmacokinetic and bio-distribution profiles;
- implementing non-invasive imaging modalities that can deliver quantitative data. Whole-body imaging technologies with the capability to image deep-seated tissue/tumours are preferred (e.g. PET, SPECT, MRI, hybrid modalities, PET/SPECT-CT), but depending on the disease area other non-ionizing methods or pre-targeting approaches can be evaluated (e.g. optical imaging and/or photoacoustic imaging of skin lesions, salivary glands, endoscopic/bronchoscopic examinations for IBD, COPD);
- pre-clinical studies to evaluate and validate the novel molecular imaging agents/immunotracers and the immune cell imaging platform as required as a proof of concept to enable translation into the clinic.

Expected key deliverables

Expected primary key deliverables of the topic include:

- identification and evaluation of promising molecular imaging agents and non-invasive imaging modalities (single platform or hybrid) suitable for use with the proposed immunotracers;
- generation of immunotracers for at least two of the following key cell types of interest: CD4+, CD8+, regulatory T-cells, B-cells, NK-cells, macrophages;
- immunotracer optimisation in the context of the planned use (e.g. with respect to pharmacokinetic and bio-distribution profile, suitability for repeated use in longitudinal studies);
- appropriate resolution and sensitivity (at least semi-quantitative) of the immunotracer and imaging modality combination(s) to allow delineation of organs of interest and determination of relative changes in tissue immune cell involvement and/or activation status;
- clinical proof of concept utilising at least one immunotracer / imaging modality combination(s) for cells and tissues of interest;
- imaging modalities and processing tools suitable for accurate co-registration of multi-modality images e.g. PET/CT to co-register anatomy and functionality.

Expected impact

Molecular imaging of immune cells could provide an early indicator of whether patients are likely to benefit from a given (immuno-) therapeutic intervention (surrogate of response). The technology to be delivered is expected to have the potential to also provide information for tissue/organ sites which are not biopsy-accessible, thus representing a significant advance in the assessment of the immune marker status for the relevant indications. Patients can be stratified by marker expression, with the potential to offer the most appropriate treatment and thereby reduce the implementation of treatment regimens that are unlikely to be efficacious and would therefore have a negative benefit-risk profile for the individual patient (personalised health care, PHC). For example, in the treatment of certain cancers, identification of particular immune cells subsets could be determined for individual patients (e.g. CD8/CD4-imaging) to determine and predict the response and which patient population would most likely to benefit from co-stimulatory treatments.

By visualising and quantifying the impact of therapy on specific target sites and related immune-mediated pathways, the planned technology is also expected to reduce ambiguity in the evaluation of efficacy during clinical trials (e.g. provide early indications of patient responses, assessment of variability between and within individuals, facilitate proof of mechanism (POM) and proof of concept (POC) studies of new mechanisms). Spatio-temporal complexity can be studied due to longitudinal imaging capabilities.

This topic is a unique instrument to strongly support and enable research and development activities addressing diseases with a strong immunological component, for which currently no or only very limited treatment options are available. Furthermore, it will have significant impact on personalised approaches to detect and better monitor these diseases already in the early and better treatable stages. It will support and guide physicians and patients in determining the most appropriate care, leading to improved efficiency in the health care system and patient benefits. It is envisioned that the topic will ultimately result in the regulatory acceptance of standardised protocols with validated immune-imaging approaches. Consequently, those approaches will significantly reduce the time and cost of clinical trials.

Small and medium-sized enterprises (SMEs) can be of great benefit to IMI2 JU projects. Their involvement in the action might offer a complementary perspective to industry and academia, and help deliver the long-term impact of the project. Therefore applicants should indicate how their proposals will impact and strengthen the competitiveness and industrial leadership of Europe by, for example, engaging suitable SMEs.

Potential synergies with existing consortia

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

In particular, the action generated by this topic should, among others consider initiatives such as the FNIH Partnership for Accelerating Cancer Therapies (PACT) <https://fnihi.org/what-we-do/current-research-programs/partnership-for-accelerating-cancer-therapies> or the IMI projects **BTCURE** (<http://btcure.eu/>), **RTCURE** (http://cordis.europa.eu/project/rcn/211964_en.html), **PRECISESADS** (<http://www.precisesads.eu/>) and **TRISTAN** (<http://www.imi.europa.eu/projects-results/project-factsheets/tristan>).

Industry consortium

The industry consortium is composed of the following EFPIA companies:

- Roche (lead)
- AstraZeneca
- Bayer
- Janssen
- Novartis
- Pfizer
- Sanofi

The industry consortium will include expertise in clinical operations, protein engineering, validation of immune cell targeting, and will contribute mainly in the form of:

- provision and detailed investigation of antibodies, antibody fragments, and/or small molecule probes;
- prospective clinical trials for selected diseases (immunotracers to be applied in these prospective on-going clinical trials with dedicated imaging activities);
- samples from prospective clinical trials;
- immuno-histochemical and other appropriate analyses of biopsy material to validate the imaging results;
- historical samples for validation;
- omics data analysis.

Indicative duration of the action

The indicative duration of the action is 60 months.

Future project extension

Potential applicants must be aware that the Innovative Medicines Initiative 2 Joint Undertaking (IMI2 JU) may, if exceptionally needed, publish at a later stage another Call for proposals restricted to the consortium already selected under this topic, in order to enhance their results and achievements by extending their duration and funding. The consortium will be entitled to open to other beneficiaries as they see fit; should appropriate imaging modalities and/or technologies are developed within the context of the consortium and require additional investigation outside the scope of the proposed sustainability plan.

Direct visualisation of immunophenotypes in target organs would advance the field by providing a mechanistic insight into the pathogenesis of disease which in turn could, with additional studies, lead to the improvement of treatment decisions for physicians and help guide therapeutics development by allowing the visualisation of response to therapy. The proposed focus is to validate existing agents that target immune cells and molecular pathways using biopsies from multiple diseases and target sites as a starting point.

Thus, the knowledge gained from the clinical validation of existing imaging reagents should help augment the development of new tracers, and the pre-clinical studies from them will speed up patient access to innovation. However, addressing all these points is outside the scope of the current initiative as the insights uncovered by this topic will be exploratory and not definitive, and will need to be followed up by future validation studies in patients.

Indicative budget

The indicative EFPIA in-kind contribution is EUR 15 000 000.

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

The financial contribution from IMI2 JU is a maximum of EUR 15 000 000.

Applicant consortium

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

- basic and clinical immunology, in particular as this relates to the proposed cell types and indications;
- strong expertise in chemistry and molecular biology to improve the target specificity of imaging agents;
- biological validation of specific immunotracers in well-characterised animal models for the particular diseases to be investigated
- expertise with appropriate non-invasive imaging technologies and optimisation of quantitative data generation and analysis;
- expertise in immunotracer development, for example in identification of (novel) selective and specific immune cell markers, generation and optimisation of targeting moiety/tracer conjugates;
- proven expertise in project administration, management and communication;
- extensive expertise in interaction and communication with global regulators, patients, practitioners and payers, who may be members of an advisory board which would be established by the action. These responsibilities will be executed in collaboration with the industry consortium;
- strong data management expertise;
- proven experience in managing and coordinating a multi-centre multi-node clinical-research data-generation activity of comparable scope;
- essential experience in dealing with the legal and ethical challenges associated with integrating multi-centre patient-derived data, as well as physical data-processing and data management practices (privacy, security);
- proven capability to deliver analytical platforms to facilitate the above-mentioned advanced analytical approaches for a range of scientific/medical and analytical communities.

In addition to academic groups, relevant SMEs with relevant proven expertise are encouraged to participate in the applicant consortium. SMEs can be of great benefit to IMI projects and, inter-alia strengthen the competitiveness and industrial leadership of Europe. Their involvement might offer a complementary perspective to industry and academia, and strengthen the long-term impact of the project. For these reasons, applicants should consider engaging SMEs throughout the proposal. Under this topic, the contribution of SMEs would be considered especially beneficial in imaging agents and technologies, advanced analytical approaches and data management practices.

The size of the consortium should be proportionate to the objectives of the topic.

Suggested architecture of the full proposal

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

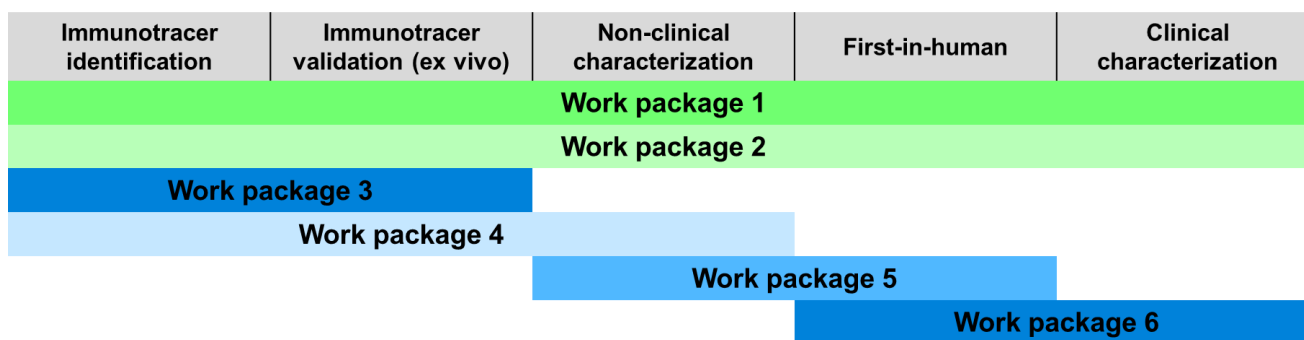
In the spirit of the partnership, and to reflect how IMI2 JU Call topics are built on identified scientific priorities agreed together with EFPIA beneficiaries/large industrial beneficiaries; these beneficiaries intend to significantly contribute to the programme and project leadership as well as project financial management.

The final architecture of the full proposal will be defined by the participants in compliance with the IMI2 JU rules and with a view to the achievement of the project objectives. The allocation of a leading role within the consortium will be discussed in the course of the drafting of the full proposal to be submitted at stage 2. To facilitate the formation of the final consortium, until the roles are formally appointed through the consortium agreement, the proposed project leader from among EFPIA beneficiaries/large industrial beneficiaries shall facilitate an efficient negotiation of project content and required agreements. All beneficiaries are encouraged to discuss the project architecture and governance and the weighting of responsibilities and priorities therein.

The consortium is expected to have a strategy on the translation of the relevant project outputs into regulatory practices, regulatory, clinical and healthcare practice. A plan for interactions with Regulatory Agencies/health technology assessment bodies with relevant milestones, resources allocated should be proposed to ensure this e.g. qualification advice on the proposed methods for novel methodologies for drug development, qualification opinion.

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

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



Work package 1 – Management, coordination, dissemination and sustainability

The goals of this work package will be as follows:

- overall coordination of the scientific and clinical work packages;
- budget administration;
- dissemination of scientific results and research data;
- development of a sustainability plan to facilitate continuation of the project beyond its anticipated duration;
- communication within the consortium and with external collaborators.

Expected applicant consortium contribution: coordination of work packages, budget administration, dissemination of scientific results and development of a sustainability plan.

EFPIA consortium contribution: communication, dissemination of results and development of sustainability plan.

Work package 2 – Data storage and analysis

The goals of this work package will be as follows:

- managing/coordinating multi-centre (clinical) research data including legal and ethical considerations;
- data sharing, data integration infrastructure, and bio-banking;
- analysis of retrospective clinical trials and design and execution of prospective clinical trials.

Expected applicant consortium contribution: coordinating a multi-centre multi-node clinical-research data-management.

EFPIA consortium contribution: prospective clinical trials for selected diseases (immunotracers to be applied in these prospective on-going clinical trials with dedicated imaging activities); provide samples from prospective clinical trials.

Work package 3 – Generation of imaging reagents to uniquely identify specific cell types

The goals of this work package will be as follows:

- specification of cell types and appropriate surface tags;
- generation of detection reagents;
- characterisation by histology and/or flow cytometry or other laboratory techniques;
- qualification of immunotracers for use in confirmatory assay types and ensuring suitability in different assay types.

Expected applicant consortium contribution: identification and evaluation of promising molecular imaging agents; generation of immunotracers for at least two of the following key cell types of interest: CD4+, CD8+, and/or regulatory T-cells, B-cells, NK-cells, and macrophages; immunotracer optimisation in the context of the planned use (e.g. with respect to pharmacokinetic and bio-distribution profile, suitability for repeated use in longitudinal studies).

EFPIA consortium contribution: immuno-histochemical and other appropriate analyses of biopsy material to validate the imaging results, historical samples for validation, omics data analysis.

Work package 4 – Imaging technique development and optimisation

The goals of this work package will be as follows:

- specification of optimal imaging modality;
- development of imaging protocol for specific immunotracers (e.g. definition of dose, imaging time point etc.) in preclinical models and with support from data from work package 5, where applicable.

Expected applicant consortium contribution: biological validation of specific immunotracers in well-characterised experimental animal models; proof of principle preclinical imaging studies using known immuno-modulators.

EFPIA consortium contribution: biological validation of specific immunotracers in well-characterised experimental animal models; proof of principle preclinical imaging studies using known immuno-modulators.

The allocation and distribution of resources will be agreed during the elaboration of the full project proposal, as this is dependent on the distribution of expertise between EFPIA and successful (academic/SME) applicant consortium partners.

Work package 5 – Validation of immunotracers in animal models (non-clinical *in vivo* characterisation)

The goals of this work package will be as follows:

- validation of novel immunotracers in rodent and/or monkey models of human disease;
- *in vivo* pre-clinical animal models will be used to measure the utility of the immunotracers;
- characterisation of non-clinical safety.

The allocation and distribution of resources will be agreed during the elaboration of the full project proposal, as this is dependent on the distribution of expertise between EFPIA and successful (academic/SME) applicant consortium partners.

Work package 6 – Human clinical trials

The goal of this work package is to confirm the safety of new immunotracers and reagents and to demonstrate clinical utility in human trials.

Expected applicant consortium contribution: contribute to the preparation of regulatory documentation (Investigator Brochure, clinical protocol, Clinical Trial Application dossier etc.).

EFPIA consortium contribution: prospective clinical trials for selected diseases (immunotracers to be applied in these prospective on-going clinical trials with dedicated imaging activities); provide samples from prospective clinical trials.

Topic 3: Development of a platform for federated and privacy-preserving machine learning in support of drug discovery

Topic details

Topic code	IMI2-2018-14-03
Action type	Research and Innovation Action (RIA)
Submission and evaluation process	2 stages

Specific challenges to be addressed

Enabled by an ever-expanding arsenal of model systems, analysis methods, libraries of chemical compounds and other agents (like biologics), the amount of data generated during drug discovery programmes has never been greater, yet the biological complexity of many diseases still defies pharmaceutical treatment. Hand in hand with rising regulatory expectations, this growing complexity has inflated the research intensity and associated cost of the average discovery project. It is, therefore, imperative that the learnings from these data investments are maximised to enable efficient future research. This could be empowered by the big data analysis and machine learning approaches that are currently driving the digital transformation across all industries. These approaches not only rely on data generated specifically within a given project to learn from (as more established machine learning approaches tend to do), they also evaluate all other available data from different data sources and types for relevance to the question at hand. This extended approach will extract the maximum information present within the data, which in turns enables a gradual virtualisation of drug discovery processes and increases efficiency in bringing more and safer drug candidates towards clinical trials.

The success of the digital transformation in the pharmaceutical industry will thus highly depend on unlocking the maximal amount of data for the learning tasks at hand, and make these data amenable to the latest approaches in machine learning. To accomplish this, the following specific challenges need to be addressed.

- Unlocking of proprietary and confidential data that is currently distributed across multiple data owners within the pharmaceutical sector without disclosure of the actual data and related assets themselves. In order to convince data owners to share their highly confidential and proprietary databases, which have been established over many years at considerable cost, the following conditions need to be fulfilled.
 - **Privacy preservation** denotes the strict protection of the confidential and intellectual property (IP)-sensitive data and assets. In drug discovery, examples of IP-sensitive data and assets include the activity data of compounds in assays, the assay annotations, and predictive models derived from these data. In the strictest sense, privacy preservation implies that these data and assets never leave the control of the respective data owners.
 - **Federated machine learning** denotes here the distribution of the learning effort over physically separated partners. This goes beyond the currently more established concept of federated databases where the data are distributed, but not the data functionalisation (i.e. the learning from the data). It is key to enable owner control over data and other assets during learning.
- Unlocking of data volumes from data sources or types that have hitherto remained untapped. In drug discovery, examples include image or transcriptional profiles or primary data points acquired in high throughput screens, all of which provide rich but hard-to-interpret biological annotation of chemical compounds.
- Adapt recent advances in machine learning such as multi-task learning and deep learning for the above data expansion strategies.

Need and opportunity for public-private collaborative research

The digital transformation that is driven by ever more exhaustive data collection and exploitation, is disrupting the entire industrial landscape. Sectors and geographies that fail to embrace this transformation will find themselves challenged in their remit by newcomers with a strong footing in data sciences.

In this context, a collaboration among pharmaceutical partners, academia and knowledge partners from small and medium-sized enterprises (SMEs) and other commercial organisations offers the perspective of doubling economies of scale in bringing better and safer drugs to patients. Firstly, it enables cost sharing and thereby bolsters the position of the European pharmaceutical industry in the global competition for data science and ICT resources. Secondly, it encourages data and method standardisation, thus expanding the volume of collective data that can fuel the big data revolution. Notably, these collective data should not be misinterpreted as a freely accessible and hence a fully precompetitive resource. Privacy-preserving approaches enable the reconciliation of collaborative investment with healthy within-sector competition.

The concepts of federated and privacy-preserving machine learning apply beyond the discovery remit, for instance in development and other clinical settings (like real-world evidence settings). They even apply beyond the health setting. Indeed, by providing data owners the confidence that their data and the corresponding predictive models will remain private, the methodologies developed will encourage the formation of data and model consortia in various commercial (including non-pharmaceutical) and non-commercial contexts where data and knowledge ownership is at play. This creates opportunities for SMEs or other commercial partners that offer front-end or back-end services in the areas of software-as-a-service products in big-data analytics, clouded high-performance computing and privacy-preserving solutions. The public-private partnership proposed enables such partners to get exposed to, on the one hand, a strong application field with relevant use cases and clear ICT and security requirements, and on the other hand, academia and other knowledge partners with deep expertise in rapidly evolving science and technology fields.

Scope

The topic aims for:

The delivery of a federated and privacy-preserving machine learning platform, initially validated on publicly accessible data, that is demonstrably safe enough (privacy-preserving in the face of legitimate and illegitimate (attempted) access and use) and scalable enough to be deployed to a significant representation of private data in the actual preclinical data warehouses of the participating major pharmaceutical companies in yearly evaluation runs. This effort will be mainly driven by the applicant consortium and enabled by the EFPIA partners.

The industry partners will subsequently drive the evaluation of the security, scalability and operational and predictive performance of the above platform on real industrial data (which is much more extensive than that in the public domain). As an indication of scale, the anticipated collective private compound and activity data sets from the industrial partners that will be used during the evaluations and that are to be accommodated comprehensively in each of the at least yearly runs, will include:

- at least 5 million chemical compounds annotated with dose-response quality activity data;
- at least 10 million chemical compounds annotated with some activity;
- at least 1 billion assay activity data points collected at single dose (low-complexity i.e. 1 to a few numerical values per compound, e.g. as from high-throughput screening);
- at least 100 million activity data points collected in dose response (over a range of doses, e.g. as from follow-up/secondary screening);
- several high-complexity activities collected at high-throughput (at least 100 thousand compounds in a standardised setting, e.g. high-resolution microscopy images or transcriptional profiles with 1000 readouts per well).

The above data are generated as part of the industry partners' normal drug discovery activities and, as such, are not generated in the scope of the project. Other than anonymised assay identifiers, the industry partner data will not include assay meta-information, such as specification of which drug target is tested. As a part of the effort, the industry partners will agree on protocols to standardise, format and normalise their private data for optimal interoperability and will openly release the software they develop to do so, to promote its broadest

adoption, within or outside of the context of the proposed machine learning platform. The applicant consortium is encouraged to closely cooperate with this aim.

The economic value of the platform lies in its ability to learn to predict the activity of chemical compounds in documented assays from descriptors of their chemical structure in the absence of meta-information such as the drug target of these assays. For training the predictive models, the platform will leverage the activity data points for all assays (which remain under the control of their respective owner) and as much of the further available side information for compounds (images and transcriptional profiles) as possible. Methods within the scope of this topic should be compatible with the full scale and richness and with the limitations of the above data. For example, given the absence of assay meta-information, no predictive performance gains can be realised by constructing models across data columns with similar or shared annotations.

Predictive performance improvements from federated learning are expected to stem from the multi-task effect across partners. In the rich data sets described above, most assays are poised to show some linear or non-linear correlation with (a combination of) other assays. In a multi-task setting, this allows the model predictivity to be boosted for chemistry that was not documented in the training set for a given assay, but that was documented in some correlated assay(s). In a federated learning setting, such information transfer will occur across partners, through common representation of tasks/assays in federated (as in shared among the data participants) model components. Privacy preservation on the other hand implies that each pharma owner/contributor of assay data builds up (on IT infrastructures under his own control) complementing model components that are specific for his own assays. Federated and privacy-preserving learning combines federated model components (enabling transfer learning across partners) and private model components (to preserve the confidential nature of the modelled assays) to yield better informed, yet overall private models for the respective data owners/contributors. This combination of better learning with preserving the privacy of the underlying data and assets is the core value of the proposed platform.

In terms of predictive performance, the concrete outcome of the evaluation of the platform will be relevant metrics of the predictive performance of the platform as a function of design and setup choices, aggregated by the platform across all the assays from all the partners. Platform-mediated aggregation ensures that contributions of the individual participants to the overall performance are anonymised, in order that here too, privacy is preserved. The aggregated performance metrics will be shared with the consortium partners to guide and improve design choices, and ultimately document the predictive performance of the final versions of the platform, a key objective of the proposal, without however disclosing the underlying confidential data and/or any predictive models derived therefrom.

For future exploitation, platform versions must be designed that can also produce the individual predictive models for the assays of respective data contributors, in a form that persists after completion of the run. It should be noted, however, that the generation of such persistent individual predictive models, which are inseparably linked to the private compound and activity data from the EFPIA partners, is not essential for the computation of the aggregated performance metrics during the cross-pharma evaluation rounds. Indeed, these aggregated performance metrics can also be computed using alternative platform versions that do not produce persistent individual predictive models, but this would burden the consortium with the development and audit of an alternative version for each platform iteration. It is crucial to understand that the preservation of privacy and confidentiality of the data to be learned from and the individual models derived therefrom is a key component in the successful implementation of the topic, not only in the current context of discovery and preclinical research but also for any potential future extensions using clinical data. It is also a condition for the involvement of the extensive private datasets of the EFPIA partners.

Technically, privacy preservation is interpreted to exclude any persistent or non-persistent consolidation of assay data or annotations, or the corresponding predictive models, which were described above as the private model components (even encrypted) outside of IT architectures under direct and sole control of their respective owners. It also implies the confidential treatment of all related data and protection from access to them by third parties.

The proposed project aims for federated machine learning which is not the same thing as machine learning on federated data. The difference is as follows: in the former case, the machine learning effort itself is distributed over the parties involved; in the latter case, the machine learning is executed centrally over federated data, which is incompatible with the proposed interpretation of privacy preservation. Upon completion of a modelling exercise, no data (derived or otherwise) should persist outside of those architectures. The pharma IT departments will consolidate their IT security requirements, including those covering compatible cloud

services proposed as part of the platform IT architecture, based on current industry standards that aim to protect against illegitimate access to or use of the data or predictive models.

The expected time and cost efficiency gains in a development context (using clinical data) will most likely far outweigh those in the current discovery setting, given the obvious privacy considerations concerning clinical data. It is, therefore, important that the platform is designed with future use in a clinical setting in mind. However, this project focuses on the core objective of developing the federated, privacy-preserving machine learning method in a preclinical setting. Tackling the complexities of clinical data handling in terms of adequately addressing ownership and privacy legislation implications would take place in a future initiative.

To further bolster the confidence in the proposed methods of the pharmaceutical partners (and of potential other future adopters), an intrinsic part of the proposal should focus on analysing the privacy preservation of the proposed methods in the case of legitimate use (targeting questions like 'can a model owner reconstruct parts of the chemical or bioactivity data of individual other parties based on model components they can legitimately access'). Public data (prepared and processed by the pharma partners using the same protocols as for their own data) can be leveraged to this end. ChEMBL and PubChem represent the main public information sources, but other open data opportunities of relevant scale can be considered.

In summary, the power of the proposed federated and privacy-preserving machine learning platform resides in the fact that it operates in such a way that it can extract a maximum of learnings without the need to directly access the underlying private data. This makes the methodology generic and widely applicable in a great diversity of settings, with a high potential in settings where learnings are envisaged from highly confidential data, such as patient-related data in a clinical setting.

Expected key deliverables

- An early software prototype for federated learning compatible with privacy preservation (not enterprise ready) is delivered by month 2 to allow the algorithm to be documented and to enable an analysis of privacy preservation by the use of legitimate modelling results. This prototype should be based on software already existing at project start.
- A coherent, federated, privacy-preserving machine learning platform that conforms with the following requirements should be delivered by month 12 and updated at least annually.
 - For each iteration, an early software prototype is made available 10-12 months ahead of the enterprise-ready release, to allow algorithm documentation and to enable an analysis of privacy preservation.
 - For each iteration, a report on the privacy preservation performance of the platform using public data, listing algorithmic or parameter options to navigate performance/privacy trade-offs, is prepared. This includes evaluating vulnerabilities to e.g. differential attacks. These reports will enable conceptual sign-off for use on the massive proprietary and confidential pharma datasets.
 - For each iteration, based on the signed-off conclusions of the privacy preservation report, enterprise-ready code is delivered, i.e. ready for independent code audit against joint pharma security requirements (that should preclude to reasonable standards illegitimate access to or use of data or models, and that covers compatible IT architecture options including cloud services). A favourable audit report is a prerequisite for exposure of the massive pharma datasets.
 - Ability to be run on a requirements-compatible IT architecture in a standalone and federated learning setting.
 - From the 2nd year onwards, the solutions should enable participants to mutually benefit from the inclusion of high throughput image or transcriptional datasets annotating sets of more than 100k compounds.
- Establishment of proof-of-concept of this platform, by deploying and evaluating it in an industrial setting.
 - EFPIA partners to propose common protocols to standardise, format and normalise their private data for optimal interoperability and openly release the software they develop to do so.
 - EFPIA partners to consolidate their necessary and sufficient IT security requirements including those covering compatible cloud services proposed by the applicant consortium as part of the platform IT architecture. Part of the infrastructure will need to be under the control of the respective data and asset owners.

- To evaluate the predictive performance of the platform when deployed on industrial scale datasets as a function of design and setup choices, by performance metrics aggregated by the platform across all assays and partners. Relevant performance metrics to include established metrics that can be used with annotated compound sets, like the AUC of the ROC curve and logarithmic loss metrics or root mean squared prediction error for all assays, aggregated as distributions across all assays and partners. In addition, performance metrics are to be collected, in an aggregated modality, that measure the information gain (i.e. certainty, credibility or precision gain) over the platform of predictions for unannotated compounds.
 - Standalone and cross partner runs yielding these performance metrics (aggregated by the platform across all assays and partners) to be executed on a requirements-compatible ICT infrastructure and comparison of the resulting aggregated metrics. The algorithmic, software and ICT infrastructure choices proposed should cost-efficiently enable a full cross-partner run to complete in maximally four weeks. This may or may not imply provision of hardware acceleration options, and – to ensure availability of such options for all participants – cloud services.
 - At least in one exercise, the aggregated predictive performance of inclusion vs. exclusion of image-derived or transcriptional features in a federated modelling run are compared head-to-head.
 - At least in one exercise, the aggregated predictive performance of the developed methodology is compared head-to-head to that of a credible established non-federated single-task method (minimally support vector machine (SVM), random forest or a comparably performant method).
- Sustainability plans that detail how the applicant consortium intends to make the developed methodologies accessible to the pharmaceutical industry and to other future adopters after the project ends.
- Publication and dissemination of guidelines, advice, detailed processes (workflows and specific technical details), ICT and security standards, and of the predictive performance (at an aggregated level) to promote the uptake of the developed methodologies in the pharma and other) sectors.
- Identification and publication of any barriers to the uptake of the proposed methodology and publication of solutions to reduce those barriers.

Expected impact

The *in silico* predictions from the platform developed within the project will increasingly replace the costly and time-consuming *in vitro* testing, resulting in cost and time savings on compound synthesis and measurement in assays and preclinical studies, and therefore increase the efficiency of pharmaceutical discovery research. Although out of the direct scope of the present topic, the application of similar concepts to clinical data to enable faster recruitment of more targeted patients holds the longer-term promise of reducing costs of development.

The concepts developed within the project will be generic and will apply not only to the pharmaceutical discovery and clinical development setting, but also to other clinical applications, including real-world evidence analysis. Beyond the health area, they will prove relevant to multiple alternative industrial and other commercial or non-commercial settings where parties are interested in different predictive models that benefit from indirect access to the same volumes of private data. By providing data owners with the confidence that their data and the corresponding predictive models will remain private, this project will facilitate access to much larger data sets and therefore improve performance over that of conventional machine learning approaches.

For knowledge and ICT partners, federated learning presents a line of research and product development beyond that of data federation.

Applicants should indicate how their proposal will impact on the competitiveness and industrial leadership of Europe by, for example engaging suitable SMEs.

Potential synergies with existing consortia

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

For example, several IMI projects have already faced the challenge of facilitating research on private data, see <http://www.sciencedirect.com/science/article/pii/S1359644615004249> and <http://www.mdpi.com/1422-0067/15/11/21136/html>

Another IMI project aims at the systematic FAIRification of data (the capture and management of data to make them Findable, Accessible, Interoperable and Reusable). The project consortium is encouraged to seek synergies with projects for the FAIRification of data (e.g. consider applying learnings and technologies from such projects), but should avoid replication of such efforts.

Industry consortium

The industry consortium is composed of the following EFPIA companies:

- Janssen Pharmaceutica NV (lead)
- Astellas Pharma Europe BV
- AstraZeneca AB
- Bayer AG
- Boehringer Ingelheim Pharma GmbH & Co. KG
- GlaxoSmithKline R&D Ltd
- Institut de Recherches Internationales Servier
- Merck KGaA
- Novartis Pharma AG

Key contributions from EFPIA partners:

- agreed protocols and solutions for processing data with the necessary and sufficient level of standardisation to enable the machine learning exercises. To encourage broader adoption, the partners will opt for open solutions where possible. Insights on data standards and technologies from ongoing EU-funded projects (e.g. those in the context of the FAIRification IMI topic) will be considered;
- the anticipated collective industry datasets outlined under Scope, above;
- data management;
- formulation of joint security requirements in line with industry standards;
- set up independent audit of all enterprise-readied code against those requirements;
- evaluation of the analysis of privacy preservation based on legitimately accessed models;
- expertise in cheminformatics and machine learning at scale in the context of this topic;
- upon enablement by the consortium (access to secure software solutions), execute provided solutions on own data (standalone);
- evaluate the aggregated predictive performance in terms of accuracy and related metrics (for annotated compounds) and information gain and precision (for unannotated compounds);
- extensive experience in drug discovery and development, including knowledge, of all *in vitro* and preclinical assays modelled;
- expertise in image and omics analysis, to facilitate the accommodation of image or transcriptional information in the developed methods;
- project management coordination across pharma;

- project management support by a subcontracted project management office;
- dissemination activities within the sector.

Indicative duration of the action

The indicative duration of the action is 36 months.

Future Project Expansion

Potential applicants must be aware that the Innovative Medicines Initiative 2 (IMI2) Joint Undertaking, may publish at a later stage another call for proposals restricted to those projects already selected under this call in order to enhance and progress their results and achievements by extending their duration and funding. Consortia will be entitled to open to other beneficiaries as they see fit. If proof-of-concept in terms of privacy and predictive performance is established in the discovery setting, there is the possibility of a restricted call that would adapt the platform developed under the present call for use on clinical datasets, i.e. deliver and evaluate an extended version of the platform that would:

1. map relevant clinical concepts to specific platform components; and
2. meet all additional legal requirements associated with the handling of patient data (e.g. those related to the protection of patient privacy).

Indicative budget

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

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 contribution.

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

Applicant consortium

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

The applicant consortium is expected to address all the research objectives and make key contributions to the defined deliverables in synergy with the industry consortium which will join the selected applicant consortium in preparation of the full proposal for stage 2. Therefore, the applicant consortium should be able to demonstrate the full scope of experience and expertise needed to effectively address all the objectives outlined in this topic. The size of the applicant consortia should reflect the expertise needed to achieve the proposed objectives within the indicated budget while ensuring the 'manageability' of the consortium as well as efficient and effective team work. Therefore, the number of members of the applicant consortium needs to be thoroughly justified in the proposal and all partners involved should make a significant contribution to the project.

To meet the ambitions of the topic and ensure a first version can be deployed by the end of year one, the applicant consortium should describe the workhorse algorithms they intend to use in their short proposal, in sufficient detail to convincingly demonstrate their compatibility with the type of data made available for this topic and with the proposed federated and privacy-preserving machine learning concepts, preferably with (not necessarily secure or enterprise ready yet) software prototypes. If there are dependencies on other than open source software, the consortium members preferably collectively hold all necessary background rights, so that licensing costs are kept minimal within project and the service can ultimately be offered at an attractive cost. This also ensures that an independent auditor can get access to all parts of the code to attest that it only comprises the intended functionalities.

Given the runs will involve the handling of private preclinical data sets at an unprecedented scale, the applicant consortium is expected to mobilise across academia, SMEs and other commercial organisations as appropriate, the following:

- demonstrated extensive hands-on expertise in solutions for big data handling at industrial scale;

- demonstrated extensive hands-on expertise in ICT security and information leakage aspects;
- demonstrated extensive hands-on expertise with deployment on high performance computing infrastructures;
- demonstrated extensive hands-on expertise in software engineering;
- demonstrated extensive hands-on expertise in machine learning technologies, including in the context of federated learning;
- demonstrated hands-on expertise of deploying computational approaches in the context of drug design, drug discovery and development;
- demonstrated hands-on expertise in general project management (ability to consistently set and achieve milestones on time and within budget; managing varying interests of multiple stakeholders) and professional communication (expertise in communication tools and systems for project management purposes), in the context of EU-funded projects.

The short proposal should include a description as to how the applicant consortium intends to make the developed methodologies accessible to the pharmaceutical and other industries after the project ends. To this end, it is suggested to allocate responsibility for ensuring sustainability (including software, licensing, infrastructure options, potential broker services) to a specific consortium partner. While a broker role is acceptable, and could for example be filled by an SME, this role must be compatible with the outlined interpretation of federated and privacy-preserving machine learning (for instance the broker function will not have access to assay data, annotation or the corresponding models).

Suggested architecture of the full proposal

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

In the spirit of the partnership, and to reflect how IMI2 JU call topics are built on identified scientific priorities agreed together with EFPIA beneficiaries/large industrial beneficiaries, these beneficiaries intend to significantly contribute to the programme and project leadership as well as project financial management.

The final architecture of the full proposal will be defined by the participants in compliance with the IMI2 JU rules and with a view to the achievement of the project objectives. The allocation of a leading role within the consortium will be discussed in the course of the drafting of the full proposal to be submitted at stage 2. To facilitate the formation of the final consortium, until the roles are formally appointed through the consortium agreement, the proposed project leader from among EFPIA beneficiaries/large industrial beneficiaries shall facilitate an efficient negotiation of project content and required agreements. All beneficiaries are encouraged to discuss the project architecture and governance and the weighting of responsibilities and priorities therein.

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

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

Work package 1 – Pre-processing of data up to a level of necessary and sufficient standardisation

The goals of this work package will be as follows:

- select methodology for standardised pre-processing of data and implement in scripts, including feature extraction, dimensionality reduction, weighted data integration;
- enable participants to deploy scripts in standardised ways compatible with the architectures proposed for the exercise;
- execute pre-processing of data and make it available (including public data for work package 3).

Industry consortium contribution

Methodology selection, implementation and execution.

Expected applicant consortium contribution

Enable architecture-compatible deployment, scientific advice.

Work package 2 – Industrial IT technical scoping and deployment

The goals of this work package will be as follows:

- joint pharma user requirements;
- independent software audit (in-kind pharma contribution) of the resulting software (from work package 5);
- enable/execute runs on ICT infrastructure under pharma control (these may be cloud services).

Industry consortium contribution

Formulation of user requirements, set-up of audit, enable runs.

Expected applicant consortium contribution

Liaison between pharma-driven work package 2 and consortium driven WP5 (software implementation), to ensure solutions match requirements and can be run on pharma controlled infrastructures.

Work package 3 – Federated machine learning algorithms

The goal of this work package will be as follows:

- development and scientific and software prototyping of the algorithm;
- initial predictive performance estimation (on public data);
- machine-learning security analysis of algorithms (on public data), to enable security evaluation.

Industry consortium contribution

Experts in machine learning applied to the domain of the topic.

Expected applicant consortium contribution

Expertise to carry out the activities listed above.

Work package 4 – Evaluation of privacy and performance balance and of predictive performance of the versions up to implementation in discovery projects

The goals of this work package will be as follows:

- evaluation of balance between performance and privacy preservation (on prototypes);
- evaluation in terms of the aggregated predictive performance metrics (enterprise-ready product) .

Industry consortium contribution

Expertise to carry out the activities listed above.

Expected applicant consortium contribution

Scientific support for activities listed above.

Work package 5 – Software Implementation

The goals of this work package will be as follows:

- balance in WP4 (scientific) and WP2 (data privacy), to be readied to the point that it can be securely deployed on the massive pharma datasets;
- this includes aspects of software engineering, ICT security, knowledge of ICT infrastructure to run on, with respect to software implications (high performance computation enablement, hardware acceleration, ...).

Industry consortium contribution

Industrial experts in ICT, security, machine learners and modelling.

Expected applicant consortium contribution

Expertise to carry out the activities listed above.

Work package 6 – Secure standalone and federated infrastructure

The goal of this work package will be as follows:

- provision of infrastructure that will operate under control of the respective EFPIA data and asset owners during standalone and federated runs (may be cloud services);
- provision of central ICT infrastructure that can connect to the infrastructures under control of the respective EFPIA data and asset owners involved, ensuring security and performance requirements;
- operation support.

Industry consortium contribution

Industrial experts in ICT.

Expected applicant consortium contribution

Selecting, setting up and providing the secure infrastructure for standalone and federated modelling runs to be procured under the action.

Work package 7 – Operations and deployment

The goals of this work package will be as follows:

- establish a detailed software and operating model with pharma organisations;
- monitoring execution of runs upon initiation by pharma.

Industry consortium contribution

Industrial experts in ICT and modelling.

Expected applicant consortium contribution

Main drivers, may include partners involved in sustainability plans.

Work package 8 – Overall project governance, project management, dissemination and sustainability

The goals of this work package will be as follows:

- grant administration;
- strategic, operational, IP and financial management;
- communication (within the consortium and with relevant external collaborators);
- dissemination of scientific results and research data to the scientific community and within the pharma sector;
- detailed sustainability plan to make results accessible beyond the duration of the action.

Industry consortium contribution

Programme leadership with respect to application and valorisation aspects, project and financial management, contribution to communication and dissemination.

Expected applicant consortium contribution

Scientific and technical programme coordination, reporting to the IMI2 JU (supported by the industry-provided project management expertise and support).

Topic 4: Centre of excellence – remote decentralised clinical trials

Topic details

Topic code	IMI2-2018-14-04
Action type	Research and Innovation Action (RIA)
Submission and evaluation process	2 stages

Specific challenges to be addressed

Developing new medicines/health solutions and improving patient health rely on the successful conduct of clinical trials to generate relevant safety and efficacy data. Recruitment and retention of patients are some of the most challenging aspects in clinical trial protocol adherence. The 2017-global CISCRP survey reported the main barriers to patients' participation as 'lack of patients' awareness of clinical trials' (~61%); and the 'geography and the distance to the clinical site' (60%)⁴⁵. This geographical burden on patients, including the duration and number of clinical visits, also drives their decision to participate in a trial. In addition, within patients who consent, an alarming 30% dropout across all clinical trials is observed.⁴⁶ Therefore, by the same token, improving the patients' experience through protocol optimisation to ease the patient burden, whether perceived or real, should improve data quality and increase the probability of success.

TransCelerate⁴⁷ and IMI initiatives have already led to significant achievements in this area. For example, the first European Electronic Health Records data platform⁴⁸, which connects more than 20 European hospitals, has already resulted in reduced recruitment times. More recently, the emergence of digital technology has increased the feasibility of decentralised clinical trials (DCTs), a disruptive approach consisting in setting the trial around the patient rather than a centralised trial site. DCTs conducted to date have allowed the patient to participate in either all or many (depending on the model) study visits remotely, either in their home or through the use of more local medical facilities. Positive results of an acne phase 2 trial that enrolled adolescents with a reduced enrolment time of 50 percent, have recently been communicated.⁴⁹ Additionally, several other trials have been conducted or are starting, such as the VERKKO trial in Europe, which will help to inform the best practices.⁵⁰

Combining the adoption of digital endpoints and telemedicine as applied to trials, the DCT model could improve patient access to trials, increase the participation of more diverse populations, and enhance data collection. In addition, the DCT model can help to fill the gap between clinical development and the real world setting, providing useful real life experience while the patient is followed from home or community care. The improved clinical trial efficiency may accelerate patient access to medical breakthroughs. Digital endpoints and tools will need to be evaluated with the goal to include some of these key enablers of the model while balancing the goal to minimize additional complexities.

Need and opportunity for public-private collaborative research

This action offers a common forum to engage key stakeholders (e.g. patients, healthcare providers (HCPs), regulators, small and medium-sized enterprises (SMEs), pharmaceutical industries) to define the European remote DCT implementation considering its environment (e.g. regulatory and ethics, International Council for

⁴⁵ Center for Information & Study on Research Participation (CISCRP). Perceptions & Insights Study. 2017

⁴⁶ Levitan, B et al. Assessing the Financial Value of Patient Engagement: A Quantitative Approach from CTTI's Patient Groups and Clinical Trial Project. Therapeutic Innovation & Regulatory Science; 2017

⁴⁷ <http://www.transceleratebiopharmainc.com/>

⁴⁸ www.ehr4cr.eu

⁴⁹ <https://www.science37.com/science-37-aobiome-complete-industry-first-virtual-clinical-trial-metasite-decentralized-operating-model> and <https://www.centerwatch.com/news-online/2016/06/22/eclinicalhealth-announces-successful-results-entirely-remote-online-clinical-trial>

⁵⁰ VERKKO trials and eClinicalHealth, e.g. Langel, K. Case Study: Remote Blood Glucose Profiling in Diabetes – Streamlining The Clinical Trial Process For Diabetes Trials. Industrial Pharmacy, Volume 50, Number 1, June 2016, pp. 11-13(3)

Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (ICH),⁵¹ Good Clinical Practices (GCP)⁵², and EU clinical trials regulations⁵³).

Since DCTs could represent a dramatic shift both in the way clinical trials are conducted in the EU, as well as in the EU environment for clinical trials, a multidisciplinary collaborative approach among all stakeholders involved in clinical research and development is essential. While improving clinical trial access is a key goal, this needs to be balanced with the top priority to maintain the safety and welfare of the patient. The role of the investigator will need to be explored to resolve how they can support the decentralized model while still maintaining the necessary oversight for the patient's medical care. Federating multiple academics, clinical centres, patients' associations, regulatory bodies, SMEs, pharmaceutical and medical technology industries will ensure the concrete positioning of remote DCTs within the clinical 'journey' including best practices, recommendations for the fully remote DCT approach and the hybrid model. This approach should seek to build trust between all stakeholders involved in clinical trials and support efficiently the process for updating ICH guidelines.

To efficiently implement the concept regarding e.g. quality process, data relevance, confidentiality, integrity, and risk assessment, a broad number of stakeholders from both the public and private sectors are needed.

- The pharmaceutical industry brings experience on running remote DCTs in the US and in the EU. The project will build upon this experience to set the scene for coordinating a pan-EU remote DCT pilot.
- Clinical centres and health care providers are necessary to provide feedback on existing and future DCT initiatives and to contribute to the definition of the best practices on running full or partly remote DCTs in the EU environment. Leading clinical centres are also needed to coordinate the pan-EU remote DCT pilot and engage other centres across the EU in a different setting than the traditional one (where each site is a principal investigator).
- Regulators and stakeholders involved in the revision of GCP and clinical guidelines are pivotal in the approach both at national and EU level to ensure the appropriate positioning of remote DCTs as well as an efficient alignment with the ICH guideline update. Obtaining regulators feedback and position on the acceptance of DCT-generated data is also a key goal.
- SMEs are necessary to contribute at different levels, such as the evaluation of the DCT process, training tools for healthcare professionals and other relevant stakeholders, and telemedicine expertise.
- Patients and patient associations are also highly important in the definition and deployment of a patient-centric approach.
- Other organisation profiles, including (but not limited to) those with telemedicine expertise and medical technology expertise, are required to implement efficiently the remote decentralised process across the EU.
- Technology enablers and sites/site networks are critical stakeholders in defining how to reduce the burden on patients and thus increase patients' access to clinical trials.

To this end, the IMI2 JU is the most efficient programme in the EU to federate all stakeholders on a well-balanced approach, building trust and defining recommendations for conducting fully remote DCTs across the EU.

Scope

The action will focus on disaggregating the current model of running clinical trials, defining building blocks and mapping new technologies (e.g. telemedicine, mobile health...) to support the new DCT model. The objective is to demonstrate the feasibility of running remote DCTs in Europe. This will increase access of patients to clinical research, enriching clinical trial data from a more diverse and representative patient population and improve patient experience during the trials, with a higher speed of recruitment and better retention.

This funded action will rely on learning from historical and ongoing case studies, conducted by the members of the winning consortium, to build on clear recommendations and define guidance for conducting remote

⁵¹ <http://www.ich.org/home.html>

⁵² https://www.ich.org/fileadmin/Public_Web_Site/ICH_Products/Guidelines/Efficacy/E6/E6_R1_Guideline.pdf

⁵³ 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.

DCTs in Europe. It will assess various options including hybrid models (combining DCTs with the traditional approach), as well as specific needs according to the disease / therapeutic area (e.g. rare diseases, HIV⁵⁴). The recommendations will consider the relevance of the model and supportive technologies for gaining approval from ethics committees, and authorities responsible for approving CTs and for securing data quality, data integrity and ultimately data acceptability by regulatory agencies.

The impact of remote DCTs on the relationship between patients and their treating physicians, according to the model (fully remote vs. hybrid) will also be investigated. The funded action will also revisit the investigating site definition, and principal investigator responsibilities according to ICH/GCP. Compliance with and respect of the General Data Protection Regulation (EU) 2016/679⁵⁵ and Clinical Trial Regulation (EU) 536/2014⁵⁶ (and/or Directive 2001/20/EC⁵⁷ and its national implementation laws) and any updates, and the enforcement of data security will also be addressed.

The proposed work is based on a 3-step approach and a transversal objective for ensuring the most reliable organisation at pan-EU level for conducting fully remote DCTs.

- Step 1: Define the best practices for the conduct of remote DCTs using individual partner case studies (US and EU) and identify the positioning of such trials among clinical development.
- Step 2: Analyse the EU clinical trial environment and upgrade accordingly the best practices for remote DCTs at EU level using the outcomes of the individual partner case studies analysed in step 1. This should result in preliminary guidance to be used for the setting-up of the pan-EU pilot.
- Step 3: Design and run a pan-EU pilot remote DCT and define the positioning of fully remote or hybrid model regarding clinical development. Although the project consortium will need to decide on a specific study and disease, the pilot will focus on the technology and clinical organisation. The particular indication(s) and investigational medicinal product(s) for piloting the remote DCT will be selected as part of the project activities. Any pilot will need to be fully transparent with all processes and data, including challenges, openly shared.
- Transversal objective: Contribute to the update of ICH guidelines on remote DCTs and provide recommendations with supporting tools for implementing fully remote DCTs in the EU.

Expected key deliverables

- Definition of best practices using case studies (historical and ongoing) from industries and academics (indicatively by month 12):
 - define and leverage set of criteria to analyse case studies;
 - define the operational feasibility;
 - assess data relevance, integrity and acceptability by regulators;
 - analyse and report on either the hybrid or fully decentralised model to facilitate the remote DCT approach in EU.
- Technology scan for remote DCTs in an end-to-end journey assessing e.g. quality and data integrity, security, connectivity, communication interface, stakeholders' feedbacks such as patients, principal investigators, regulators, sponsors (indicatively by month 24). The scan on 'remote DCT technologies' will include an assessment of a broad technology range (available or with a validated proof-of-concept) in order to enable seamless communication, data monitoring and collection from distant locations. The 'technology package' is composed of:

⁵⁴ Stephenson, R., Freeland, R., Sullivan, S. P., Riley, E., Johnson, B. A., Mitchell, J., McFarland, D. and Sullivan, P. S. (2017). Home-Based HIV Testing and Counseling for Male Couples (Project Nexus): A Protocol for a Randomized Controlled Trial. *JMIR Research Protocols*, 6(5), e101. <http://doi.org/10.2196/resprot.7341>

⁵⁵ 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

⁵⁶ 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.

⁵⁷ [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.

- a connected central platform enabling the management of all information collected and generated in a remote DCT, e.g. central management of information and data, communication with the enrolled patients and their ecosystem (including webpages or generating personalised text message reminders/alerts). It should enable local connectivity with various sets of connected devices or wearables and collection of data on the fly;
- a 'mobile technology/app with/without wearables' designed for patient enrolment and to ensure communication between patients and their ecosystem: physicians, nurses, medical laboratory staff and investigators. This mobile technology will be connected to the central platform (defined above). All data generated should be eligible for collection by this platform and open to real time data integration with more traditional existing safety and efficacy calculation systems;
- related services: recruitment/retention strategy, recruitment networks/patient group, recruitment advertising, project management, investigator management, records retention.

All the technologies stated above should comply with GCP (Good Clinical Practices), GDPR and CTR, e-Signature process and security standards on health data.

- External review of the technology scan for remote DCT and approval of the final 'technology package' to be tailored and used for running the pan-EU pilot remote DCT.
- Review and analysis of the EU clinical trial ecosystem, and anticipated changes for the pan-EU 'remote decentralised clinical trial centre' (indicatively by mid-term):
 - preliminary guidance for the launch of the pan-EU DCT including hybrid model and to support ICH guidelines;
 - changes/adaptations to the EU environment for clinical trials;
 - definition of metrics to measure success including approved technology specificities.
- Pan-EU pilot study designed and launched from a 'central' access (by a referenced public centre) using a remote DCT approach.
- Final recommendations on the fully remote DCT and the hybrid model.
- Final set of tools (training materials, contract templates, technology requirements...) to be used for remote DCTs in Europe.

Expected impact

Combined with the adoption of digital endpoints, the funded action should have the following **main expected impacts**:

- increase flexibility of patient follow-up during clinical trials, reducing the burden both on patients and hospitals;
- increase the frequency and quality of data collection;
- improve patient recruitment and retention in trials;
- accelerate clinical research and the access by the patients to more breakthrough innovative therapies;
- support directly the update of the ICH guidelines all along the process by generating evidence;
- reorganise the patient journey and the clinical environment;
- redefine the clinical trial framework in compliance with the EU regulations.²⁰⁻²²

Other expected impacts include:

- increase the participation of more diverse populations in clinical trials and reduce drop out;
- collaborating with specialty patient networks to decrease patient burden;
- support patients in managing better their disease(s) and their treatment(s) and increasing their knowledge⁵⁸;

⁵⁸ Example of a Danish research monitoring at home patient suffering from diabetic foot ulcers; though non statistically significant, patients who used the sensors had healed wounds and less pain after 6 months, and did not need to travel to outpatient clinic. The

- increase digital literacy among healthcare providers, facilitating later development of telehealth;
- provide evidence for supporting the European policy on telehealth and telemedicine applied to remote patient monitoring in Europe, beyond the scope of clinical trials.

Applicants should indicate how their proposal will impact the competitiveness and industrial leadership of Europe by, for example engaging suitable small and medium-sized enterprises (SMEs).

Potential synergies with existing consortia

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

The synergies should be explored with:

- consortia utilising electronic health records for recruiting patients;
- consortia developing informed consent forms to be used across the EU;
- consortia involved in digital monitoring of patients, including endpoints, outcomes and quality of life;
- consortia involved in disease-specific research at international and European level (to be determined based on indication(s) selected);
- [Transcelerate](#)⁵⁹;
- [CTTI](#)⁶⁰;
- companies offering technology solutions that would support the implementation of the platform for running the pan-EU pilot remote DCT;
- consortia of European clinical trial centres such as the European Clinical Trial Infrastructure Network ([ECRIN](#))⁶¹;
- relevant biotechnology consortia;
- relevant EFPIA groups (e.g. Clinical Development Expert Group...);
- national/local ethics committees or IRBs;
- consortia funded under [ECSEL JU](#)⁶² developing the technology required in the action.

Industry consortium

The industry consortium is composed of the following EFPIA partners:

- Sanofi (lead)
- Allergan
- AstraZeneca
- Bayer
- Boehringer Ingelheim
- Covance
- IQVIA
- Janssen

majority of patients using this new type of care gained more knowledge about the treatment of their wounds, were very satisfied with their home care and satisfied with the collaboration between their care providers (2015 eHealth in the WHO European region report)

⁵⁹ <http://www.transceleratebiopharmainc.com/>

⁶⁰ <https://www.ctti-clinicaltrials.org/>

⁶¹ <http://www.ecriin.org/>

⁶² <http://www.ecsel-ju.eu/>

- Medtronics
- Nokia
- Novartis
- Pfizer
- Takeda
- Teva
- UCB

In addition, the industry consortium includes JDRF as an IMI2 JU Associated Partner.

The industry partners will bring the following expertise:

- clinical operations
- clinical statistics
- supply chain / IP distribution
- telemedicine, medical technology and digital health
- telecom-, cloud-platform- and IoT (Internet of Things) architecture and deployment
- IoT security and end-point (connected device) security
- connectivity- and device management
- quality control and quality assessment
- legal matters for DCT (patients' rights, data collection, data transfer, data analysis)
- regulatory matters (including GDPR, CTR)
- public affairs
- patient advocacy
- patient engagement.

In addition, the industry partners will bring at least 5 remote DCT case studies (either as hybrid or fully remote DCTs). The organisational elements of these DCTs in terms of activity flows and quality criteria will be analysed in the funded action to establish best practices for running remote DCTs in Europe.

Indicative duration of the action

The indicative duration of the action is 60 months.

Following the delivery of the technology package, a project review will be held to review the proposed technology package (see expected deliverables) and ensure the action is on track to deliver the expected impacts within the five year period.

Future project expansion

Potential applicants must be aware that the IMI2 JU may, if exceptionally needed, publish at a later stage another Call for proposals restricted to the consortium already selected under this topic, in order to enhance their results and achievements by extending their duration and funding. The consortium will be entitled to open to other beneficiaries as they see fit. The decision for this will be based on progress of the action and decisions made in the sustainability work stream of the action. This process could be envisioned to build upon this running pan-EU pilot remote DCT with the following objectives (not all inclusive):

- (i) add complementary modules that required public-private collaborations such as block chain approach,
- (ii) extend the country representativeness in the pan-EU pilot, or
- (iii) even deploy the pan-EU pilot for other therapeutic areas not selected in the initial action.

These objectives are developed to generate additional evidence of the reliability of the remote DCT approach that could be required for extending the acceptance at EU level of remote DCTs.

Indicative budget

The indicative in-kind contribution from EFPIA partners and the IMI2 JU Associated Partner is EUR 21 600 360. This contribution comprises an indicative EFPIA in-kind contribution of EUR 21 512 860 and an indicative IMI2 JU Associated Partner contribution of EUR 87 500.

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.

The financial contribution from IMI2 JU is a maximum of EUR 19 037 000.

Given the rapid speed of technological innovation in the telemedicine field, it is likely that technology available at project start will be outdated by the time the pilot remote DCT is planned to start (indicatively at month 42). Therefore, in order to ensure access to state-of-the-art technologies for the launch of the pilot DCT at month 42, the consortium may consider enrolling additional technology participants to fulfil the tasks identified in the technology package delivered at month 24. This technology package and proposed additional technology participants should be selected through an open call⁶³ by the funded consortium and approved by the independent review panel during the project review at month 26. To allow for these state-of-the-art technologies to be incorporated following this review, 30 % of the overall IMI2 JU funding should be reserved for such tasks and expertise.

Applicant consortium

The applicant consortium is expected to address all the topic objectives and make key contributions to the defined deliverables in synergy with the industry consortium.

The consortium shall include all relevant stakeholders involved in the clinical trial environment including SMEs to build the remote DCT Centre of Excellence:

- regulatory agencies to contribute to the definition of guidance for remote DCTs and to ensure the alignment with the updating of the ICH guidelines;
- standards organisations on good clinical practices to implement the guidance in an ethical and legal manner;
- SMEs with past and present experience on remote DCTs and deep expertise in Good Clinical Practice (GCP) using technology for recruiting and monitoring patients;
- telemedicine, medical technology companies to contribute to the new integrated mobile environment of patients including expertise in data validation, approved medical devices into clinical trials for data capture and continuous monitoring and their associated devices;
- patient associations and patient groups to ensure the co-design approach of patients in the remote DCT design and execution, as members or potentially as advisors to work on guidance and the patient-specific challenges;
- academics/clinical trial centres to co-design and implement the remote DCT, managing already trial programmes that could be adapted to DCT approach;
- academics involved in medical devices to contribute particularly in the technology scan of the remote DCT in an end-to-end journey and the subsequent deployment of the pan-EU pilot;
- health insurance organisations to support the telemedicine at patients' homes.

When planning the set-up of the pan-EU remote DCT pilot, the applicant consortium should consider more than a single EU country to ensure the wider acceptance of this model.

⁶³ The conditions and criteria for the open call shall be established in the full proposal

Suggested architecture of the full proposal

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

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

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

The consortium is expected to have a strategy on the translation of the relevant project outputs into regulatory, clinical and healthcare practice. A plan for interactions with regulatory agencies/health technology assessment bodies with relevant milestones and resources allocated should be proposed to ensure the deployment and acceptance of the remote DCT concept at a pan-EU level for clinical development.

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

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

All work package activities described below **should comply** with all EU regulations and more particularly with GDPR²⁰ and CTA Regulations²¹.

Work package 1 – Collecting and analysing study information on previous and ongoing experiences of remote DCTs (benefits, process, patient’s surveys, process data) and compilation of best practices / recommendations (liaise with WP3)

The goals of this work package will be as follows:

- defining criteria for analysing the DCTs model and processes, including the set-up, recruitment, enrolment, informed consent process, and data collection, data quality and relevance;
- analysing process information from ‘individual partner studies’ (either US or EU if any) including challenges confronted and solutions, e.g. Science37 model including provisions from GDPR and CTR²⁰⁻²² context;
- defining good practices and detailed SWOT on setting up ‘remote DCTs’ using individual partner experience in regard also to GDPR^{Error! Bookmark not defined.} and CTR⁵³ context;
- upgrading the ‘individual partner studies’ using the good practices developed in this funded action’;
- guidelines to set up the pan-EU pilot remote DCT including compliance with GDPR and CTR²⁰⁻²²;
- analysing protocol suitability for remote DCT including how to establish criteria for selecting trials for the remote DCT model.

Expected key deliverables

The expected key deliverables will be as follows:

- definition of criteria to analyse each case study (either hybrid/fully decentralised) and report to build up the remote DCT approach in the EU;

- review of previous case studies (remote decentralised clinical trials/home monitoring) available from industries and investigation sites (public/private) to date to define and share challenges and solutions in remote DCT/home monitoring for application in an EU setting;
- definition of first best practices using individual partner case studies;
- definition of first recommendations for remote DCTs (to be implemented in the pan-EU pilot remote DCT – cf. work package 2);
- criteria defined for selection of appropriate trials.

Industry contribution

Clinical operational experts; statisticians; IT experts (telemedicine activities and digital health); quality control; pharmaceutical research scientific domain experts; legal experts; patient engagement experts. Experience from previous or on-going remote DCT case studies to build up the best practices (mainly from US) and upscaling the best practices into case studies for setting-up the EU DCT model; data validation; expertise on using approved medical devices in clinical trials for data capture (mainly for pharmaceutical sponsors and mainly continuous monitors and their associated devices).

Expected applicant consortium contribution

Principal investigators; hospitals; clinicians; experts in the conduct of multisite clinical trials as a minimum, preferably in remote DCT trials including home monitoring; clinical statisticians; IT experts in the development of platforms for patients; supply chain / IP distribution; legal experts; previous or ongoing case studies to be used to build up the best practices regarding EU regulations²⁰⁻²² and any subsequent updates.

Work package 2 – Pan-EU ‘remote DCTs’ pilot (liaise with WP3)

The goals of this work package will be as follows:

- design a pan-EU pilot using guidelines developed in WP1, potentially in a way that allows for comparison with a ‘traditional’ study – for example run part of the same study in a remote DCT model, while the rest is traditional, or find a previously conducted study / studies that allows for some comparison – and integrate & tailor the ‘technology package’ approved by the external review panel for the pan-EU pilot remote DCT;
- set-up and run the pan-EU pilot remote DCT;
- analysing process information from the pan-EU pilot to define the scientific and operational quality of the pilot and proposed optimisations;
- refining key performance indicators (KPIs) to qualify and quantify the flow of activities in the pan-EU pilot, e.g. (but not limited to) recruitment rate, retention rate, patient burden/satisfaction, data quality, confidentiality and integrity compared directly during a trial (half traditional and half DCT) or retrospectively through benchmark data.

Expected key deliverables

The expected key deliverables will be as follows:

- setting-up of a pan-EU pilot study or multisite study. Pilots should be private-public collaborations to the extent possible, and organised by a referenced public centre;
- final evaluation of the pan-EU pilot regarding the KPI defined including conditions of DCT use compared to traditional trial and acceptability of the model at pan-EU level.

Industry contribution

Clinical operational experts; statisticians; IT experts (telemedicine activities and digital health); quality control; pharmaceutical research scientific domain experts; supply chain / IP distribution; legal experts; patient engagement experts; investigate and design new technologies/logistics for distant monitoring in DCT; medical technology experts; upgrading the best practices on remote DCT in their respective trials; regulatory experts.

Expected applicant consortium contribution

Principal investigators; hospitals; clinicians; experts to set up and run the pan-EU remote DCT pilot including home monitoring (if feasible); IT experts in the development of platforms for remote DCTs; regulators in agencies; patient associations; medical technology experts.

Work package 3 – Technologies – identification of barriers and enablers and data management

The goals of this work package will be as follows:

- data quality and management (WP1 and 2) - activity flows;
- assessment of a wide range of 'technology packages' (as defined in the deliverable section) either as available or as a validated proof-of-concept including all supporting services that are likely going to be required ('virtual site' with phone / email / chat support, logistics, home or online nurses...);
- recommendations on technologies evaluated and data quality/data relevance including evaluation of some technologies available as well as in a validated proof-of-concept;
- propose refinement of work package 3 activities after the selection of the 'technology package';
- tailor the technology package to be used for the pan-EU pilot remote DCT.

Expected key deliverables

The expected key deliverables will be as follows:

- technology scan for remote DCT in an end-to-end journey assessing e.g. quality and data integrity, security, connectivity, communication interface, stakeholders' feedbacks such as patients, principal investigators, regulators, sponsors. The scan on 'remote DCT technologies' will include an assessment of a broad technology range (available or with a validated proof-of-concept) in order to enable seamless communication, data monitoring and collection from distant locations (described in the specific deliverable section);
- tailored 'technology package' for running the pan-EU pilot to be deployed in the pan-EU pilot remote DCT.

Industry contribution

Clinical operational experts; statistical experts (telemedicine activities and digital health); legal experts including data privacy experts; experts in clinical outcomes; patient engagement experts; experts in data flows and app developments for home monitoring of patients; expertise in using approved medical devices in clinical trials for data capture, continuous monitors and associated devices.

Expected applicant consortium contribution

Principal investigators; hospitals; clinicians; IT experts on digital health; patient engagement experts; experts in data flows and app developments for home monitoring of patients; platform developers and services related to technologies used for remote DCTs; regulatory experts; regulators in agencies; expertise in approved medical devices into clinical trials for data capture; continuous monitors and associated devices.

Work package 4 – Ethics, data privacy, legal, GCP, regulatory issues and recommendations

The goals of this work package will be as follows:

- continuous assessment of EU environment and the EU regulation (including digital policy, GDPR, CTR...) to be implemented for remote DCT approach;
- ethics organisation of remote DCTs in EU;
- defining the legal, GCP and data management for 'remote DCT' approach including data quality and regulatory acceptability of DCT approach;
- upgrading using regulation changes;
- stakeholders' working group to align the strategy of remote DCTs with ethics, data privacy.

Expected key deliverables

The expected key deliverables will be as follows:

- SWOT analysis of the barriers and enablers for the implementation of remote DCTs in EU for ethics, data privacy, regulation...;
- best practices on remote DCTs (first and final version) in EU and US;

- final recommendations on remote DCTs in the EU including intermediary model (hybrid studies).

Industry contribution

Legal and data privacy experts; regulatory experts on the use of digital tools in clinical trials; GCP experts.

Expected applicant consortium contribution

Regulatory experts (including from agencies); ethics experts; GCP experts; legal and data privacy experts.

Work package 5 – Communication, dissemination and stakeholders’ engagement in changing the paradigm of remote DCTs

The goals of this work package will be as follows:

- interviews of stakeholders on the EU view and EU experience in remote DCTs (patients, regulatory agencies, ethics committees, principal investigators, study coordinators, hospitals, pharmaceutical companies...) to reassess the barriers and enablers;
- mapping of paradigm change on patients and HCPs between current approach and induced changes in remote DCTs;
- assess and tailor the related services of the ‘technology package’ for the communication activities;
- check-list on best practices for setting-up a remote DCT in EU (public deliverable);
- training kits for deploying pan-EU ‘remote DCTs’ for principal investigators, HCPs, patients, inspectors, pharmaceutical companies, clinical research organisations;
- company providers/developers of technologies to be deployed for remote DCTs.

Expected key deliverables

The expected key deliverables will be as follows:

- mapping of paradigm changes in the relationships between HCPs and patients;
- report on changing stakeholders’ roles and responsibilities and proposals from stakeholders to overcome any challenges;
- set of tools for remote DCT including training materials for stakeholders (e.g. principal investigators, patients, regulatory representatives and inspectors...), and contract templates for ‘remote DCT’;

Industry contribution

Representatives for stakeholder engagement at regulatory, HCP and patient engagement and data privacy levels; communication experts; clinical outcomes experts.

Expected applicant consortium contribution

Experts in stakeholder engagement and communication for the relevant fields of this future action; patients organisations; IT and communication tools to support paradigm changes in remote DCTs; training to engage relevant stakeholders.

Work package 6 – Project management

This work package will establish effective governance and internal communication procedures to allow for the flow of information within the project. It will also fulfil the administrative tasks associated with management of this project. It will also take into account the particular conditions relative to the ‘technology package’ and inclusion of new technology partners.

Industry contribution

Project management expertise.

Expected applicant consortium contribution

Project management expertise.

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 14 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-IMI2-2018-14-two-stage
Type of actions	Research and Innovation Action (RIA)
Publication Date	15 March 2018
Stage 1 Submission start date	15 March 2018
Stage 1 Submission deadline	14 June 2018 (17:00:00 Brussels time)
Stage 2 Submission deadline	11 December 2018 (17:00:00 Brussels time)
Indicative Budget	
From EFPIA companies and IMI2 JU Associated Partners	EUR 84 920 360
From the IMI2 JU	EUR 82 357 000

Call Topics

<p>IMI2-2018-14-01</p> <p>Targeted immune intervention for the management of non-response and relapse</p>	<p>The indicative contribution from EFPIA companies is EUR 40 320 000</p> <p>The financial contribution from IMI2 JU for each subtopic is :</p> <p>Subtopic 1 (Profiling & Informatics): a maximum of EUR 16 128 000.</p> <p>Subtopic 2 (DC1 - SLE, RA, and MS): a maximum of EUR 12 096 000.</p> <p>Subtopic 3 (DC2 - UC and CD): a maximum of EUR 8 064 000.</p> <p>Subtopic 4 (DC3 – Asthma and COPD): a maximum of EUR 4 032 000.</p>	<p>Research and Innovation Action (RIA)</p> <p>Two-stage submission and evaluation process.</p> <p>At stage 1, applicant consortia to this topic will submit short proposals to address one of the four subtopics. Applicants can submit proposals to any of the subtopics. If applicant consortia wish to submit for more than one subtopic, separate short proposals should be submitted. Applicants are not obliged to apply for all.</p> <p>For each subtopic, only the applicant consortium whose proposal is ranked first at the first stage is invited for the second stage. At stage 2, the first ranked consortium from each subtopic shall merge into a single consortium with the industry consortium.</p>
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<p>IMI2-2018-14-02 Non-invasive clinical molecular imaging of immune cells</p>	<p>The indicative contribution from EFPIA companies is EUR 15 000 000</p> <p>The financial contribution from IMI2 JU is a maximum of EUR 15 000 000</p>	<p>Research and Innovation Action (RIA)</p> <p>Two-stage submission and evaluation process.</p> <p>Only the applicant consortium whose proposal is ranked first at the first stage is invited for the second stage.</p>
<p>IMI2-2018-14-03 Development of a platform for federated and privacy-preserving machine learning in support of drug discovery</p>	<p>The indicative contribution from EFPIA companies is EUR 8 000 000</p> <p>The financial contribution from IMI2 JU is a maximum of EUR 8 000 000</p>	<p>Research and Innovation Action (RIA)</p> <p>Two-stage submission and evaluation process.</p> <p>Only the applicant consortium whose proposal is ranked first at the first stage is invited for the second stage.</p>
<p>IMI2-2018-14-04 Centre Of Excellence – decentralised clinical trials</p>	<p>The indicative contribution from EFPIA companies is EUR 21 512 860.</p> <p>The indicative IMI2 JU Associated Partners contribution is EUR 87 500</p> <p>The financial contribution from IMI2 JU is a maximum of EUR 19 037 000.</p>	<p>Research and Innovation Action (RIA)</p> <p>Two-stage submission and evaluation process.</p> <p>Only the applicant consortium whose proposal is ranked first at the first stage is invited for the second stage.</p>

Annex II - IMI2 Call 15 topics text

Introduction

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

The Innovative Medicines Initiative 2 Joint Undertaking (IMI2 JU) has been created⁶⁴ 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 World⁶⁵.

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 companies⁶⁶, 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)⁶⁷ is the main reference for the implementation of research priorities for IMI2 JU. The scientific priorities for 2018 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.

⁶⁴ 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.

⁶⁵ http://www.who.int/medicines/areas/priority_medicines/en/

⁶⁶ Under IMI2 JU, mid-sized companies having an annual turnover of EUR 500 million or less not being affiliated entities of companies with an annual turnover of more than 500 million; the definition of 'affiliated entities' within the meaning of Article 2(1)(2) of Regulation (EU) No 1290/2013 applies mutatis mutandis. Where established in an EU Member State or an associated country, are eligible for funding.

⁶⁷ 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) 2016/679⁶⁸ and Clinical Trial Regulation (EU) 536/2014⁶⁹ (and/or Directive 2001/20/EC⁷⁰) and any relevant legislation⁷¹.

Before submitting a proposal, applicant consortia should familiarise themselves with all Call documents such as the IMI2 JU Manual for submission, evaluation and grant award⁷², 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).

⁶⁸ 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.

⁶⁹ 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.

⁷⁰ 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.

⁷¹ 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.

⁷² http://www.imi.europa.eu/sites/default/files/uploads/documents/apply-for-funding/call-documents/imi2/IMI2_ManualForSubmission_v1.6_October2017.pdf

Topic 1: Integrated research platforms enabling patient-centric drug development

Topic details

Topic code	IMI2-2018-15-01
Action type	Research and Innovation Action (RIA)
Submission and evaluation process	2 stages

Specific challenges to be addressed

Never before has there been more hope for patients, given the spectacular advancement in fundamental and applied biomedical research. Translation of these scientific revelations into useful treatments, however, remains disappointingly ineffective, inefficient, expensive and slow. Despite good progress in many areas of healthcare, it seems that clinical development rather than discovery research is the limiting factor for innovative new products and treatment options to reach patients. Many patients with severe diseases still suffer as medical needs are not being met, and diagnosis and treatments are difficult, costly and insufficiently tailored to individuals. This is especially true for a number of priority diseases that this topic focuses on.

It is understood that the root causes of this include (i) siloed and competitive development process focussed on single compounds with transient clinical trial infrastructures, (ii) insufficient collaboration among industry and between industry, not-for-profit product developers and academia, (iii) limited patient-centric alignment of stakeholders, and, (iv) in general, the limited focus on individual patient-tailored treatments.

As a result of these, there is a clear shortage of (i) investigators & investigational sites for phase 2-3 clinical trials, (ii) patients for enrolment in such trials, (iii) sharing of insights and use of real-world data, and (iv) investigations of combination treatments, in particular from different sponsors.

This integrated research platform (IRP) topic aims to address these issues and bring together a broad consortium of private and public stakeholders to create, in a collaborative rather than competitive manner, a reusable and modular approach for the design and execution of patient-centric platform trials. Such platform trials create synergy from sharing inferences across all treatment arms, including common controls. They allow for a higher level of data quality and comparability across drugs; and have the potential of allocating each patient to a treatment or combination of treatments best fit for that patient, given the data [1] [2].

There are successful examples of ongoing platform trials in oncology and neuropsychiatric indications, e.g. the I-SPY2 [3], EPAD [4], and GBM AGILE trials [5] [6]. These trials were however created in isolation, without common scientific, operational and legal frameworks, and have not been codified in any reusable methodology but certainly offer invaluable learnings for standardising best practices for platform trials.

Need and opportunity for public-private collaborative research

To transform the current siloed approach to clinical trials into a collaborative IRP-based paradigm, a lasting culture shift is required throughout the entire ecosystem of stakeholders. Individual stakeholders alone can neither induce nor sustain such a culture shift; all stakeholders involved in the invention, development and use of medical innovations must be involved and contribute to the design and implementation of IRPs.

IMI2 JU provides a transparent platform for such multi-stakeholder collaborations, to spark the culture shift, and ensure that all provide their indispensable contributions.

- *Patient groups* contribute their unique insight in patient needs, to inform the important attributes that new interventions should have and the definition of relevant trial endpoints. Their input is critical to ensure feasibility of studies, to define processes for sharing privacy-sensitive data, and to facilitate building of longitudinal natural history studies and trial readiness cohorts.
- *Healthcare providers, investigators and hospitals* contribute disease and healthcare (delivery) expertise, expertise in ethics (ethics committees) and contribute access (respecting informed consent and privacy processes) to information contained in electronic health records (EHRs). They also have a pivotal role in enabling the clinical network, accessing and engaging patients in IRPs and in the implementation of platform trials.
- *Academic research groups* contribute to the quantitative design and statistical methodology, the development of biomarkers to characterise disease and predict outcome, and to technological innovations and data interoperability needed for EHRs networks and trial assessments.
- *Commercial and not-for-profit pharmaceutical developers and adjacent industries* bring deep expertise in drug development and trial design, and contribute to processes, systems, capacity and quality systems for trial execution and data management/analysis, including patient-level data and other real world data (RWD). Importantly, they are essential for making available (information on) their innovative investigational treatments to validate the IRP approach, within and beyond this action.
- *Health authorities (HAs; including regulatory agencies for pharmaceuticals), health technology assessment (HTA) bodies and payer organisations* provide their broad perspectives on diseases, interventions and societal value in the design of IRPs, and ensure that the data generated can inform down-stream development of interventions and regulatory decision-making.
- *Small and medium-sized enterprises (SMEs)* can contribute their specialised expertise and capabilities to complement expertise contributed by academia and industry in areas such as statistical modelling & simulation, technology for processing and querying patient-level databases and registries, and legal and intellectual property (IP).

Collaboration of public and private partners is essential to develop common standards, create efficiencies, and build sustainable infrastructure to handle large platform trials. Collectively all stakeholders will acquire invaluable learnings and experience that will be reused in further optimising and accelerating the development of innovative new medicines.

Scope and objectives

The action will transform experimental clinical development concepts into a reusable and endorsed methodology that is broadly accepted for application in new drug development. It will create best practices, tools and guidelines for establishing multi-company platform trials by leveraging, extending and improving concepts from previous pioneering multi-company platform trials to new disease areas.

The proposal is divided into (i) a set of **common foundational elements** applicable to all disease areas, (ii) **clinical networks and networks of patient-level data** and (iii) **disease-specific integrated research platforms** in several disease areas. Figure 1 depicts a schematic drawing of the scope of the proposal. It also includes the subsequent execution of platform trials; however, this is out of scope in this Call topic.

The disease areas major depressive disorder (MDD), tuberculosis (TB), non-alcoholic steatohepatitis (NASH) and neurofibromatosis (NF) were selected (i) to be of high unmet medical need, (ii) to represent an expanded range of diverse diseases areas, (iii) to include a model case for a disease most prevalent in the developing world and (iv) to include a model case for rare diseases. Together with prior experience in oncology and neuropsychiatry these will serve to inform the development, testing and further refine the common foundational elements, allowing future broad implementation across diverse disease areas.

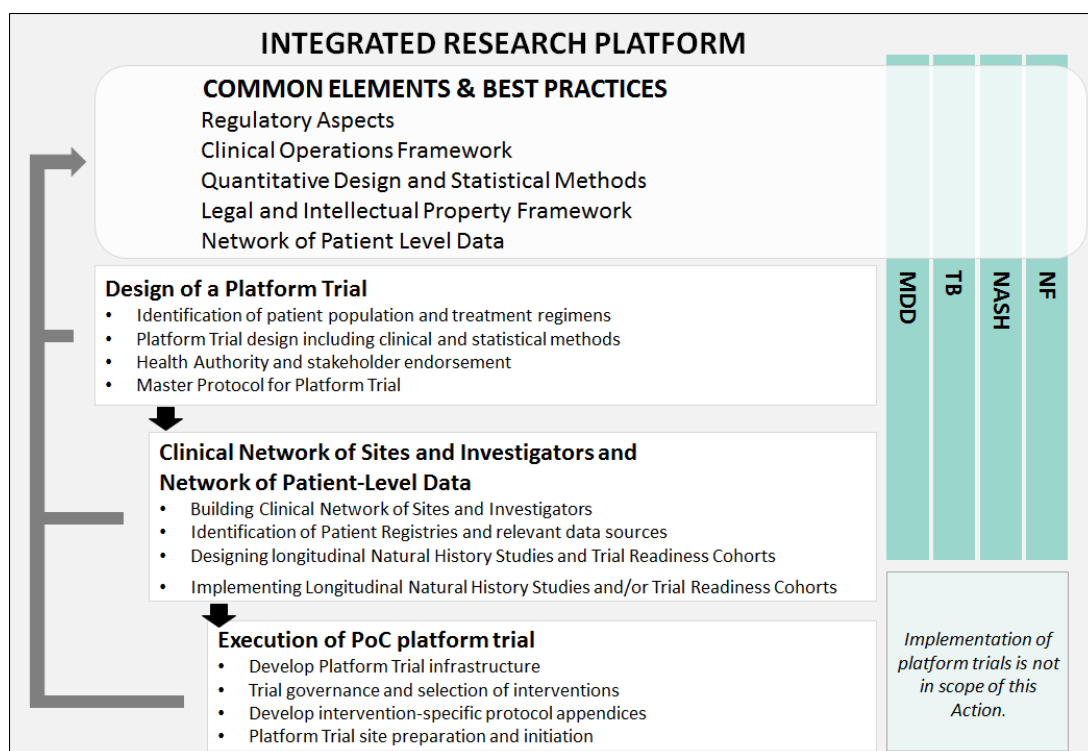


Figure 1 Schematic overview of the IRP project.

1. Common foundational elements

Common foundational elements will be established to address key elements applicable to IRPs in all disease areas. Multi-stakeholder input will be solicited and integrated into aligned and endorsed best practices, tools, templates and guidances, and be shared with the scientific community and society, for re-use in future IRPs.

Four (4) domains are planned as focus areas:

a) Regulatory aspects

Support from, and alignment with HAs is essential to achieve progress in the conduct of IRPs and their platform trials. Dedicated focus will be given to regulatory innovation needed to achieve the intended transformation of the drug development paradigm. Review and gap analysis of current and new clinical trial legislation will be undertaken to understand how IRPs and their platform trials fit within the legislative framework and ensure that there are no legislative barriers to obtain regulatory and ethics approval of platform trials. The relevance of all work in this action to healthcare policies, including pricing and reimbursement, will be considered and to the extent possible ensured.

As drug development is global in nature, IRPs and platform trials are likely to span multiple regions. Therefore, the scope of this work includes other territories beyond the EU, including the USA, and working closely with the European Medicines Agency (EMA), EU national agencies and the U.S Food and Drug Administration and other health authorities is important to develop clear guidance.

b) Clinical operations framework

Documented and generally available best practices will enable efficient setup and execution of IRPs and their platform trials, and ensure data quality and compliance with guidelines and regulations. To achieve reusability, alignment with HAs and ethics committees will be critical.

Areas to address include, but are not limited to:

- patient engagement, informed consent process, privacy and data protection;
- ethical considerations, ethics submission and review process;
- definition of roles, responsibilities, and accountabilities for execution;
- definition of trial sponsor(s) and responsibilities for oversight and compliance;
- treatment allocation and randomisation;
- clinical supplies processes.

c) Quantitative design and statistical methods

At the core of each IRP is a platform trial to test multiple interventions, or combinations thereof, in a shared infrastructure and control group. The actual execution of a platform trial is out of scope of this project. Experience and best practices from prior platform studies across indications will be analysed and structured into template master protocols, addressing design elements common to all interventions, and intervention-specific appendices (ISAs) that address elements to allow inclusion of a specific intervention in the trial.

Input from HAs will be incorporated into the master protocol. Innovative methodologies and tools for data analysis will be refined and expanded for the design and analysis of adaptive clinical trials. They will incorporate Bayesian statistical approaches for selecting treatments arms, addressing placebo effect, dropping treatment arms and introducing new treatment arms, including drug combinations [7]. Biomarkers will be selected to effectively divide the patient populations into subclasses.

d) Legal and IP framework

Prior experience indicates that legal and IP questions will arise when moving from an established clinical development pathway to a new development paradigm of IRPs. This includes, but is not limited to, identification of a pre-competitive space, preservation of confidentiality and IP, patient privacy and data protection, sponsor definition and responsibilities, data sharing between participating partners, and data dissemination. The legal framework should be compliant to the IMI2 Joint Undertaking (JU) framework and ensure sustainability of the IRPs beyond completion of this project.

2. Clinical network and network of patient-level data

With sponsors that collaborate rather than compete, the proposed new trial paradigm will create and maintain for each IRP a sustainable network of hospitals, healthcare providers and investigators who will leverage rather than duplicate efforts in preparation and execution of platform trials. When fully implemented, these networks will have two main components, both with common-foundational and disease-specific dimensions.

a) Clinical network of sites and investigators

For full IRP and platform trial implementation, enduring multinational networks⁷³ of disease-expert physicians and investigators capable of recruiting patients in longitudinal natural history studies, trial readiness registries and platform trials should be formed. Under this proposal, a general framework for establishing clinical

⁷³ The programme as indicated is aimed at confirmatory (phase 2/3) trials and thus requires a global network of sites and investigators.

networks of sites and investigators will be developed. This will include the necessary legal and contractual processes, tools and accountability instruments to enable defining activities needed for establishing, running, coordinating and funding the clinical network in a multi-sponsor environment. These collaborative disease-specific networks will be established around coordinating centres. The international clinical networks would be set up as a permanent disease-specific, trial-ready infrastructure, able to engage with both patient organisations (patient advocacy groups) and medical community to support research programmes.

Beyond establishing the general framework for clinical networks, the feasibility of creating such networks will be assessed and explored for IRPs in MDD, TB, NASH and NF. The framework will be codified in best practice documents and be freely available for the creation of future clinical networks.

To guide development of the framework, it is expected that, once live, the clinical networks will receive on an ongoing basis, all necessary Good Clinical Practice (GCP)- and IRP-specific training and use common test materials and instrumentation to accelerate identification of patients and study start up. However, training and common test materials and instrumentation are not deliverables of this Action.

As appropriate, driven by the needs of the disease-specific IRPs, clinical networks will design longitudinal natural history studies to better characterise and understand disease progression and to research and identify biomarkers predictive of response and clinical outcome.

Finally, the requirements and planning of readiness registry trials will be developed as needed to provide to the IRPs, once live, cohorts of trial-ready patients with a well-characterised background medical history to enable faster recruitment in platform trials.

b) Network of patient-level data

An effective and streamlined infrastructure for sharing and mining patient-level data, including EHRs, patient registries and other research data and real world data (RWD), will be critical for the identification of potential research participants, for identification of predictive biomarkers, and for developing trial readiness cohorts. An effort will be undertaken to develop common interoperability processes and standards to further enhance data-driven research. This will build on ongoing efforts such as the IMI Electronic Health Records for Clinical Research (EHR4CR) and the future IMI European Health Data Network (EHDN) projects, and databases from other existing and future EHR solutions/platforms. This effort will define requirements and standards needed to allow cross-platform interoperability components to be built to create a federated network of EHR platforms. During this project, complementary components will be built, to execute demonstration projects, such as query builders and connections via application programming interfaces (APIs) (see figure 2 for a high-level schematic).

During the project, use of claims databases will be evaluated as it may offer valuable information in certain disease areas, as complementary source of information.

Ongoing efforts to expand the network of connected hospitals to EHR platforms will need to be amplified, when possible, to include centres that will form the clinical network, described in section 2a) above, from both hospital sectors as well as from primary care sectors.

Work will be undertaken to develop generally accepted and cost-effective methods to enable unstructured data from EHRs to be utilised. This is to maximise use of available data and provide full power expected from secondary use of EHRs to support research programmes.

To deliver systems that are trustworthy, it will be needed to develop data quality assessment methods and tools to assess consistently the level of data quality and implement improvement actions to maximise the quality of health data for clinical research.

Important in all of this is to develop standards and processes that facilitate re-usability of patient-level data while in full compliance with data privacy legislation and expectations, and to address IP and liability considerations in the sharing of patient-level and aggregate medical data. Consideration will be given to EU-level and global alignment of ethical and data privacy standards to ease sharing and secondary use of patient-level data for research.

Beyond establishing the general framework, standards and processes for the networks of patient-level data, the feasibility of creating such networks will be assessed and explored in the disease areas in scope of this proposal and any gaps will be identified. The framework of standards and processes will be codified in best-practice documents and be freely available for creation of future networks of patient-level data.

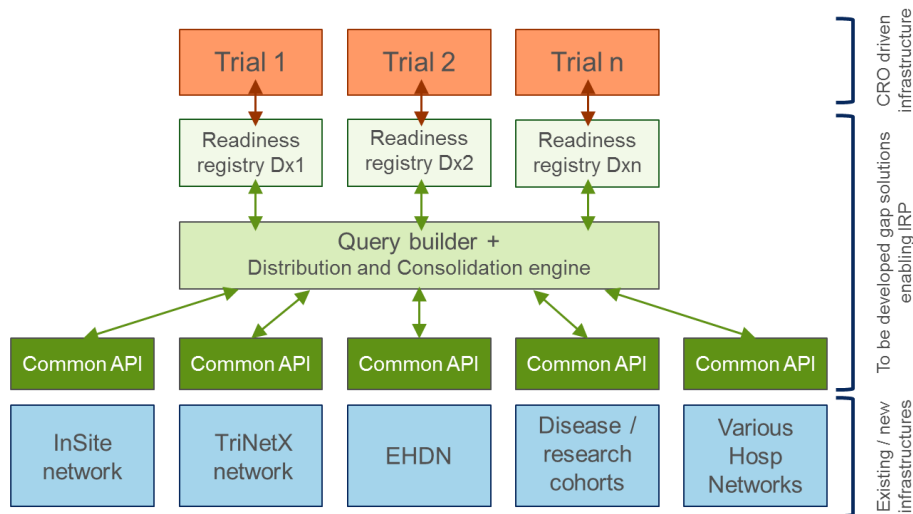


Figure 2: High-level schematic of technology components of patient-level data network

3. Disease-specific integrated research platforms

The objective is to design and prepare IRPs for four diseases with high unmet medical need:

- major depressive disorder (MDD);
- tuberculosis (TB);
- non-alcoholic steatohepatitis (NASH);
- neurofibromatosis (NF).

A platform trial that would go into execution would include a master protocol, ISAs, multinational clinical network(s) to build a longitudinal natural history study(ies) and trial readiness cohort(s) where required, as well as operational readiness to execute the platform trial.

However, in this topic, none of the disease-specific IRPs will advance to platform trial execution. The anticipated deliverables are limited to the design of the platform trial and the master protocol, initiation of the clinical network to be ready for future activation by the platform trial, feasibility assessment of the network of patient-level data and planning activities that would be needed for platform trial execution. Also in scope are negotiations with HAs to facilitate that data on successful interventions can inform further development and registration.

The design of all IRPs will follow a consistent, scalable and modular approach that can be extended to different indications beyond the current project scope, including rare diseases and paediatric indications.

The objective of this topic is not to investigate, (i) the discovery of new clinical uses or dosage regimens (including therapeutic indications) of an investigational medicinal product (IMP) used to validate the networks, (ii) manufacturing methods for such IMPs, including any starting materials and intermediates, and (iii) physical properties, forms, formulations, route of administration, dosing regimes, structure, and characteristics of the IMPs. No accidental or specific findings related thereto are to be considered as findings made towards the Action objectives.

Expected key deliverables

The common foundational elements work stream will provide common solutions to the disease-specific work streams, and integrate learnings and feedback obtained from the disease-specific work streams to enhance and extend the collection of common solutions. This process will iterate throughout the life of the project resulting in a collection of published, endorsed common methodology, standards and best practices, templates and/or guidance documents. This may be achieved by overlapping participation of members in the common and disease-specific work streams, or mechanisms established by the project consortium.

Specific key deliverables to achieve this are:

1. common foundational elements: common methodology, standards and best practices, templates and guidance documents forming a toolbox for trials in service of all disease area IRPs:
 - general framework for design of platform trials with multiple companies and public stakeholders, including the definition of trial sponsorship, oversight responsibilities and compliance;
 - compound selection procedure for inclusion in platform trials;
 - clinical network: legal, contractual processes, tools and accountability instruments, evaluation methods;
 - common process and technology to utilise EHRs to identify patients for platform trials, leveraging IMI-EHR4CR, the future IMI-EHDN and other available EHR platforms. Cross platform interoperability standards to be developed to enable querying a federated network of EHRs platforms. Query building and connections via Application Programming Interfaces (APIs) to required databases (EHR platforms / network) to identify potential patients and establish disease cohorts;
 - statistical methodologies: general questions to be addressed will be informed by questions encountered in implementation of each disease-specific IRP;
 - clinical operations methodologies: general questions to be addressed will be informed by questions encountered in designing each disease-specific IRP including patient-centric considerations;
 - regulatory methodologies for:
 - IRP-related clinical trial applications including the role of the sponsor, management of specific responsibilities in the context of IRPs with multiple products, different manufacturers and company confidential information. This includes safety reporting, protocol amendments, urgent safety issues, drug safety update reports, file management, inspections etc.,
 - adaptive platform trial designs, including pooling of placebo / comparator groups; randomisation and consent process; non-contemporaneous recruitment; acceptability of transitioning from phase 2 to phase 3, and issues of bias and unblinding etc.,
 - evaluation of applicability of existing and emerging regulatory guidance for specific diseases or populations; evaluation of the need for additional guidance on broader diseases / populations to be studied,
 - use of investigational product combinations in the context of IRPs,
 - scientific input from health authorities and HTA bodies on prognostic and predictive biomarkers and potential diagnostic tests in the context of IRPs,
 - an assessment of current limitations due to varying data privacy and ethical regulations, and a proposal for aligning ethical and legal standards governing the patient-data sharing and patient data re-use for research purpose considering EU regulation on personal data protection,
 - mechanisms for frequent, timely and collaborative engagement with stakeholders e.g. medicines & device regulators and ethic committees, beyond existing scientific advice procedures;
 - formal regulatory procedures, e.g. scientific advice or protocol assistance (or ex-EU equivalents) as appropriate and needed;
 - templates for collaboration agreement among platform trial partners, addressing (among others) patient privacy considerations;
 - templates for clinical trial agreements;

- templates for enabling combination therapy development (e.g. contractual considerations/language to enable two or more compounds to be tested in one study arm);
 - framework, processes and templates to facilitate sharing of data and information among and between IRP partners and platform trial partners, including patient-level data, and to enable the creation, protection and use of IP as appropriate;
 - templates for platform trial master protocol and intervention-specific appendix (ISA);
2. key performance indicators (KPIs) for performance and execution IRPs and platform trials;
 3. KPIs to evaluate value creation, performance and execution IRPs, and evaluating the long-term impact of the Action on clinical development paradigm and on innovative new treatments reaching patients;
 4. communication strategy and engagement with key opinion leaders (KOLs) and competent authorities (health authorities, HTA bodies, ethics committees) to enhance acceptance and adoption of IRPs;
 5. governance structure for participation in IRPs and to coordinate activities across disease-specific IRPs, including the associated longitudinal natural history studies and trial readiness cohorts;
 6. disease-specific IRPs (one per disease with indicated components):
 - best practices and standardisation:
 - identify and leverage common methodology, best practices, standards, and guidance documents (if available) through interaction with common foundational elements work stream,
 - capture and communicate learnings from the project to enhance and extend the knowledge captured and published in the common foundational elements work stream;
 - design of platform trial:
 - master protocol for platform trial,
 - identification of patient population to be included in platform trial design,
 - selection of potential biomarkers to include in platform trial design, and qualification as needed,
 - identification of potential treatment regimens to be foreseen in platform trial design,
 - simulation guided platform trial design; evaluation of operating characteristics and statistical analysis plan using common methodologies to be established over the course of this proposal,
 - statistical methodologies tailored to each disease-specific IRP, taking into consideration common methodologies established over the course of this proposal,
 - regulatory methodologies tailored to each disease-specific IRP taking into consideration common methodologies and regulatory guidance established over the course of this proposal,
 - clinical operations planning tailored to each disease-specific IRP taking into consideration common methodologies which will be established over the course of this proposal,
 - regulatory and ethics consultation for platform trial,
 - obtaining regulatory endorsement for platform trial,
 - obtaining ethics endorsement for platform trial,
 - sustainability plan to include planning for transition from design to implementation, and to ensure continuation of IRP and platform trial beyond the IMI2 JU project horizon;
 - clinical network of investigators and patient-level data:
 - determine requirements and design for a clinical network of sites and investigators to contribute patients to registries, longitudinal natural history studies and/or trial readiness cohorts, and/or to participate in the platform trial,
 - identify potential sites for such clinical network of sites and investigators,
 - initiate such clinical network of sites and investigators,

- evaluate overall readiness of sites to contribute data and/or to participate in the platform trial, and identify any common gaps,
 - evaluate site Biosafety Level 3 (BSL3) microbiology laboratory capabilities (TB only),
 - identify, evaluate and assess feasibility of networks of patient-level data (e.g. existing EHR systems or other public data networks) to facilitate identification and recruitment of patients. Leverage IMI-EHR4CR, IMI-EHDN and to-be-developed common methodologies and qualify remaining gaps to fully address this need,
 - identify existing patient registries and/or create protocol for patient registries to enrol in a longitudinal natural history study and/or trial readiness cohort,
 - design and create protocol for longitudinal natural history study (MDD, NASH and NF only),
 - developing funding model for platform trial, including sustainability plan for any activities foreseen beyond the project duration;
 - developing a disease-specific sustainability that includes at least (i) a blueprint and funding model to move from planning to implementation of the IRPs and platform trial execution, (ii) approach for retention of current and attracting new commercial and not-for-profit pharmaceutical development partners and (iii) the mechanism to fully fund and sustain platforms beyond the period of this action, including knowledge and infrastructure sustainability;
7. dissemination and publication of best practices and results;
 8. overarching sustainability plan for governance, maintenance, expansion and improvement of the common foundational elements and of the frameworks for clinical networks and networks of patient-level data;
 9. Memorandum of Understanding (MoU) with TBDDN consortium (from Call 15 topic 8) to cover collaboration and sharing of information on TB-related activities.

Expected impact

The objectives, deliverables and impact of the resulting Action are well aligned with the mission and goals of IMI2 JU. Designing common methodology for IRPs and platform trials that is endorsed by regulatory agencies will deliver a transformational new approach to accelerate development of new medicines for diseases of high unmet need in scope of the World Health Organisation (WHO) priority medicines list.

Through the paradigm shift in knowledge sharing and leveraging of operational infrastructure among private and public partners, both in the precompetitive and competitive space, clinical trials performed to demonstrate clinical proof of concept will be quicker and are expected to be more successful, at a lower burden to patients, investigators and sponsors, and the feasibility of such trials will be enhanced.

This will allow patients to benefit quicker from medical innovations, both through accelerating new medicines development in general but also through faster enrolment in clinical trials with a lower chance of being randomised to the placebo, and potentially a higher likelihood of being allocated to the most promising treatments for individual patients, including multi-company combinations of medicines.

There will be increased participation of patients in the design of clinical trials and in the development of predictive biomarkers and trial endpoints that are clinically meaningful and approved by regulators.

Developing the proposed reusable IRP and platform trial approach in Europe will deliver a tangible advantage for developing innovative new medicines, and for advancing fundamental and applied medicines research in general, in academia and industry. This includes four platform trial protocols fully ready for execution. Applicants should indicate how their proposal will impact the competitiveness and industrial leadership of Europe by, for example engaging suitable SMEs.

Potential synergies with existing consortia

Applicants should take into consideration, while preparing their short proposal, relevant national, European, and non-European research projects and infrastructure initiatives. Synergies and complementarities should be considered in order to incorporate past achievements, available data and lessons learnt, thus avoiding

unnecessary overlap, duplication of efforts and funding. Examples of relevant IMI and non-IMI projects/initiatives are:

- disease-specific biomarker initiatives such as (incomplete list, examples only):
 - IMI-EMIF (European Medical Information Framework), an IMI project integrating existing in-depth Alzheimer's Disease databases with large scale EHRs <http://www.emif.eu/>,
 - IMI-LITMUS (Liver Investigation – Testing Marker Utility in Steatohepatitis) <https://www.imi.europa.eu/projects-results/project-factsheets/litmus>,
 - complementary international initiatives (e.g. Foundation for National Institute of Health (FNIH)-sponsored Non-Invasive Biomarkers of Metabolic Liver Disease (NIMBL) which are focused on generating the data necessary for qualification of non-invasive NASH biomarkers);
- IMI-EPAD platform trial in Alzheimer prevention <http://ep-ad.org/>;
- relevant registries and projects ongoing at national levels;
- International Consortium for Health Outcome Measurement (ICHOM);
- IMI portfolio of knowledge management projects: eTRIKS, DDMORE, Open PHACTS, IMI-EHR4CR (and the resulting i~HD), and RADAR-CNS (<https://www.imi.europa.eu/projects-results/project-factsheets>);
- TransCelerate BioPharma bringing standardisation to trial conduct processes across sponsors <http://www.transceleratebiopharmainc.com/>;
- future IMI2 JU project resulting from the topic European Health Data Network (EHDN) IMI2 – Call 12, which will deliver an operational, federated network in order to have direct access to RWD for developing new or incremental services in healthcare area http://www.imi.europa.eu/sites/default/files/uploads/documents/IMI2Call12/IMI2_Call12_CallText.pdf;
- The Bill and Melinda Gates Foundation (BMGF), Critical Path Institute and TB Alliance (TBA) initiative 'Critical Path to TB Drug Regimens (CPTR) initiative';
- Global Alliance of Mental Illness Advocacy Networks (GAMIAN) of patients and providers;
- EMA/Heads of Medicines (HMA) Agency task force on big data;
- innovative clinical trial design initiatives such as I-SPY, GBM AGILE and other innovative (platform) trials;
- European Reference Networks (ERNs) are virtual networks involving more than 900 highly-specialised healthcare units from over 300 hospitals in 26 EU countries. 24 ERNs are working on a range of thematic issues including bone disorders, childhood cancer and immunodeficiency https://ec.europa.eu/health/ern_en; https://ec.europa.eu/health/ern/networks_en;
- ECRIN as a not-for-profit infrastructure supporting multinational clinical research projects in Europe may contribute to building the sustainable networks of hospitals, healthcare providers and investigators with regard to this topic (<http://www.ecrin.org>);
- Connect4Children (c4c) with a focus on the creation of a pan-European collaborative paediatric network (<http://conect4children.org>).

The list above is not necessarily complete; other research projects and research infrastructure initiatives should be considered.

Industry consortium

The industry consortium is composed of the following EFPIA partners:

- Janssen (lead)
- Novartis (co-lead)
- Allergan
- AstraZeneca
- Novo Nordisk
- Otsuka
- Pfizer
- Sanofi
- Servier
- Teva

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

- Children's Tumor Foundation
- SpringWorks Therapeutics
- TB Alliance

The industry consortium will contribute the following expertise:

- expertise and experience in leading and managing large scale public-private partnerships;
- drug development expertise in the disease areas in the proposal, including compound selection and design, execution of large global clinical studies, and development and validation of appropriate assays to support clinical trials;
- quantitative science expertise with adaptive clinical (platform) trial designs, including modelling and simulation techniques and statistical methodology development;
- expertise in designing longitudinal natural history studies, disease patient registries and trial readiness cohorts;
- expertise in regulatory sciences and in strategic approaches to collaborate with health authorities to introduce innovative clinical development methodologies;
- expertise in operationalising the execution of platform trials and adaptive clinical trials, including site and hospital networks selection, site readiness assessment and education, patient registries and trial readiness cohorts to support enrolment;
- legal expertise related to intellectual properties management, and complex partnership co-development structures;
- expertise and experience with and access to research and clinical networks as part of the disease-specific initiatives listed above;
- expertise in building hospital networks and technologies to utilise EHRs.

Specific industry contributions are listed under the relevant work packages (WPs) and need to be taken into account by the applicant consortia. Although full implementation of IRPs and execution of platform trials for the selected disease areas is not included in this proposal, the industry consortium may rely on certain background knowledge of existing and investigational treatments to inform the IRPs and platform trial designs.

Indicative duration of the action

The indicative duration of the action is 42 months.

Indicative budget

The indicative in-kind and financial contribution from EFPIA partners and IMI2 JU Associated Partners is EUR 12 365 000.

This contribution comprises an indicative EFPIA in-kind contribution of EUR 10 190 000 and an indicative IMI2 JU Associated Partners in-kind contribution EUR 2 175 000. This includes activities related to NF registry data and a TB biorepository of well-documented TB specimens to support activities in WP7 and WP5, respectively.

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

The financial contribution from IMI2 JU is a maximum of EUR 12 005 000.

Applicant consortium

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

The applicant consortium is expected to address all the research objectives and make key contributions to the defined deliverables in partnership with the industry consortium which will join the selected applicant consortium in preparation of the full proposal for stage 2. This requires mobilising, as appropriate:

- experience in leading, managing and measuring impact of public-private partnership consortia;
- expertise in programme management, project management services, grant administration and compliance;
- communication expertise, preferably for alliance management of large-scale consortia;
- expertise in drug development policy, regulatory decision-making and health technology assessment;
- regulatory expertise relevant for the development of IRPs and platform trials;
- statistical and statistical modelling expertise relevant for the design and analysis of platform trials and longitudinal natural history studies;
- legal expertise related to clinical trials and IP;
- expertise in developing clinical networks and networks of patient-level data (EHRs);
- expertise in RWD, use of clinical databases and patient registries, data management and security, patient privacy and consent, sharing of information related to clinical trials and data standards;
- research, clinical and development expertise in the disease areas identified in this proposal;
- expertise in biomarker identification and qualification, clinical endpoint definition and trial design;
- expertise in longitudinal natural history studies and trial readiness cohorts;
- leadership of and access to clinical site consortia and networks in the disease areas in scope;
- expertise in clinical trial operations, clinical programme management and clinical trial regulations;
- expertise in patient recruitment and design and implementation of clinical databases;
- ethics expertise and experience in obtaining ethics approval;
- experience with GCP responsibilities and ability to serve as clinical trial sponsor role.

It may also require mobilising, as appropriate, resources to identify and have access to:

- existing RWD and patient-level datasets which can be used for platform trial design;
- existing cohorts and patient populations for the disease areas in scope;
- existing clinical networks for the disease areas in scope.

SMEs including specialised service providers can be of great benefit to IMI projects and can strengthen the competitiveness and industrial leadership of Europe. Their involvement in the action might offer a complementary perspective to industry and the academia, and help deliver the long-term impact of the project.

For these reasons, applicants should consider engaging SMEs throughout the proposal. Contribution of SMEs would be considered especially beneficial in providing the following expertise and activities:

- statistics and modelling & simulation;
- technology for querying EHRs, registries and RWD;
- legal and IP;
- project management and communication;
- medical & scientific writing supporting regulatory interactions;
- business process design;
- clinical operations;
- patient engagement.

The applicant consortium is expected to be multidisciplinary and include patients/patient advocacy groups, healthcare providers, investigators and hospitals, academic research groups, health authorities and HTA groups, SMEs, and regulatory agencies.

While preparing their proposals, applicant consortia should also ensure that needs of patients are adequately addressed and, where appropriate, patient involvement is encouraged.

Suggested architecture of the full proposal

The applicant consortium should submit a short proposal which includes their suggestions for creating a full proposal architecture, taking into consideration the industry contributions and expertise provided below. The architecture below is a suggestion; different innovative project designs are welcome, if properly justified.

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

The consortium is expected to have a well-defined strategy for the translation of the relevant project outputs into clinical trial, regulatory and clinical healthcare practices. A plan for interactions with HAs and HTA bodies with relevant milestones and resources allocated should be proposed to ensure, for example, qualification advice on the proposed novel methodologies for drug development and qualification advice on the impact on marketing approval and market access decision-making.

A strategy and high-level plan for aspects related to sustainability of the IRPs, facilitating continuation beyond the duration of the project, should also be proposed. More specifically, as part of the project a detailed plan should be developed and executed to ensure sustainability of the knowledge, infrastructure and governance of the IRPs to enable continuation of use beyond the project duration, and adoption by other disease areas.

Work package 1 – Governance and project management

This work package will contain leadership representation from all other work packages, ensure investments and deliverables of all project components and ensure delivery on the primary objectives of the Action. Professional project management approaches will be deployed to achieve synergies between the common foundational elements, clinical networks and networks of data, and disease-specific IRPs.

This work package includes:

- project management and communication (within and outside the consortium);
- grant administration;

- dissemination of scientific results, methodology, standards, best practices and guidance documents;
- project governance for common methodology;
- governance for disease-specific aspects for the disease areas in scope: MDD, TB, NASH and NF;
- development of a general framework for compound selection process, criteria and governance;
- development of a set of key performance indicators (KPIs) to evaluate long term impact of the IRPs;
- strategy and overall sustainability plan facilitating continuation beyond the duration of the action;
- establishing and coordinating collaborations with ongoing initiatives.

Industry contribution:

- experience in leading and managing large scale public-private partnerships;
- expertise in programme and/project management;
- broad general drug development expertise;
- clinical drug development expertise in all disease areas in scope;
- business expertise in sustainability planning;
- expertise in defining measurable and actionable KPIs;
- access to key opinion leaders (KOLs).

Expected applicant consortium contribution: In addition to contributions listed under 'Applicant consortium' the following is expected for WP1:

- programme management and project management services;
- communication across a wide range of stakeholders and audiences;
- experience in leading and alliance management for large scale public-private partnership consortia;
- grant administration and compliance;
- define KPIs for public partners in public-private partnerships.

Work package 2 – Common foundational elements

Referring to the scope and objectives described earlier, the goals of this work package will be as follows:

- regulatory: establish HA interactions to support IRP/platform trials of a particular design. Pressure test proposals through regulatory authority and patient organisation input;
- clinical operations: develop and disseminate best practices (processes, standards, guidance documents) to enable the efficient setup and execution of IRPs;
- quantitative design: develop and disseminate statistical methodology and trial simulation tools (e.g. computer software, codes) to enable efficient design and execution of disease-specific and future IRPs;
- legal: develop and disseminate legal and IP frameworks and agreement templates/language to enable the efficient setup and execution of IRPs.

Industry contribution:

- expertise in quantitative modelling/simulation methodologies for adaptive- and platform-trial designs;
- expertise in drug development and experience in compound selection for clinical studies;
- expertise in operationalising the execution of platform trials and/or adaptive trials;
- expertise in regulatory sciences and strategic approaches to introduce innovative methodologies;
- legal expertise related to clinical trials, IP and cross-company collaboration;
- expertise in clinical operations, medical writing, data privacy;
- access to KOLs;

Expected applicant consortium contribution: In addition to contributions listed under 'Applicant consortium' the following is expected for WP2:

- meta-analysis reviews to identify best practices and standardisation of practice;
- statistical and modelling expertise, including Bayesian statistics and adaptive trial designs;
- operationalise the execution of platform trials;
- regulatory expertise through highly experienced regulatory experts. Extensive experience with providing input and scientific advice on complex adaptive clinical trial designs to support marketing authorisation;
- ethics committee expertise in reviewing platform trials or other complex adaptive clinical trial designs; expert knowledge of related privacy laws, regulations and issues;
- legal expertise related to clinical trials and IP;
- protocol design; informed consent for platform trials; management of uncertainties for patients related to adaptive approaches; patient's acceptance of platform trials and their value;
- project management;
- clinical trial sponsor duties for platform trials.

Work package 3 – Clinical network and network of patient-level data

This work package will explore synergy with the growing InSite hospital network (Champion Programme) and with the future IMI EHDN project to ensure complementarity and leveraging of solutions.

The goals of this work package include the following layers and modules.

- Develop an approach and interoperability network components for efficiently interrogating existing networks such that potential candidate-patients for the trial readiness cohorts can be identified.
- Set up a common query workbench that includes distributing search queries over the different relevant data networks and which can consolidate results.
- Identify a common informed consent solution for use across IRPs for the recruitment of patients.
- Identify or develop shared common underlying technical solutions across disease registries with disease-specific aspects and sufficiently common and modular elements to allow for support of registries in multiple different disease areas. Data security and privacy protection are of the utmost importance.
- Use of 'eResearch' platforms that conform to the required regulatory validation. This platform should be modular, allow for electronic data capture across different disease areas and support other necessary functionalities for trial execution.
- Identify or develop structures/solutions for patient-driven trial participation in which patients as holders of their personal health data decide with whom to share their data. Identify or develop solutions in which patients can provide additional outcomes-related data (patient-reported outcomes) or in which connected devices can capture and deliver data.
- Install governance bodies for overall data management and security, patient privacy and consent, data quality, etc., to include participating data providers, with input and collaboration from other stakeholders including patients and healthcare providers.

The clinical network will work with other consortium members to explore the establishment of EHR endpoints for both longitudinal and IRP studies.

Industry contribution:

- expertise in working in federated data networks;
- expertise leveraged from prior IMI projects such as EHR4CR, EMIF and EPAD;
- expertise in RWD management, standardisation and harmonisation;
- data security methods;
- clinical trial data management and interpretation of clinical information;

- leadership in building sites and hospital networks to support clinical phase 0-4 studies;
- technologies to utilise EHRs.

Expected applicant consortium contribution: In addition to contributions listed under 'Applicant consortium' the following is expected for WP3:

- experience from prior relevant projects where RWD sets have been used as recruitment pool for platform or other trials, preferably within multi-stakeholder and international projects;
- leadership in RWD related to nesting clinical research within existing hospital infrastructures;
- resources to develop the technical modules to bridge the gap between the existing RWD networks and the trial platforms;
- expertise in data management, working with data standards (such as Observational Medical Outcomes Partnership common data model (OMOP CDM), CDISC, ICHOM); secure hosting of patient-level data;
- input and solutions for patient centric trial participation, including patient privacy and consent;
- connectivity and access to EHRs or other relevant data sets, with capability to support identification of patients for trial readiness cohorts and longitudinal natural history studies.

Work package 4 – Integrated research platform for major depressive disorder (MDD)

Major depressive disorder (MDD) is the leading cause of disability in the world. With current antidepressants, only half of patients have $\geq 50\%$ reduction in depressive symptoms, remission is achieved in only 20-30% of patients, and many patients inadequately respond to any treatment and develop treatment-resistant depression (TRD). Therefore, a need exists to develop new medications with novel mechanisms of action for patients with TRD and for patients without TRD but require augmentation of antidepressant treatment. This work package will develop an IRP to efficiently test the clinical potential of new medications to treat MDD.

The goals of this work package are to:

- develop a master protocol for a phase 2 proof of concept platform trial (PT) in patients with TRD or adjunctive-MDD;
- develop consensus disease definitions for lack of adequate response, partial response, TRD, adequate dose and duration of treatment, etc. to establish consistent definitions of these patient populations;
- design and develop a protocol for a longitudinal natural history study (LNHS) in MDD to understand the clinical course of inadequately responding patients, to identify clinical biomarkers predictive for patients likely to develop TRD, and to establish the parameters for a readiness cohort of patients for PTs;
- define key operational components required for implementing the PT and LNHS;
- conduct feasibility assessments for patients and investigators to participate in this program;
- obtain regulatory and ethics committee endorsement for the PT and LNHS;
- plan, design and initiate a clinical network of sites and investigators comprised of primary care and mental health referral centres to serve as centres for PT and LNHS studies as well as referral networks;
- evaluate overall site readiness and identify common gaps and barriers to initiate PT and LNHS studies;
- assess regulatory, ethical and technical feasibility of using EHRs to identify potential patients;
- develop a sustainability plan for funding and sustaining the IRP, LNHS and PT.

Industry contribution:

- expertise in MDD drug development; knowledge about compounds characteristics to be potentially included in future clinical trials (note that compound testing is out of scope of the current action);
- expertise in adaptive trial design; design platform trial;
- set up clinical network of sites and investigators to enable PT execution;
- build hospital networks and technologies to utilise EHRs;

- design and implementation of disease registries and trial readiness cohorts;
- expertise in clinical operations, site start-up and patient recruitment;
- interact with health authorities;
- develop a sustainability plan for full implementation, funding and sustaining the IRP and PT.

Expected applicant consortium contribution: In addition to contributions listed under ‘Applicant consortium’ the following is expected for WP4:

- expertise in MDD; clinical trial design; identification of suitable MDD patients;
- clinical trial design, biomarker identification and endpoint definition;
- develop clinical networks and establish networks of patient level data (EHRs);
- design and implementation of disease registries; access to MDD patient registries;
- develop queries and analyse large data from clinical networks, patient registries and EHRs;
- ability to serve as, or identify, a trial sponsor for implementing the PT.

Work package 5 – Integrated research platform for tuberculosis (TB)

Despite recent progress, tuberculosis (TB) remains a deadly communicable disease with 10.4 million cases reported in 2016, 600 000 cases resistant to first-line drugs and 1.8 million deaths. TB disproportionately affects the world’s poorest and most vulnerable, but also in the developed world TB remains a significant medical and societal problem [8] [9]. The pipeline for TB drugs shows significant promise to deliver phase-2-ready clinical candidates over the next 3 years [10]. Therefore, a need exists to establish methodology and setups for efficiently testing new combinations of 3-4 drug therapies, comprised of existing and novel compounds, that are expected to be ready to enter the learn phase of the platform trial around mid-2020.

The goals of this work package are to:

- develop a master protocol for a learn (phase 2) and confirm (phase 3) platform trial (PT) in drug sensitive and drug resistant TB;
- develop a set of selection criteria that will qualify drugs or drug combinations to enter the PT;
- develop decision criteria for drug combination to advance from the learn to the confirm phase;
- coordinate with consortia and compound owners to generate non-clinical (e.g. toxicology) and early clinical (e.g. drug interaction) information required to support the selection and entry of the desired treatment combination and duration;
- develop plans to implement the PT, tailored to TB-endemic developing countries;
- develop plans to evaluate site readiness and for filling in any gaps in operational readiness;
- develop requirements and assessment procedures for standardisation of microbiology laboratories and specialised laboratory setup such as BSL3 microbiology capability;
- assess feasibility of integrating public data networks, existing hospital/regional/national EHR systems, and patient tracking/contact methods through community health workers to facilitate patient identification, diagnosis and enrolment;
- develop a sustainability plan for full implementation, funding and sustaining the IRP and PT.

Industry and Associated Partner contribution:

- expertise in TB clinical drug development; knowledge about compound characteristics to be potentially included in future clinical trials (note that compound testing is out of scope of the current action);
- expertise in adaptive trial design; design platform trial;
- microbiology technologies and assays to support TB drug development and trial conduct;

- expertise in clinical operations, in particular of large scale studies in the developing world;
- interact with local authorities and health authorities;
- connecting with relevant R&D consortia (e.g. TB Drug Accelerator (TBDA), Critical Path to TB Drug Regimens (CPTR), Pan-African Consortium for the Evaluation of Antituberculosis Antibiotics (PanACEA), Tuberculosis Trial Consortium (TBTC)).

Expected applicant consortium contribution: In addition to contributions listed under 'Applicant consortium' the following is expected for WP5:

- expertise in TB research and TB regimen paradigms in low resource settings;
- diagnostic capabilities for rapid identification and recruitment of DS and DR TB patients;
- experience with healthcare systems and infrastructures in resource limited settings;
- knowledge of and access to patient-level data networks in TB prevalent countries;
- expertise in clinical operations in TB-endemic countries, and implementing adaptive trials;
- expertise in drug development policy, obtaining ethics approval and regulatory decision-making;
- ability to serve as, or identify, a trial sponsor for implementing the PT.

Significant efforts will be required outside the EU by the applicant consortium. Consideration to (financial) planning of required efforts globally, in the context of EU/IMI guidelines is therefore necessary.

Work Package 6 – Integrated Research Platform for Non-alcoholic Steatohepatitis (NASH)

Non-alcoholic fatty liver disease (NAFLD) impacts 20-30 % of adults in Western countries, with obesity and type 2 diabetes mellitus (T2DM) among its major risk factors. About 20 % of NAFLD patients have non-alcoholic steatohepatitis (NASH), a more significant disease with liver inflammation, fibrosis and an increased long-term risk of cirrhosis, hepatocellular carcinoma, other cancers and death [11]. Current treatments for NASH include weight loss, pioglitazone (patients with T2DM) and vitamin E (patients without T2DM) [12] [13]. None of these adequately address the medical need. The diagnosis and prognosis of NASH currently require liver biopsies that are highly invasive, subject to sampling bias and have operator-dependent variability in performance [14]. Combinations of (new) non-invasive tools are needed to substitute for liver biopsy and facilitate drug development. Many new therapies to treat NASH are being developed but the need for biopsies and the myriad of companies evaluating new treatments lead to increasing recruitment bottleneck and study delays. An IRP will be developed to efficiently test multiple new medications.

The goals of this work package are to:

- design and develop a master protocol to evaluate (combinations of) compounds in phase 2b, phase 3/4, or both, in NASH patients with well-characterised biomarkers and clinical phenotypes;
- enable biomarker research and validation by collaborating with the IMI2 LITMUS consortium and FNIH-funded NIMBLE program;
- plan, design and initiate a clinical network of sites and investigators;
- identify, evaluate and assess feasibility of networks of patient-level data to identify potential patients;
- obtain regulatory and ethics committee endorsement of the PT;
- define key operational components required for implementing the PT;
- evaluate overall site readiness to contribute data and participate in the PT, and identify common gaps;
- develop a sustainability plan for full implementation, funding and sustaining the IRP and PT.

Industry contribution:

- expertise in and development of new investigational treatments for hepatic and metabolic diseases; knowledge about compound characteristics to be potentially included in future clinical trials (note that compound testing is out of scope of the current action);
- expertise in adaptive trial design; design platform trial;

- set up clinical network of sites and investigators to enable PT execution;
- build hospital networks and technologies to utilise EHRs;
- design and implementation of disease registries and trial readiness cohorts;
- expertise in clinical operations, site start-up and patient recruitment;
- interact with **health authorities**.

Expected applicant consortium contribution: In addition to contributions listed under ‘Applicant consortium’ the following is expected for WP6:

- expertise in NASH and adjacent diseases; identification of suitable patients;
- compound selection and knowledge to design clinical trials;
- clinical trial design, biomarker identification and endpoint definition;
- design and implement disease registries, and create trial readiness cohorts;
- access to NASH **registries and large patient datasets**;
- develop queries and analyse large data from clinical networks, patient registries and EHRs;
- ability to serve as, or identify, a trial sponsor for implementing the PT.

Work Package 7 – Integrated research platform for neurofibromatosis (NF)

Neurofibromatosis type 1 (NF1), type 2 (NF2) and Schwannomatosis (SWN) are rare neurogenetic syndromes caused by loss of function mutations in tumour suppressor genes that manifest with multiple tumours throughout the central and peripheral nervous system. The overall incidence is in the order of 1/3,000 [15] [16]. Although it is unclear whether there is an increased risk for malignancy in NF2 and SWM, the risk for malignancy in NF1 is widely described. The diverse presentation, variable progression and relevance of NF in malignant cancer make NF an attractive candidate for building an IRP to study natural progression and identify informative biomarkers, and to design a platform trial to test multiple (combinations of) treatments.

Clinical research on rare diseases faces many difficulties resulting in limited therapeutic options and difficult patient access to diagnostic tools and proper care. An IRP for NF is a case model for other rare diseases.

The goals of this work package are to:

- design and develop a master protocol for a seamless phase 2-3 platform trial (PT) in NF1 and NF2 patients below 18 years of age;
- design and develop a protocol for a broad longitudinal natural history study (LNHS) in NF, all types and all ages, to investigate disease progression and to identify biomarkers for disease characterisation, prediction of disease progression and selection of promising treatments for individual patients;
- define key operational components required for implementing the PT and LNHS;
- conduct feasibility assessments for patients and investigators to participate in this programme;
- obtain regulatory and ethics committee endorsement for the PT and LNHS;
- building on expertise and ongoing efforts of the Children’s Tumor Foundation, design and initiate a clinical network of sites and investigators for the IRP and PT;
- evaluate overall site readiness and identification of common gaps;
- assess regulatory, ethical and technical feasibility of using existing patient registries, EHRs and other patient-level data to identify and select potential patients;
- develop a sustainability plan for full implementation, funding and sustaining the IRP and PT.

Industry and Associated Partner contribution:

- expertise in oncology clinical drug development, NF in particular, and knowledge about compounds characteristics to be potentially included in future clinical trials (note that compound testing is out of scope of the current action);
- expertise in adaptive trial design; design platform trial;
- build hospital networks and technologies to utilise EHRs;
- design and implementation of disease registries and trial readiness cohorts;
- expertise in clinical operations, site start-up and patient recruitment;
- interact with health authorities;
- connect with NF clinical consortia;
- advocacy to expand leanings of NF experience to other rare disease communities.

Expected applicant consortium contribution: In addition to contributions listed under 'Applicant consortium' the following is expected for WP7:

- expertise in NF trials; knowledge of currently used and investigational treatments;
- clinical trial design, biomarker identification and endpoint definition;
- access to sites and to caregiver- and patient organisations;
- design and implementation of disease registries, and access to NF patient registries;
- develop queries and analyse large data from clinical networks, patient registries and EHRs;
- ability to serve as, or identify, a trial sponsor for implementing the PT.

References

- [1] Woodcock, J. and L.M. LaVange, *Master Protocols to Study Multiple Therapies, Multiple Diseases, or Both*. New England Journal of Medicine, 2017. **377**(1): p. 62-70.
- [2] Saville, B.R. and S.M. Berry, *Efficiencies of platform clinical trials: A vision of the future*. Clinical Trials, 2016. **13**(3): p. 358-366.
- [3] I-SPY2. Available from: <http://www.ispytrials.org/>.
- [4] EPAD. Available from: <http://ep-ad.org/>.
- [5] AGILE, G.; Available from: <https://www.curebraincancer.org.au/>.
- [6] GBM AGILE Trial Press Launch, J.W., November, 11, 2012. Available from: <https://www.youtube.com/watch?v=nHqUil9P32E>.
- [7] Berry, D.A., *Bayesian clinical trials*. Nat Rev Drug Discov, 2006. **5**(1): p. 27-36.
- [8] Report, W.G.T. 2015.
- [9] *UNITAID TB Executive Board meeting 24th Special Session 2016*.
- [10] *Working Group on New Drugs (Stop TB Partnership /TBA)*.
- [11] Targher, G., C.P. Day, and E. Bonora *Risk of Cardiovascular Disease in Patients with Nonalcoholic Fatty Liver Disease*. New England Journal of Medicine, 2010. **363**(14): p. 1341-1350.
- [12] Cusi, K., *Treatment of patients with type 2 diabetes and non-alcoholic fatty liver disease: current approaches and future directions*. Diabetologia, 2016. **59**: p. 1112-1120.
- [13] Chalasani, N., et al., *The diagnosis and management of nonalcoholic fatty liver disease: Practice guidance from the American Association for the Study of Liver Diseases*. Hepatology, 2018. **67**(1): p. 328-357.
- [14] Singh, S., et al., *Magnetic Resonance Elastography for Staging Liver Fibrosis in Non-alcoholic Fatty Liver Disease: A Diagnostic Accuracy Systematic Review and Individual Participant Data Pooled Analysis*. European radiology, 2016. **26**(5): p. 1431-1440.
- [15] Evans, D., et al., *Malignant peripheral nerve sheath tumours in neurofibromatosis 1*. Journal of Medical Genetics, 2002. **39**(5): p. 311-314.
- [16] Huson, S.M., Harper, P. S., & Compston, D. A. , *Von Recklinghausen neurofibromatosis. A clinical and population study in south-east Wales*. Brain, 1988. **111**(pt6): p. 1355-1381.

Topic 2: Blockchain Enabled Healthcare

Topic details

Topic code	IMI2-2018-15-02
Action type	Research and Innovation Action (RIA)
Submission and evaluation process	2 stages

Specific challenges to be addressed

The pharmaceutical value chain and the extended healthcare ecosystem have many areas that suffer from complexity, a lack of transparency, coordination and trust. Examples include:

- counterfeit medicines market estimated at EUR 160 billion with a huge impact on patient health;
- lack of access to medicines, especially in developing countries, impacting patient health;
- data accessibility leading to lost opportunities for improved research and new innovative medicines;
- patient privacy considerations (patient consent) hindering clinical trial recruitment and execution;
- lack of visibility and shared 'source of truth' leading to friction and costs in development and distribution;
- increasing risk of cyber threats, especially with central data storage and sharing.

By addressing these challenges through a public-private consortium, the evaluation, design, and accelerated adoption of blockchain-enabled healthcare solutions across the industry can be fostered. This will facilitate the delivery of true innovation benefiting both patients and the industry.

Need and opportunity for public-private collaborative research

Blockchain adoption in the healthcare industry requires consensus across multiple parties and needs to have representation from all segments of the pharmaceutical value chain to ensure end-to-end operability, scalability and connectivity. This includes but is not limited to:

- patient representatives who will ensure patient needs are prioritised;
- clinical parties (investigators, labs, clinical research organisations) supporting drug development;
- healthcare providers such as hospitals, clinics, pharmacies as patient-facing organisations;
- manufacturing and supply chain partners including carriers, distributors, and re-packagers responsible for end-to-end product tracking and product quality;
- health authorities that define regulations for drug submission, distribution and data handling;
- SMEs (small and medium-sized enterprises) including technology vendors with expertise and capability to realise blockchain technology solutions;
- academia to support advancement in computer science and medical innovation.

By combining forces in a public-private consortium, an effective solution utilising blockchain can address the challenges mentioned above. As the realisation and prioritisation of the use cases in the project will depend upon their initial evaluation, the project will focus the stakeholder engagement on this evaluation.

Scope

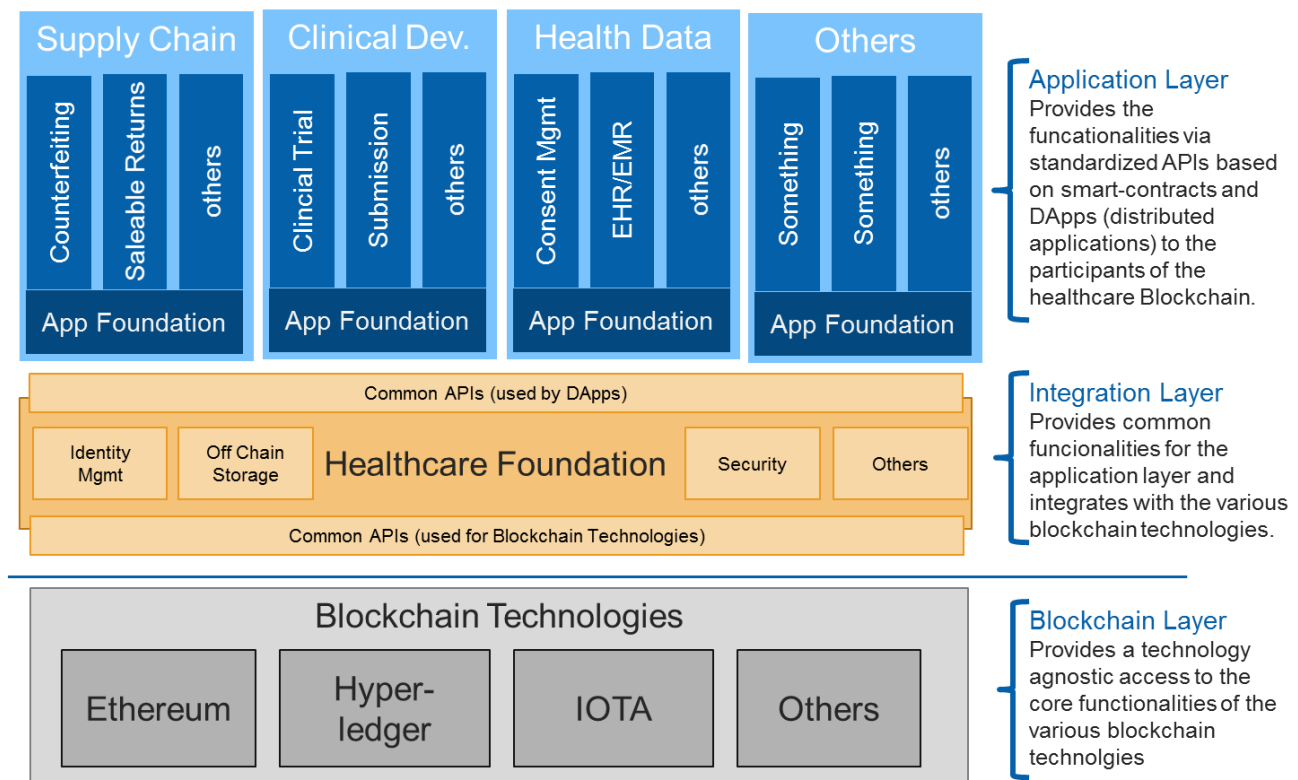
The overall objective of the agile project generated by this topic is to establish a common blockchain ecosystem for pharmaceutical development, manufacturing, and distribution that provides an incentive and serves as the basis for all participants to engage, adopt, and benefit from.

The project will initially establish an effective governance organisation and approach to enable continuous improvement and open competition among service providers, while ensuring that critical factors such as data integrity, privacy, regulatory compliance and efficiency are built into a 'Healthcare Foundation' which serves as an integration layer between underlying blockchain technologies and the business application layer (see architecture diagram).

The project aims to drive the agile delivery of use cases prioritised by clearly defined business value, benefits (return on investment, ROI) and feasibility. Use cases fall into the domains of supply chain, focusing on supply chain integrity and efficiency; clinical development, focusing on clinical trials and submission; and health data, which among others should enable blockchain-based machine learning data marketplaces. A likely focus for prioritised delivery is enabling end-to-end product tracking with blockchain technology to address the issue of counterfeit medicines, taking into account existing initiatives such as the proposed European Medicines Verification System. The project will also evaluate the use of medical devices across multiple use cases in order to ensure the integrity of device, data and services to enable the benefits of the internet of things (IoT). The initial technology deliverable is an architectural framework enabling such factors as digital identity management, efficient consensus mechanism, off-chain storage, global scalability, security, and high performance. Other use cases can be added based on a value analysis during the project lifetime and proposals from the selected applicant consortium. The scope includes a reference implementation of the solution but does not include specific industry partner implementations.

The project envisions a future state where application of blockchain technology extends beyond use cases in scope as an enabler for digital transformation of the industry. Therefore, the project deliverables must ensure scalability after the project has finished and ensure sustainability of the solutions.

The following diagram depicts the high-level architecture of the three-level blockchain-enabled healthcare system:



Expected key deliverables

Comprehensive project planning and preparation coupled with an agile methodology will enable accelerated delivery and realisation of benefits. At this time, the intention is that all deliverables are public, in order to increase credibility through transparency, one of the core benefits of blockchain itself.

- **Governance.** Formalisation of an independent governance model with equitable representation by all participants for oversight accountability to enable sustainability, and the continuous improvement of the healthcare blockchain framework. This deliverable is framework (not project) governance.
- **Business use cases.** Definition of common requirements and evaluation of blockchain technology benefits for the pharmaceutical value chain and healthcare ecosystem processes. Design of process, system, data and organisational model for each use case. Clearly defined business value and ROI for each use case and an agreed implementation plan based on the use case priority. The use case requirements and benefits evaluation will be completed by around the sixth month of the project. The evaluation serves to focus the delivery of the project and to clearly identify which use cases can benefit from blockchain adoption, and those use cases which at the current time do not provide benefit over existing technologies.
- **Healthcare blockchain standards.** Leveraging existing standards such as Ethereum, Hyperledger Fabric/ Sawtooth or standardisation activities like ISO TC 307 or IEEE BCI and development of complementary standards if required. The focus is on enabling services that directly benefit patients with trusted data available in drug development and the supply chain (e.g. providing data integrity in clinical trials and data transparency for patients where their data could form part of their electronic health records, consent management, trial recruitment, product authentication, provenance, updated electronic safety labelling, recalls, and drug interaction). It also includes evaluation and proposal of standards for integration of medical devices (IoT) and services on the blockchain. The analysis and requirements for new standards will be a major deliverable of the first year of the project (approximately in the first 12 months of the project).
- **Framework and reference implementation.** Definition and implementation of an open-source reference architecture for an industry-wide blockchain network or networks as the basis for application specific solutions such as anti-counterfeiting or clinical trials as specified in the business use cases. The project delivers an operational reference implementation of the solution to validate design and operation. The reference implementation will enable realisation of the prioritised use cases and serve as a foundation for future use cases. Therefore the design will ensure the sustainability of the solution beyond the life of the project.
- **Regulatory, legal & data privacy.** Identification of and compliance with existing and anticipated drug development, manufacturing and distribution regulations, which could be harmonised to benefit patients and strengthen overall security and data integrity. Clarification of intellectual property considerations as well as legality of 'smart contracts'. Compliance with the EU General Data Protection Regulation (EU GDPR)⁷⁴ and country-specific data privacy regulations.
- **Change management.** Includes a methodology adoption or how-to 'handbook' tailored to small, medium or large industry partners. Addresses both technical and organisational components.

Expected impact

The project generated by this topic will generally position the industry as a leader in innovation and serve to improve the overall trust and reputation of participants. Full realisation of the envisioned benefits will require a transformation of many core processes in organisations over several years beyond the life of the project. The project will establish a strong foundation to enable these benefits in accelerated manner. Envisioned long term benefits include:

- Patients will have earlier access to both the medicines they need and information on drug provenance; this will improve overall transparency, and with it trust in and the reputation of the industry. The supply chain will be more secure through anti-counterfeiting measures, building on the solutions designed to fulfil the

⁷⁴ 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, OJ L 119, 4.5.2016, p. 1–88.

Falsified Medicines Directive (FMD). The project will evaluate and define additional potential patient-centric services.

- Permissioned and secure healthcare data sharing will be enabled between patients, healthcare providers, researchers and other stakeholders. Patients will have full control of their health data and be able to join clinical, sensor and behavioural data into a self-sovereign 360 degree health record. Patients will be able to donate data or grant access to their data for a defined / limited time or purpose to research and real world registries in a trusted and anonymous manner. If seeking information on clinical trials, patients will have recommendations made to them based on their health profiles.
- Healthcare providers will use limited resources more efficiently by streamlining clinical trials and eliminating expenses for counterfeit and substandard medicines. Automation of processes and reliability of data will enable significant improvements to the current status quo.
- The pharmaceutical industry will benefit from widely accepted standards and demonstrated actions to ensure the integrity of drug development and distribution to the patient. Accelerated adoption of digital technology will additionally result in efficiencies across the industry with improved transparency, visibility and availability of drugs to the market. It can also better position the industry for new innovative therapies relying on the patient's own cells (chain of identity).
- The applicant consortium will benefit from investments in research programmes and early adoption of innovative solutions.

Applicants should indicate how their proposal will impact the competitiveness and industrial leadership of Europe by, for example engaging suitable SMEs.

Potential synergies with existing consortia

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

Synergies are apparent with existing consortia and the project would continuously strive to leverage existing and emerging advances wherever possible. Examples:

- **MyHealthMyData (MHMD)** (<http://www.myhealthmydata.eu/>) is a Horizon 2020 Research and Innovation Action that aims at fundamentally changing the way sensitive data are shared. MHMD is poised to be the first open biomedical information network centred on the connection between organisations and individuals, encouraging hospitals to start making anonymised data available for open research, while prompting citizens to become the ultimate owners and controllers of their health data.
- The **PhUSE Blockchain project** (http://www.phusewiki.org/wiki/index.php?title=Blockchain_Technology) was started in 2017 by UCB as lead and co-lead with other companies to increase awareness of the new technology as well as a need for an initiative to accelerate the adoption of blockchain in the pharmaceutical and healthcare industries. It includes at least 17 companies (and continues to grow) from pharmaceutical companies, academia, professional organisations, consulting and service companies, vendors, and patient advocate groups. PhUSE is a non-profit organisation which collaborates with the FDA (Food and Drug Administration) and EMA (European Medicines Agency), and allows all participants to share and exchange information freely. The first project consists of writing a white paper to explain the characteristics of blockchain and propose at least two use cases for proof-of-concept. The second project is to start piloting one of the use cases.
- The **EU Blockchain Observatory and Forum** (<https://www.eublockchainforum.eu/>) was launched in February 2018 as a European initiative to accelerate blockchain innovation and the development of the blockchain ecosystem within the EU and so help cement Europe's position as a global leader in this transformative new technology. The mission is to promote blockchain in Europe by mapping existing blockchain initiatives, analysing and reporting on important blockchain themes, promoting blockchain education and knowledge sharing, and holding events to promote debate and discussion

Industry consortium

The industry consortium is composed of the following EFPIA companies:

- Novartis (lead)
- Abbvie
- AstraZeneca
- Bayer
- Janssen
- Novo Nordisk
- Pfizer
- Sanofi
- UCB

Industry participants will provide primarily resources in the form of experts in the areas of:

- clinical trial and drug submission experts; regulatory affairs experts;
- procurement experts experienced in supplier qualification and raw material purchasing;
- pharmaceutical packaging experts including specialists in artwork, anti-counterfeiting, serialisation and product tracking and tracing;
- pharmaceutical manufacturing and supply chain experts including experts in trade compliance, temperature monitoring, personalised medicine logistics;
- quality experts in drug development, manufacturing and distribution;
- IT enterprise, technology and integration architects, blockchain developers, business analysts, project managers;
- product security, information security, cyber security, compliance, data privacy, legal, risk, integrity, environmental, and financial experts.

The industry consortium will leverage its membership or relationships to other pharmaceutical industry associations (distributors, investigators, laboratories, hospitals, pharmacies, payers, governments) and industry/ supply chain associations (such as GS1, IIEEE, ISO, EMVO, EFPIA, GIRP, Medicines for Europe, PGEU, HOPE).

Indicative duration of the action

The indicative duration of the action is 36 months.

Indicative budget

The indicative EFPIA in-kind contribution is EUR 9 680 000.

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

The financial contribution from IMI2 JU is a maximum of EUR 8 330 000.

Future project expansion

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

include additional use cases. Project expansion is only considered in an exceptional case. The preferred approach is for a new, separate project.

Applicant consortium

The applicant consortium will be selected based on submitted short proposals. Given the agile nature of the project in a rapidly evolving environment, it is very important that the consortium covers the scope of the project but does so with a manageable number of organisations/size in order to ensure consistent communications and efficient alignment. The applicant consortia must be ready to 'hit the ground running' in the project without significant ramp-up or on-boarding time.

The applicant consortium must address the objectives and make key contributions to the defined deliverables in synergy with the industry consortium that will join the selected applicant consortium in preparation of the full proposal. It is also expected that the applicant consortium will include a project management capability experienced in the delivery of healthcare industry, multi-disciplinary, multi-company and multi-cultural programmes (ideally with IMI programme experience).

The applicant consortium must have knowledge of the healthcare industry and processes and bring evidence of its capacity to mobilise, as appropriate, the following expertise as part of the consortium:

- patients, patient representatives, and public health institutes and non-governmental agencies (e.g., World Health Organisation);
- universities, research institutions and SMEs: researchers related to pharmaceutical drug development and operations and blockchain and distributed ledger technology;
- healthcare providers (hospitals, pharmacies, payers, governments);
- regulatory agencies: regulatory experts in health industry compliance;
- solution providers of IT technology and system integrators, blockchain developers, project managers, software and technology experts. This could include relevant SMEs.

Applicants should bring a unique value proposition to the project but are also encouraged to leverage existing working groups, standards and solutions. Ideally the applicants have experience in blockchain technology projects and can demonstrate thought leadership with evidence (white papers, viable products, reference projects). There are numerous working groups, projects and standards that must be leveraged to the maximum extent possible (from the healthcare industry and other industries). It is not the intention to 'reinvent the wheel' when existing or developing industry standards or solutions can be leveraged to avoid duplication of effort and redundancy. The principle of this project is to leverage what exists, to complement with standards that need to be defined to enable healthcare with blockchain.

Suggested architecture of the proposal

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

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

The full consortium will define project aspects such as governance, guiding principles and project plan. The architecture below for the full proposal is a suggestion; different innovative project designs are welcome, if properly justified.

There will be an agile/iterative approach to assure a tight integration between the high-level requirements, evolving regulations and the rapidly maturing blockchain technology. It will also adopt a multi-speed approach to apply different timelines for different use cases depending on complexity.

Work package 1 – Business use cases

The goal of this work package will be to define a use case strategy and build up use cases with benefit realisation, and define industry requirements for each use case. There is the potential to have one workstream per group of use cases (e.g. supply chain, clinical development).

Deliverables

- evaluation of **blockchain technology benefits** for pharmaceutical value chain including good lab, good manufacturing, good clinical research and good distribution practices (GLP, GMP, GCP and GDP);
- **use case identification** and user story for each use case;
- **industry requirements** for identified use cases (e.g. counterfeiting, consent management, etc.);
- design of process, system, data and organisational model for each use case;
- clearly defined business value and ROI for each use case and an agreed implementation plan based on the use case priority.

Work package 2 – Healthcare blockchain standards & solutions

The goal of this work package will be to identify existing standards, develop complementary standards if required, develop specifications, and build the solution with identified partners for each use case. This workstream could be split into several subworkstreams for each use case (e.g. supply chain solutions, clinical development solutions).

Deliverables

- **standards**, which includes identification of existing standards for each use case and creation of complementary standard as per need;
- **standards for enabling patient-centric value-adding services**, which include securing the supply chain against counterfeit medicines, but also defining additional areas where patients can directly benefit from trusted data available in the drug supply chain (i.e. provenance, shelf-life expiration notifications, updated electronic safety labelling, recalls, and drug interaction);
- **standards** for providing data integrity in clinical trials and data transparency for patients where their data could form part of their electronic health records;
- **standards** for other solutions as per defined and agreed use cases.

Work Package 3 – Architecture framework & healthcare foundation

The goal of this work package will be to provide an architecture framework, and design and develop the blockchain healthcare foundations. This may result in a healthcare private blockchain network to be installed by healthcare companies.

Deliverables

- development of a **framework and a roadmap for blockchain-enablement** where there are incentives and clear benefits for patients and partners to be realised, while minimising barriers for adoption;
- evaluation and proposal of standards for **integration of medical devices** (IoT) and services on the blockchain;
- definition and implementation of an **open-source based foundation** for an industry-wide blockchain network or networks as the basis for application specific solutions such as anti-counterfeiting, consent management or others.

Work Package 4 – Governance, operating model

The goals of this work package will be to formalise an independent governance model enabling sustainability, continuous improvement and equitable representation by all key stakeholders.

Deliverables

- formalisation of an independent governance model enabling sustainability, continuous improvement and equitable representation by all industry participants.

Work Package 5 – Regulatory, legal & data privacy framework

The goals of this work package will be to define the regulation, legal and data privacy framework for healthcare blockchain.

Deliverables

- identification of and compliance with **existing and anticipated drug development, manufacturing and distribution regulations** which could be harmonised to benefit patients and strengthen overall security and data integrity.

Work Package 6 – Culture & adoption

The goals of this work package will be to drive a shift in mindset (e.g. 'distributed ledger') and ensure fast adoption.

Deliverables

- collaboration platform;
- development of a methodology for blockchain technology adoption or how-to 'handbook' tailored to small, medium or large industry partners;
- marketing campaigns and public healthcare blockchain events.

Regulatory strategy

As indicated above, the consortium is expected to have a strategy for the translation of the relevant project outputs into regulatory, clinical and healthcare practice. A plan for interactions with regulatory agencies/health technology assessment bodies with relevant milestones and sufficient resources should be proposed to ensure that advice can be obtained on the proposed methods for novel methodologies for drug development⁷⁵.

Sustainability

A draft plan for aspects related to sustainability, facilitating continuation beyond the duration of the project should be provided in the short proposal and further detailed in the full proposal.

Dissemination

A draft 'plan for the dissemination and exploitation of the project's results' should be provided in the short proposal and further detailed in the full proposal.

Data management plan

A draft data management plan (DMP) outlining how research data will be handled and made available during the project, and after it is completed, should be provided in the short proposal and further detailed as part of the full proposal.⁷⁶

⁷⁵ See <http://europa.eu/!ww84Xw>

⁷⁶ See http://ec.europa.eu/research/participants/data/ref/h2020/grants_manual/hi/oa_pilot/h2020-hi-oa-data-mgt_en.pdf

Topic 3: Microenvironment imposed signatures in tissue and liquid biopsies in immune-mediated diseases

Topic details

Topic code	IMI2-2018-15-03
Action type	Research and Innovation Action (RIA)
Submission and evaluation process	2 stages

Specific challenges to be addressed

Unmet medical need:

Biological therapies have provided significant therapeutic benefit to patients with immuno-inflammatory diseases, but many patients fail to respond completely and efficacy is lost in many patients over time. The tissue microenvironment interacts with and influences immune cells to form functional cellular niches that play a role not only in the onset and progression of disease but also in the response to therapy. Inaccessible tissue and invasive biopsy procedures have prevented in-depth interrogation of these microenvironments, resulting in a major gap in our basic understanding of immune cell action mechanisms. Therefore, how they interact with each other and their environment, and how they can be monitored and pharmacologically manipulated to better control disease, remain elusive.

This topic aims to profile tissue-specific microenvironments to improve knowledge of pathophysiology of various immune-mediated diseases (such as inflammatory bowel disease: Crohn's disease and ulcerative colitis; and skin related diseases e.g. atopic dermatitis, cutaneous lupus, psoriasis) and identify signatures that can be correlated in body fluids (i.e. blood), 'circulating signatures', to inform on disease progression and to monitor treatment.

Challenges for medicines development:

Medicine development strategies that are based on reliable organ and tissue specific signatures that reflect the disease-specific tissue microenvironment have the potential to tailor treatment to patient-specific needs and have the potential to be transformative. Such strategies are currently unavailable and therefore reliable and validated signatures have to be established.

Scientific opportunities:

Understanding the role of the crosstalk of tissue and immune system for progression/remission of immune diseases will uncover disease-relevant, actionable parameters in tissue. Correlating these signatures with 'circulating signatures' in blood ('liquid biopsies') will improve and enable human target validation and patient stratification, as well as develop more effective and safer therapies.

Need and opportunity for public-private collaborative research

The proposed work with a focus on inflammatory bowel disease and skin diseases, will advance our understanding and help accelerate the development of personalised drug treatments for patients. However, in immune mediated diseases where the underlying science is so complex, no critical mass exists to make significant progress. The magnitude of the challenges to be addressed by the successful consortium requires a large international scientific collaborative project that includes: i) the clinical and technological excellence in academia; ii) the clinical development expertise of pharmaceutical industry; iii) technological expertise of small and medium-sized enterprises (SMEs) and; iv) advice on signatures validation and adoption for clinical trials from regulatory authorities, coupled with a critical amount of high quality data. Such collaboration of a consortium of pharmaceutical companies and public institutions will enable evaluation of both existing and novel technologies to identify and validate tissue-specific signatures. The cross-industry nature of the collaboration will allow consorted validation of such signatures to enable regulatory suitability and adoption into future trials. Advice from regulatory authorities, such as the U.S. Food and Drug Administration (FDA) and/or European Medicines Agency (EMA), will be sought to facilitate regulatory suitability of identified signature(s) for future clinical trials and medicine development.

To achieve significant impact and drive a timely change in the field, it is necessary to kick-start the process by building on all available assets and learnings via a combination of key resources globally and mobilising stakeholders in EU Member States and H2020 Associated Countries and potentially beyond.

Scope

Overall objective of the project

The ultimate goal to be achieved by the consortium is to identify key organ and disease-specific signatures with correlates in body fluids that may predict disease, track progression and/or therapeutic response. These signatures will enable tailored treatment pathways to the disease mechanism and ultimately provide superior therapeutic benefit to patients.

Scope for the project

In order to achieve the ambitious overall objective, a set of specific objectives should be addressed by the applicants.

1. Identify and evolve the state-of-the-art novel technologies to interrogate both immune and non-immune cells in target tissues at single cell level to better understand pathways regulating disease and to define tissue/disease-specific signatures, which can be correlated in peripheral blood. The technologies for the identified signature need to be adaptable and of sufficient robustness for use in clinical trial.
2. Evaluate above technologies in existing clinical retrospective cohorts as well as samples from ongoing clinical trials made accessible by both academic and industry partners.
3. Perform a bespoke, enabling clinical study to verify signatures. This will be a non-interventional prospective study, run as a collaborative effort between industry and academic partners.

Expected key deliverables

With the aim of profiling tissue-specific microenvironments and identifying circulating signatures necessary to inform disease progression and monitor treatment, the following key deliverables are expected:

- identification and optimisation of promising technologies and/or platforms suitable to profile cells in a disease-specific tissue microenvironment. A non-exhaustive list of examples of such technologies can include but is not limited to: single cell sequencing, multiplex immunohistochemistry, immunophenotyping, immune repertoire and 'omic' approaches, such as metabolomics, autoantibody profiling, miRNA profiling, epigenomics, microbiomics, transcriptomics, etc.;
- generation of both tissue and body fluid (e.g. blood) profiles using above outlined technologies using existing clinical material, including longitudinal samples, available from biobanks, academic partners and/or industry partners. In addition to existing clinical samples (if applicable), industry partners are expected to provide clinical material and clinical parameters from prospective studies;
- evaluation of comparability of tissue profiles between fresh and stored (e.g. fresh frozen, formalin-fixed paraffin-embedded (FFPE)) samples;
- mapping of tissue profiles against profiles from body fluids (e.g. blood) and clinical parameters to identify specific and robust liquid signatures representative of disease tissue microenvironment;
- validation of identified signature(s) in both tissue and body fluid in longitudinal patient cohorts made available from prospective clinical trials performed by industry partners. These include, but are not limited to, samples from placebo cohort and baseline samples;
- correlation of clinical profiles and parameters to determine the stability of the signature and/or the ability of the signature to track clinically relevant changes of disease progression and/or response to treatment;
- generation of raw data repositories with access for all consortium partners;
- development of software and bioinformatics packages for full data integration and analysis;
- design and development of a database/IT infrastructure allowing for query of data sets and long-term housing of data within the consortium. Design and execution of a high-quality, multi-centre, non-interventional, longitudinal study to verify the identified tissue and blood signature(s) in at least one disease (gut or skin related) involving both academic and industry partners;

- further confirmation of signatures by analysing samples from independent prospective clinical trials in complementary indications, performed by the EFPIA industry partners.

Expected impact

In-depth characterisation of the tissue microenvironment will provide better disease understanding, which represents a significant advance in the assessment of both immune and non-immune markers in relevant diseases. The signatures, but potentially also the relevant (novel) underlying technology, will advance clinical monitoring in both clinical trials and standard patient care. These tools will allow earlier detection of disease progression or identify patients at risk and therefore will allow earlier or more tailored treatment. In clinical trials, these less invasive tools will allow better or earlier detection of treatment response, but may also allow better patient stratification and prediction of treatment response. The proposed non-interventional clinical study will allow verification of signatures and facilitate the implementation of these signatures as decision-making tools for other clinical studies. The less invasive nature of the detection of these signatures is highly attractive, as it will significantly reduce the burden to patients in clinical trials and can complement diagnosis.

The multi-partner, multi-stakeholder and cross-sector approach of this consortium will also allow for a more standardised future adoption of these signatures across industry and pave the way for regulatory approval of improved, clinically relevant tools to monitor disease progression.

Applicants should indicate how their proposal will impact the competitiveness and industrial leadership of Europe by, for example engaging suitable SMEs. In particular, the inclusion of SMEs into the consortium will maximise the opportunity for suitable technology for the identification of disease-specific signatures of the tissue microenvironment to be identified and, more importantly, ultimately implemented in multi-centre clinical trial settings under good laboratory practice (GLP) conditions.

Potential synergies with existing Consortia

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

The following completed, ongoing or forthcoming initiatives (the list is not exhaustive) have been identified and could be considered by the applicants.

IMI projects:

- **BTCURE** (<http://btcure.eu/>)
- **RTCURE** (http://cordis.europa.eu/project/rcn/211964_en.html)
- **PRECISESADS** (<http://www.precisesads.eu/>)

Please note that during the project implementation phase the applicants could also consider other potential knowledge generated by the forthcoming projects under IMI2 JU in the area of genome-environment interactions in inflammatory skin disease (https://www.imi.europa.eu/sites/default/files/uploads/documents/apply-for-funding/open-calls/1.%20IMI2_C13_TOPICS%20TEXT_EN.pdf) and targeted immune intervention for the management of non-response and relapse (https://www.imi.europa.eu/sites/default/files/uploads/documents/apply-for-funding/call-documents/imi2/IMI2%20CALL%2014%20TOPICS%20TEXT_EN.PDF).

Other European and international initiatives:

- Human Immunology Project Consortium (HIPC) (<https://www.immuneprofiling.org/hipc/page/show>),
- Inflammatory Bowel Disease Biomarkers Programme (IBD-BIOM) (<http://www.ibdbiom.eu/>),
- Inflammatory Bowel Disease Characterisation by a multimodal integrated biomarker study (IBD-CHARACTER) (https://cordis.europa.eu/project/rcn/106191_en.html),
- A System Medicine Approach to Chronic Inflammatory Disease (SYSCID) (<http://syscid.eu/>),
- Biological Therapy Cycles Towards Tailored, Needs-driven, Safer and Cost-effective Management of Crohn's Disease (BIOCYCLE) (<https://biocycle-project.eu/>),

- SLE: Accelerating Medicines Partnership (AMP) (<https://www.nih.gov/research-training/accelerating-medicines-partnership-amp>),
- Relapses prevention in chronic autoimmune disease: common mechanisms and co-morbidities (RELENT) (<https://www.relent.eu/>),
- Lupus Europe (<http://www.lupus-europe.org/>),
- Systems medicine of chronic Inflammatory Bowel Disease (Sysmed IBD) (<https://www.sysmedibd.eu/>),
 - A comprehensive transdermal therapy concept for non-healing wounds and other skin disorders (DERMADROP) (https://cordis.europa.eu/project/rcn/197053_en.html),
- Integral cell-biology platform for the development of the first effective treatment of radiodermatitis (SkinXCare) (https://cordis.europa.eu/project/rcn/206799_en.html),
- Neuron/mast cell interactions in skin diseases (NEMESIS) (https://cordis.europa.eu/project/rcn/211014_en.html).

Industry consortium

The industry consortium is composed of the following EFPIA companies:

- GSK (lead)
- Sanofi (co-lead)
- Eli Lilly
- Novartis
- Pfizer

The industry consortium will provide bio-samples (e.g. blood, urine, tissue biopsies) and patient-characterised data sets (deep-clinical phenotyping) from various prospective clinical trials (baseline, active comparator and/or placebo) for IBD including ulcerative colitis and Crohn's disease and skin disease, including atopic dermatitis, cutaneous lupus and psoriasis. Furthermore, industry partners will contribute activities related to these samples as in-kind contribution. Note that there will be a difference in design of these clinical trials, and the specificities of the available bio-samples will be confirmed during the full proposal preparation. It is also expected that longitudinal analysis of these bio-samples may be limited in comparison to bio-samples from cohort available to public partners due to the relatively short duration of most clinical trials. In addition, the availability and disease type of the bio-samples obtained from future prospective clinical trials performed by the industry consortium carries some attrition risk due to discontinuation of development activities, incompatibility of informed consent for certain profiling and analyses and/or legal considerations.

The activities related to samples or data generated in the context of the aforementioned prospective clinical studies sponsored by the respective company will only be reported as in-kind provided that i) the cost to generate and provide relevant samples or data is incurred during the term of such Action (project), ii) the relevant activities are described in the Full Proposal and Grant Agreement's Description of Action, iii) and that these samples and data are necessary to achieve the objectives of the Action.

As a non-exhaustive list of examples such in-kind costs incurred may include full time equivalent (FTEs), clinical research organisation (CRO) costs, lab/assay costs, investigator fees, per each company's usual cost accounting practice.

The industry consortium may contribute with technology platforms for bio-sample analysis to complement technologies provided by the public participants.

The industry consortium will include informatics and systems biology experts and clinical statisticians. Immunology expertise to contribute to the validation of liquid signatures will be made available, as well as biomarker expertise to support validation activities and assay development implementation into regulated environment e.g. GLP.

Clinical expertise will be provided to design and follow the verification trial.

Indicative duration of the action

The indicative duration of the action is 60 months.

Future project expansion

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

In the context of this topic, it is envisaged that data generated by the consortium in the early stages will provide key information that may warrant applying for a project expansion to allow inclusion of additional clinical trials that will enable verification of signature in diseases that are outside the current scope. Such extension could also include cross-disease comparison and/or even interventional clinical studies with existing or new therapeutics.

Indicative budget

The indicative EFPIA in-kind contribution is EUR 15 500 000.

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.

The financial contribution from IMI2 is a maximum of EUR 15 500 000.

Applicant consortium

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

- basic and clinical immunology, which relates to the following indications: inflammatory bowel disease (Crohn's disease and ulcerative colitis) and skin related disease e.g. atopic dermatitis, cutaneous lupus and psoriasis;
- expertise in clinical care of patients with inflammatory bowel disease or skin diseases;
- demonstrated access (e.g. patient consent, waiver consent, etc.) to resources of existing longitudinal, clinical bio-specimens and/or samples from biobanks as well as from the ongoing clinical studies related to the above conditions, to enable evaluation of existing and novel technologies as outlined in the key deliverables section. Strong expertise and proven delivery of technologies, as outlined in the key deliverables section, that are suitable to characterise the tissue microenvironment. Such technologies should allow for an identified signature to be readily and feasibly implemented in clinical trial settings i.e. GLP conditions. In particular, single cell profiling technologies are of interest;
- consequently, partners providing medical record-based information as project background must be mindful that they, as background contributor, should have sufficient title to said background to authorise its use within the project pursuant to the IMI2 JU IP and legal framework. A similar approach should also be applied in case of additional information that may be introduced after the start of the project but which is not listed as project background at start date;
- proven capability to deliver analytical platforms to facilitate the above-mentioned advanced analytical approaches for a range of scientific/medical and analytical communities;
- proven experience in managing and coordinating a multi-centre, multi-node, clinical-research, data-generation activity of comparable scope;
- expertise in clinical study design;
- essential experience in dealing with the legal and ethical challenges associated with integrating multi-centre patient-derived data, as well as physical data-processing and data management practices (privacy, security);
- essential experience in operationalising large multi-centre clinical trials.

In addition to academic groups, SMEs with relevant proven expertise, relevant technology and proven record of delivery of peer-reviewed data sets are encouraged to participate in the applicant consortium. SMEs can be of great benefit to IMI projects and strengthen the competitiveness and industrial leadership of Europe. Their

involvement might offer a complementary perspective to industry and academia, and strengthen the long-term impact of the project. For these reasons, applicants should consider engaging SMEs throughout the proposal. Under this topic, the contribution of SMEs would be considered especially beneficial in technologies to characterise the tissue microenvironment or body fluids, advanced analytical approaches and data management practices.

In addition, the applicant consortium is expected to include resources for project administration, management and communication.

At the full proposal stage, the pharmaceutical companies with other industry partners are expected to bring expertise in novel or existing technologies to characterise tissue, blood and other matrices. They will provide clinical samples, including clinical profiles and parameters, from prospective clinical trials that will be used for identification and validation of signatures of the tissue microenvironment. In addition, they can also provide support by provision of specific technology, bioinformatics analysis and/or clinical trial expertise.

The consortium will engage with regulatory authorities, such as the FDA and EMA to seek advice on utilisation and validation of identified signature(s) for the clinical trial, as described in work package 6, and for adoption by other future clinical studies outside this proposal.

The topic is focused on technology evaluation followed by validation of signatures in a non-interventional trial. Engagement with and input from patient groups will be sought later in the process when validated technologies and signatures have been established.

The size of the consortium and expertise provided within it should be proportionate to achieve all the objectives of the topic.

Suggested architecture of the full proposal

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

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

All beneficiaries are encouraged to discuss the project architecture and a plan for aspects related to sustainability, facilitating continuation beyond the duration of the project, should also be proposed.

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

Work Package 1 – Project management

This work package will contain details of the proposed structure for project management to track progress of deliverables and individual work packages. The goal of this work package is the overall project coordination and communication, including:

- define work expectations of different work streams, deliverables, dates and activities and review progress regarding adherence to budget, timelines and quality;
- ensure legal and contractual management;
- ensure the set-up of joint governance structure;
- ensure appropriate communication/dissemination within the consortium and with the external scientific community and the public;
- ensure interaction with regulatory bodies, as necessary (e.g. for qualification process/advice of identified signatures);

- develop and manage communication via a web portal and other social media tools with a repository of key documents;
- quality assessment of documents;
- ensure that key cross-functional partners are engaged;
- define project interdependencies, stakeholders and risks;
- ensure ethics issues management.
- development of a sustainability plan including a strategy for access to data beyond the duration of the consortium.

Work Package 2 – Identification and characterisation of tissue specific signatures using new and existing technologies

The goals of this work package are to characterise the tissue microenvironment and accessible matrices, such as blood, using multiple technologies, both novel and existing. Selected technologies will be evaluated in a non-interventional clinical study (work package 6) and will need to be GLP compliant. Signatures found in blood or other matrices will be correlated with signatures found in the tissue (not necessarily identified by the same technology). Technologies to be considered, but not limited to, are:

- single cell sequencing or profiling of isolated cell types in blood and tissue;
- multiplex analysis FFPE tissue;
- 'omics' analysis.

Work Package 3 – Utilisation and validation of disruptive liquid biopsy methodology

The goal of this work package is to evaluate disruptive liquid biopsy technologies, such as ultrasound-induced liquid biopsies, in a translational setting to establish specific diseases signatures in blood. These technologies and subsequent qualification of pre-analytical procedures will evaluate whether the tissue microenvironment can release soluble mediators into the blood stream that can be measured and used as a signature of the tissue microenvironment.

Work Package 4 – Bioinformatics approaches

This work package will describe the bioinformatics platforms and analyses strategies that will be built and used to analyse and correlate the data from work packages 2 and 3. These platforms and strategies will be defined at stage 2 of the proposal, but will include: the generation of data repositories for raw data with access for all consortium partners; development of software and bioinformatics packages for full data integration and analysis; and the design and implementation of a database and IT infrastructure to allow for query of data sets and long-term housing of data within the consortium.

Work Package 5 – Validation of identified signatures

The goal of this work package is to validate signatures that are identified in work packages 2 and 3 using longitudinal biopsy and blood (or other matrices) patient samples that are made available from consortium partners as part of ongoing prospective clinical trials or ongoing clinical monitoring.

Work Package 6 – Verification of identified signatures in a clinical multi-partner study

The goal of this work package is an extension of work package 5 by designing and delivering a non-interventional, enabling clinical trial to validate the identified signatures to better understand disease progression.

It is expected that the pharmaceutical partners will provide key input in the regulatory framework, trial design and clinical protocol etc., while the academic partners will operationalise the study. The final design of the study and selection of patient populations is to be decided by the consortium and will commensurate with the available budget, but aims to recruit in excess of 500 participants (for a single disease). The trial will include multiple centres and include patients with different degrees of disease severity. Patients will receive standard of care requiring a sufficient number of patients to be recruited across different treatment regimens and will require follow up on disease progression of at least one year, with liquid samples taken at multiple time points and

biopsies at both baseline and one year follow up. Although this will be a non-interventional study, patient reported outcomes and clinically relevant disease measurements will need to be included. This will enable any identified signatures to be rapidly adopted into future, interventional, clinical trials and help with better monitoring of disease progression and/or treatment response.

Industry contribution:

Key contributions from industry partners will include:

- bio-informatics expertise (work package 4);
- provision of clinical trial bio-specimens and/or corresponding analytical data, including clinical parameters. These include bio-specimens from new, prospective clinical trials (work package 5), but can also include existing samples (work package 2);
- clinical trial development expertise (work package 6).

Expected applicant consortium contribution:

Key contributions from applicants are expected to be:

- technologies to characterise tissue and easily accessible matrices, such as blood (work package 2 and 3);
- provision of bio-specimens to aid in technology evaluation (work packages 2, 3 and 5);
- bioinformatics expertise (work package 4), including input into and implementation of software and bioinformatics packages for deep profiling, full data integration and analysis;
- provision of technologies to allow implementation of identified signatures for measurement in GLP environments and allow validation of identified signatures (work package 5 and 6);
- operationalisation of the multi-centre, non-interventional clinical study to include recruitment of in excess of 500 participants for a single disease (work package 6).

Topic 4: Emerging translational safety technologies and tools for interrogating human immuno-biology

Topic details

Topic code	IMI2-2018-15-04
Action type	Research and Innovation Action (RIA)
Submission and evaluation process	2 stages

Specific challenges to be addressed

There is an urgent need to better understand inherent risks of innovative therapeutics for immuno-oncology and immuno-inflammatory disease indications including cytokine release syndrome, infection, malignancy and autoimmunity during early (non-clinical) stages of drug development. The toxicities induced by immunomodulatory therapeutics in patients are often not detected in the young healthy animal models that are routinely used for toxicology studies either due the lack of expression of appropriate drug targets/pathways or due to differences in drug target genetics, expression and functions between animal models and the intended patient populations. Thus, innovative translational safety assessment tools, technologies, models and resources are needed to facilitate the development of novel immunomodulatory drugs (either immunostimulatory or immunosuppressive). Improving the predictivity of non-clinical models will help deliver safer efficacious immunomodulatory medicines to patients and contribute to the principles of the 3Rs (i.e replacement, reduction, and refinement of the use of animals for research). The topic requires a strategic consortium that will enable the sharing of experience from regulators, academia, and pharma industry, in fast evolving immune cell phenotyping technologies, complex *in vitro* model development, and characterisation of engineered and disease state animal models, as well as facilitating access to extensive immune cell and tissue biobanks (including patient-derived material). Immunomodulatory therapeutic modes of action (spanning both oncology and non-oncology therapeutic indications) for which there is existing non-clinical and clinical safety experience within the pharma industry, academia and health authorities, provide a powerful framework within which the utility of innovative non-clinical models and endpoints can be assessed for potential use in future Investigational New Drug (IND)/Clinical Trial Application (CTA)-enabling safety assessment packages.

Need and opportunity for public-private collaborative research

This topic focuses on a defined subset of immunomodulatory therapeutic modes of action (spanning both oncology and non-oncology therapeutic indications) for which there is existing non-clinical and clinical safety experience within the pharma industry, academia and health authorities. The assessment of the potential utility of integrating safety data derived from innovative non-clinical animal models and/or human *in vitro* immune cellular system into IND/CTA is unlikely to be within the scope of investment and capabilities for any one company or organisation, but collaborative efforts in a public-private partnership are most likely to harness all the skills and expertise required. Such non-clinical models and endpoints will need to be customised for specific immunomodulatory therapeutic modes of action, disease indications and/or anticipated toxicities. The importance of early engagement and alignment plans with a broad range of public and private stakeholders is exemplified by the themes discussed in several recent workshops and publications on the safety assessment of innovative immunomodulatory therapeutics (<https://www.healio.com/cardiology/hf-transplantation/news/print/cardiology-today/%7B0387a9d3-2eb8-4ec8-a9d5-0b32f59fe1fa%7D/fda-workshop-focuses-on-cancer-immunotherapy-associated-myocarditis-other-cv-toxicities>; <http://www.bionow.co.uk/events/safetyofimmunecheckpointinhibitors.aspx> [1][2][3]).

Scope

This topic aims to establish a public-private consortium that will enhance translational safety assessment approaches for immunomodulatory therapeutics (spanning oncology and non-oncology indications) through development and validation of innovative non-clinical tools and technologies, supported by access to *in vitro*, *ex vivo* and *in vivo* model-derived immune cell and tissue resources, with an emphasis on evaluating human-relevance. Potential toxicities induced by immunomodulatory therapeutics in patients are often not evident in traditional animal models due to lack of expression of appropriate targets, pathways and/or differential expression/functions versus intended patient populations (e.g. species differences in immune cell repertoire and functions including checkpoints and MHC/peptide complex formation). Patient-derived and advanced animal models should thus enable a better understanding of the interplay between drug target and disease state-associated immune cell repertoires.

At present, *in vitro* human immune cell assays currently used to assess potential effects of immunomodulatory therapeutic agents on functional endpoints such as cytokine release or T cell activation are typically derived from healthy animals and human donors. Thus, there is a need to more accurately model the complex signaling interactions between multiple immune cells in both healthy and disease states (e.g. tumor microenvironment). Therefore the generation of comparative (cross-species) molecular, biochemical, cellular immuno-biology resources coupled to functional and phenotypic outcomes should provide better definition of limitations in the translatability of *in vivo* and *in vitro* test systems to patients and guide optimal non-clinical safety assessment strategies based on therapeutic target, modality, disease indication(s) and patient susceptibility factors (e.g. genotype; biomarkers of immune memory).

Moreover, investing in novel human relevant immune-competent microphysiological systems to assess risks associated with immunomodulatory drugs (e.g. immune-related adverse events, infection, malignancy) will contribute to the effort of reducing animal use while improving predictivity of preclinical models.

The following objectives are within the scope of this topic:

1. development of innovative comparative (cross-species) *in situ* and *ex vivo* molecular, biochemical tools and cellular profiling of immune cells (including patient-derived clinical samples) and association with functional/phenotypic endpoints to enable:
 - enhanced understanding of therapeutic target and pathway biology,
 - enhanced pharmacological and toxicological mechanistic insight and biomarker identification supporting therapeutic index determination for drug candidates and drug modalities,
 - identification of novel endpoints/biomarkers to help support safe starting dose selection for first in human studies e.g. determination of minimum pharmacologically active dose (mPAD) and minimum anticipated biological effect level (MABEL);
2. establishment, refinement and validation of non-clinical tools and models to enable the development of novel classes of immunomodulatory medicines supporting *in vitro-in vivo* and cross-species translation:
 - comparative assessment of performance of established human *in vitro* immune cell assays (e.g. cytokine release assays; T cell activation and target cell interaction assays) based on healthy volunteer versus patient-derived cells representing specific disease states,
 - development and validation of human immune-competent organotypic and microphysiological systems for efficacy and safety profiling of immunomodulatory drugs (including back translation of clinical findings),
 - development and validation of animal models (e.g. humanised mice, genetically engineered animal models, disease models) as tools for efficacy and safety assessment of immunomodulatory drugs (including refined models to predict risk of infection / malignancy / immune-related adverse events),
 - deployment of computational biology approaches for assessment and integration of large multivariate immuno-biology datasets (e.g. phenotypic-anchoring of molecular, biochemical and cellular endpoints derived from both non-clinical models and clinical trials) to reveal novel immune-biology mechanisms and translational biomarkers.

Given the significant technical and logistical challenges associated with sourcing patient-derived samples to support customised safety assessment studies, the topic will also aim to establish a network to facilitate sourcing of human-derived immune cell and tissue samples via centres of excellence for specific disease areas (patient organisations / medtech / academic partners).

Expected key deliverables

- Prioritisation of immunomodulatory therapeutic modes of action (MoA) (including immuno-oncology and immuno-inflammatory disease indications) for which there is extensive non-clinical and clinical safety experience but suboptimal prediction of human toxicities based on input from regulators.
- Development/evaluation of innovative molecular and cellular immunophenotyping biomarkers across conventional toxicology models, 'engineered' animal models, and human *in vitro* models. Provide enhanced molecular and cellular biomarkers for determination of therapeutic index (TI) and first-in-human (FIH) maximum recommended starting dose (MRSD). Benchmark biomarker performance versus patient-derived samples and assess utility for determination of minimum pharmacologically active dose (mPAD) and minimum anticipated biological effect level (MABEL).
- Development/evaluation of human *in vitro* systems (healthy donor- and/or patient-derived) and 'engineered' animal models that are customised for specific therapeutic MoA and patient-relevant cell types/tissue microenvironments in order to recapitulate target engagement, pharmacodynamics and clinically-relevant toxicity phenotypes.
- Leverage consortium approach to enable sharing of experience, tools, models, biobanked samples and databases between regulators, academia and pharma industry (contributing to the principles of the 3Rs).
- Establishment of a network to facilitate sourcing of human-derived immune cell and tissue samples for specific disease areas based on input from patient organisations, medical technology companies and academic centres of excellence.
- Development of customised non-clinical safety assessment strategies (e.g. human *in vitro* / *ex vivo* models and/or engineered animal models) for immunomodulatory therapeutics based on therapeutic target, modality, disease indication(s), and clinical safety experience; aligned with regulatory expectations.

Expected impact

The action generated by this topic will ultimately help deliver safer medicines to patients via:

- provision of new tools and models to enable a better understanding of the inherent safety risks of immunomodulatory therapeutics during early (non-clinical) stages of drug development;
- improvement of drug development processes and regulatory assessments for immunomodulatory therapeutics through the characterisation of innovative immune-biology models and biomarkers that complement and enhance existing non-clinical safety assessment approaches;
- better definition of limitations in the translatability of non-clinical test systems to patients, which will enable the most appropriate and efficient combinations of test systems to be used for future safety assessment of immunomodulatory therapeutics, and will also contribute to the principles of the 3Rs.

Small and medium-sized enterprises (SMEs) can be of great benefit to IMI2 JU projects. Their involvement in the action might offer a complementary perspective to industry and academia, and help deliver the long-term impact of the project. Therefore, applicants should indicate how their proposals will impact and strengthen the competitiveness and industrial leadership of Europe by, for example, engaging suitable SMEs.

Potential synergies with existing consortia

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

In particular, the action generated by this topic should, among others, consider initiatives such as:

- Collaborative Network For Immunological Safety Research in Minipigs (CONFIRM) Initiative (<https://minipigs.dk/knowledge-base/the-confirm-initiative/>)
- BioSafe Expert Working Group on improving translational value of *in vitro* and animal models for assessing the pharmacology and toxicology of ImmunoOncology therapeutics (<https://www.bio.org/events/biosafe-meeting-agenda>)
- IMI2 Call 14 Topic 2 'Non-invasive molecular imaging of immune cells' (https://www.imi.europa.eu/sites/default/files/uploads/documents/apply-for-funding/call-documents/imi2/IMI2%20CALL%2014%20TOPICS%20TEXT_EN.PDF).
- MIROCALS: Efficacy and safety of low-dose IL-2 (Id-IL-2) as a Treg enhancer for anti-neuroinflammatory therapy in newly diagnosed Amyotrophic Lateral Sclerosis (ALS) patients (<http://www.mirocals.eu/>)
- SO-CMA: Improving the safety of oral immunotherapy for cow's milk allergy in children (https://cordis.europa.eu/project/rcn/195347_en.html)
- DermalTherapy: Membrane fusion mediated dermal allergy immunotherapy (https://cordis.europa.eu/project/rcn/196982_en.html)
- SAFEIMMUNOSUPPRESS: Development of immunosuppressive treatments with better safety (https://cordis.europa.eu/project/rcn/200182_en.html)
- APERIM: Advanced bioinformatics for personalised cancer immunotherapy (<http://aperim.eu/>)

Industry consortium

The industry consortium is composed of the following EFPIA partners:

- Novartis (lead)
- Roche (co-lead)
- Bluebirdbio
- Boehringer-Ingelheim
- Covance
- MerckSerono
- Sanofi
- Servier
- Transgene AG

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

- JDRF

The industry consortium will include expertise in *in vitro* and *in vivo* safety assessment models and biomarkers and will contribute mainly in the form of:

- design and deployment of prospective *in vitro* and *in vivo* studies; provision of historical safety-related *in vivo* phenotypic data for defined therapeutic modes of action (e.g. discontinued development compounds; marketed compounds); *in silico* prediction of immunomodulatory drug-related adverse events;
- provision of advanced technology platforms and bioinformatic support for cross-species molecular, biochemical and cellular phenotyping of immune cells e.g. spatial molecular profiling of RNA/proteins/metabolites; integrated transcriptomic and epigenomic profiling of immune cell subsets

enriched by flow cytometry and/or at single cell resolution; mass cytometry characterisation of signalling pathways;

- provision of human blood- and tissue- samples to support deployment of advanced immune cell phenotyping technologies and/or *in vitro* model development (baseline, antigen-challenged, pharmacologically-stimulated, disease states);
- emerging human-centric *ex-vivo* / *in vitro* technologies (patient-derived and healthy volunteer-derived) will be evaluated and/or further refined for their potential to recapitulate *in vivo* human immune biology (e.g. *in vitro* modelling of human immune responses including impact of genetic variants and immunogenicity; 3-D bioprinting and microfluidic technologies, including organ-on-a-chip or hollow-fiber systems and spheroid/organoid modelling, to enable derivation of complex organotypic and microphysiologic systems.

Indicative duration of the action

The indicative duration of the action is 72 months.

Indicative budget

The indicative industry in-kind contribution is EUR 11 000 000.

This contribution comprises an indicative EFPIA in-kind contribution of EUR 10 895 000 and an indicative IMI2 JU Associated Partners in-kind contribution of EUR 105 000.

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

The financial contribution from IMI2 JU is a maximum of EUR 11 000 000.

Applicant consortium

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

- regulatory expertise (either as project beneficiary or member of a Regulatory Advisory Board of the project) on selection of immunomodulatory therapeutic case studies for assay/model validation and for refining criteria used to make future project decisions e.g. validation using existing examples of discontinued compounds based on clinical evidence/outcomes. Regulators from global health authorities will contribute to the selection of representative immunomodulatory therapeutic modes of action for which there is perceived to be an opportunity to enhance translational safety assessment;
- expertise in customised/innovative immune cell assay/model/bioinformatics development;
- expertise in innovative technology platforms for molecular, biochemical and cellular phenotyping of immune cells;
- provision of human blood- and tissue- samples to support deployment of advanced immune cell phenotyping technologies and/or *in vitro* model development;
- ability to develop *ex-vivo* / *in vitro* technologies for recapitulating *in vivo* human immune-biology;
- given the significant technical and logistical challenges associated with sourcing patient-derived samples to support customised safety assessment studies, significant experience in the establishment of a network to facilitate sourcing of human-derived immune cell and tissue samples via academic and clinical centres of excellence for specific disease areas that may include engagement of relevant patient organisations.

In addition to academic groups, relevant SMEs with relevant proven expertise are encouraged to participate in the applicant consortium. SMEs can be of great benefit to IMI projects and, inter-alia strengthen the competitiveness and industrial leadership of Europe. Their involvement might offer a complementary perspective to industry and academia, and strengthen the long-term impact of the project. For these reasons, applicants should consider engaging SMEs throughout the proposal. Under this topic, the contribution of

SMEs would be considered especially beneficial in the provision of innovative, engineered animal models and/or *in vitro* models that mimic human immuno-biology.

The size of the consortium should be proportionate to the objectives of the topic.

Suggested architecture of the full proposal

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

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

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

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

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

Work package 1 – Management, coordination, dissemination and sustainability

The goals of this work package will be as follows:

- overall coordination;
- liaise with regulatory advisors to establish a framework for selection of immunomodulatory therapeutic modes of action that will be assessed using new models and biomarkers during the project. The selection of specific therapeutic modes of action / drugs for evaluation in innovative non-clinical models will be managed via a face-to-face full consortium meeting (including regulatory advisory board input) during the first few months of the active project timeline (i.e. post-launch);
- dissemination of scientific results and research data;
- active communication of promising biomarkers and/or non-clinical models for the safety assessment of immunomodulatory therapeutics into the public domain via stakeholder workshops, publications and presentations;
- development of a sustainability plan.

Expected applicant consortium contribution: project management including coordination of work package deliverables, periodic reporting and budget administration, dissemination of scientific results and development of a sustainability plan.

EFPIA consortium contribution: leadership of overall project goals with respect to safety assessment applications, communication, dissemination of project results and development of sustainability plan.

Work package 2 – Innovative models for safety assessment of immuno-oncology therapeutics

The goals of this work package will be as follows:

- selection of clinically validated immunomodulatory therapeutic modes of action (including both small molecule and biotherapeutic immuno-oncology therapeutics) for which there is perceived to be an opportunity to enhance translational safety assessment;
- deployment of customised non-clinical models (with a particular emphasis on improved modelling of contributions from tumour target antigens and tumour microenvironments including biological barriers such as the intestine epithelium or the blood-brain barrier) to complement existing clinical and non-clinical safety profiles. It is envisaged that a customised combination of animal models and human *in vitro* models will need to be deployed for enhanced characterisation and/or prediction of clinical toxicities associated with specific immunomodulatory therapeutic modes of actions / drug targets.

Expected applicant consortium contribution: co-lead work package, study design, provision/deployment of models and/or biomarkers, and dissemination of results.

EFPIA consortium contribution: co-lead work package, study design, provision/deployment of models and/or biomarkers, and dissemination of results.

Work package 3 – Innovative models for safety assessment of immuno-inflammatory disease therapeutics

The goals of this work package will be as follows:

- selection of clinically validated immunomodulatory therapeutic modes of action (including small molecule and biotherapeutic immuno-inflammatory disease oncology therapeutics) for which there is a perceived opportunity to enhance translational safety assessment;
- deployment of customised non-clinical models (with a particular emphasis on improved modelling of contributions from inflammatory disease target biology and tissue microenvironments including biological barriers such as the intestine epithelium or the blood-brain barrier) to complement existing clinical and non-clinical safety profiles. It is envisaged that a customised combination of animal models and human *in vitro* models will need to be deployed for enhanced characterisation and/or prediction of clinical toxicities associated with specific immunomodulatory therapeutic modes of actions / drug targets.

Expected applicant consortium contribution: co-lead work package, study design, provision/deployment of models and/or biomarkers, and dissemination of results.

EFPIA consortium contribution: co-lead work package, study design, provision/deployment of models and/or biomarkers, and dissemination of results.

Work package 4 – Innovative biomarkers for translational safety assessment of Immunomodulatory therapeutics

The goals of this work package will be as follows:

- develop innovative comparative (cross-species) *in situ* and *ex vivo* molecular, biochemical tool and cellular profiling of immune cells (including patient-derived clinical samples) and association with functional/phenotypic endpoints (e.g. autoantibodies, cytokine release, skin toxicity, neurotoxicity);
- deploy computational biology approaches for assessment and integration of large multivariate immunobiology datasets (e.g. phenotypic-anchoring of molecular, biochemical and cellular endpoints derived from both non-clinical models and clinical trials) to reveal novel immune-biology mechanisms and translational biomarkers;
- apply established discovery and validation approaches for biomarker development in order to ultimately contribute to facilitating patient stratification and monitoring based on biopsy and minimal invasive liquid biopsy testing.

Expected applicant consortium contribution: co-lead work package, study design, provision/deployment of biomarker analytical and analysis technologies, and dissemination of results.

EFPIA consortium contribution: co-lead work package, study design, provision/deployment of biomarker analytical and analysis technologies, and dissemination of results.

Work package 5 – Clinical sample management – sourcing and logistics for assay and model development

The goals of this work package will be as follows:

- establish an IMI project-coordinated network to facilitate sourcing of human-derived immune cell and tissue samples via centres of excellence for specific disease areas;
- establish appropriate logistics for sample tracking and biobanking;
- establish a framework for ensuring appropriate ethical and legal review of proposed consortium research use of human-derived cells and tissues;
- qualify pre-analytical procedures for sample collection and implementation of novel workflows/devices minimising pre-analytical variances for enabling reliable molecular diagnostics, implement/confirm multi-modal & multi-analyte diagnostic approaches.

Expected applicant consortium contribution: Lead work package, engage key stakeholders from academic clinical centres of excellence and patient organisations, establish an ethical review board.

EFPIA consortium contribution: Co-lead for work package, definition of specific human immune cell and tissue samples that would support model development, provision of guidance for sample tracking and biobanking.

References

- [1] Lebec H, Brennan FR, Haggerty H, Herzyk D, Kamperschroer C, Maier CC, Ponce R, Preston BD, Weinstock D, Mellon RD. HESI/FDA workshop on immunomodulators and cancer risk assessment: Building blocks for a weight-of-evidence approach. *Regul Toxicol Pharmacol* 2016, 75:72-80.
- [2] Grimaldi C, Finco D, Fort MM, Gliddon D, Harper K, Helms WS, Mitchell JA, O'Lone R, Parish ST, Piche MS, Reed DM, Reichmann G, Ryan PC, Stebbings R, Walker M. Cytokine release: A workshop proceedings on the state-of-the-science, current challenges and future directions. *Cytokine* 2016, 85:101-108.
- [3] Fernández-Ruiz M, Meije Y, Manuel O, Akan H, Carratalà J, Aguado JM, Delaloye J. ESCMID Study Group for Infections in Compromised Hosts (ESGICH) Consensus Document on the safety of targeted and biological therapies: an infectious diseases perspective (Introduction). *Clin Microbiol Infect* 2018.pii: S1198-743X(18)30147-2.

Topic 5: Development and validation of translational platforms in support of synaptopathy drug discovery

Topic details

Topic code	IMI2-2018-15-05
Action type	Research and Innovation Action (RIA)
Submission and evaluation process	2 stages

Specific challenges to be addressed

Central nervous system (CNS) disorders are some of the most prevalent, devastating and poorly treated illnesses that impact individuals, families and society. It is estimated that annually in Europe alone, approximately 38 % of the population will suffer from a CNS disorder. When adjusted for age and comorbidities, this equated to 164.8 million people in 2010 and notwithstanding the emotional and social burden to patients and families, the financial cost was determined to be approximately EUR 798 billion [1]. Due to its unique complexity, the brain is susceptible to a variety of CNS disorders that can develop throughout all phases of life. For example, neurodevelopmental illnesses such as autism spectrum disorders first appear in early childhood, whilst psychiatric disorders are typically diagnosed during teenage years or early adulthood, and as we age we become increasingly susceptible to Alzheimer's disease (AD), Parkinson's disease (PD), and other neurodegenerative diseases. As a direct consequence of disease complexity and heterogeneity, identifying commonalities between CNS disorders has proved somewhat elusive, but there is now mounting evidence demonstrating that subtle, albeit persistent disturbances in synaptic functioning may underlie a number of brain disorders.

The term 'synaptopathy' was first coined in 2003 and is typically used to describe CNS disorders caused by synaptic deficits, irrespective of whether the alterations are primary or caused by underlying pathophysiological processes [2]. Synaptic deficits can be triggered by changes in the intrinsic pre- or post-synaptic molecular machinery, or by alterations in the surrounding synaptic environment. For example, approximately 600 genetic variations, many of which specifically affect synaptic proteins, are linked to autism spectrum disorders and despite the considerable diversity of these genes, many of these map onto common synaptic pathways [3]. Impaired synaptic function is also a core feature of several neurological disorders including AD and PD. AD brains contain extracellular deposits of amyloid beta (A β) peptide and intracellular neurofibrillary tangles (NFTs), mostly composed of aggregated tau protein. Although several hypotheses have been proposed for the cause of AD, the most common being the amyloid cascade hypothesis [4][5] and the tau hypothesis [6], the precise mechanisms of A β and tau toxicity are still not fully understood. It is noteworthy that neither plaques nor NFT volumes correlate well with disease severity, whereas the loss of nerve endings and associated synaptic dysfunction more closely track cognitive impairments [7][8][9].

Within psychiatric disorders, several studies have demonstrated that major depressive disorder (MDD) is associated with profound reductions in key brain regions that regulate mood and cognition, including the prefrontal cortex and the hippocampus, and that these areas show significantly reduced synapse numbers. Antidepressants have been shown to block or reverse these deficits. In addition, and more recently, ketamine, an N-methyl-D-aspartate receptor antagonist that elicits a rapid antidepressant response in treatment-resistant patients, has been shown to elicit synaptogenesis and reverse synaptic deficits caused by chronic stress in preclinical species [10]. Finally, one of the most consistent observations from schizophrenia patients is pronounced grey matter loss, which is accelerated during adolescence. Several post-mortem studies have demonstrated spine density alterations in the brain regions showing the greatest grey matter loss, and these results support the notion that spine density changes contribute directly to grey matter loss [11].

Whilst our emerging understanding of how synapses are pathologically altered in certain brain disorders is leading to innovative opportunities for drug discovery, there are considerable challenges impeding effective research that still remain. For instance, whilst there has been some recent headway, many of the utilised preclinical disease models, both *in vitro* and *in vivo*, are typically selected based on tenuous links to alterations in synaptic pathology. This is a direct consequence of the fact that many of the disease, pharmacodynamic and efficacy models were developed and validated on historical neurotransmitter modulation approaches and whilst successful in their day, may not prove to be amenable for synaptopathy drug discovery. Furthermore, the current technologies and platforms employed within early drug discovery are not fully characterised with respect to their predictive translational value, thus leading to a high risk of failure once compounds are progressed into the clinic. What is desperately needed therefore is the identification and validation of robust, sensitive and translational platforms capable of quantifying synaptic alterations both preclinically and clinically. Such platforms should be fit for purpose to detect and quantify dynamically both disease and treatment effects. Finally, we need to demonstrate the value of these new tools and methods for supporting drug discovery and development efforts across a spectrum of therapeutic CNS indications, including neurodegenerative, neurodevelopmental and psychiatric disorders. This will show that synaptopathy is a fundamentally treatable trait of these otherwise diverse conditions and will foster a leap forward towards innovative medicines for these diseases.

Need and opportunity for public-private collaborative research

CNS disorders are a ticking time bomb under the European economy due to the considerable societal costs and to the fact that these expenses will increase exponentially due to an ever-growing aging population. Despite this concern and the current efforts of the European scientific community, there is still a major discrepancy between the impact of CNS disorders and the modest resources that are directed to brain research. At the other end of the value chain, innovative treatments for patients are lacking. To improve efficiencies and ultimately drive success, it is imperative that intensive, collaborative research programmes be implemented. These should connect experts across sectors and disciplines, breaking silos and allowing pooling of resources and expertise from industry, academia and small and medium-sized enterprises (SMEs). Only such partnerships can ultimately deliver a heightened understanding of the contribution of synapse dysfunction to CNS disorders together with a battery of robust, validated, decision-making preclinical and clinical platforms to facilitate drug development. Expertise in drug discovery and development from industry, and academic expertise ranging from basic to clinical neuroscience should be brought together. Integration of SMEs which can play an important role as innovators in the field is also critical. Finally, yet importantly, patients and regulators must be part of the collaborative research efforts to ensure significant impact. The Innovative Medicines Initiative public-private partnership model is best placed to implement such collaborations to achieve a leap forward in scientific understanding and deliver a robust and highly validated platform of tools and technologies that can be exploited to deliver much needed novel CNS medicines.

Scope

The science linking alterations in synaptic function, genetics, and underlying pathways with CNS disorders is emerging. What still needs to be addressed is how these alterations are causal in the development of brain disorders, if they represent a common pathophysiological mechanism across disorders, and, finally, if targeting such alterations is feasible for the development of new treatments. The overarching aim of this topic is to develop an improved understanding of the causative or contributory role of synaptic alterations in CNS disorders, which must be valid and applicable to drug discovery and development across the diverse therapeutic CNS areas. The aim is to construct a precompetitive research consortium focused on furthering our scientific understanding of how synaptopathies can elicit or contribute to brain disorders. In addition, the focus will be to develop and validate both existing and innovative translational tools and platforms to facilitate drug discovery targeting synaptic health. If successful, the knowledge and validated technologies derived from this effort will facilitate the delivery of promising pharmaceutical therapies for the treatment of CNS disorders, for example neurodevelopmental, psychiatric and neurodegenerative disorders that are linked to deficits in synapse function.

To achieve the overall aim of the topic, applicants should focus on at least one of the four major brain disorders namely Alzheimer's, Parkinson's disease, major depression and schizophrenia, and ideally at least two, one in the neurodegenerative and one in the psychiatric/neurodevelopmental field. This is to ensure appropriate assessment of the role that synapse alterations play in both psychiatric and neurodegenerative disorders and is in line with the key disease areas of focus for the EFPIA partners. In their short proposal, the applicants should convincingly address how their approach and specifically their choice of technologies, disease models, preclinical and clinical platforms together with selected patient cohorts are optimal for achieving the topic objectives as outlined below:

1. bolstering scientific understanding of how synaptic alterations cause or contribute to CNS disorders and pave the way to efficient and effective synaptopathy drug discovery, with demonstration of the applicability beyond an individual brain disorder and its specific pathophysiology;
2. developing and characterising of *in vitro* and *in vivo* preclinical models of synapse function using both existing and innovative technologies to identify those that demonstrate improved sensitivity and predictive translational value;
3. developing and characterising both existing and novel clinically applicable platforms and treatment sensitive biomarkers capable of quantifying synaptic health, leading to the selection of improved endpoints for use in patient studies.

Specifically, the effort should be divided into two key areas.

1. Deep clinical phenotyping of CNS disorder patients to enable the development of robust tools to measure disease and treatment effects on the synapse

Although the science concerning synapse physiology and function and its contribution to brain disorders is emerging, systematic clinical phenotyping of CNS patient cohorts using platforms/technologies including but not exclusive to imaging, electrophysiology and clinical assessment scales are required to strengthen the fundamental knowledge base and identify clinical measurements with heightened sensitivity for disease and treatment effects. To this end, the most appropriate patient populations (including at least one of the four major brain disorders namely Alzheimer's, Parkinson's, major depression and schizophrenia) and assessment platforms should be selected and utilised to deeply phenotype CNS patient cohorts. This should allow the delivery of robust platforms/technologies for clinical measurement of disease and treatment effects on the synapse, and a significant leap forward in the knowledge base of synaptopathy in the context of major brain disorders.

2. Characterisation of existing and development of novel preclinical synaptopathy disease models

Although a variety of *in vitro* and *in vivo* disease models are available for CNS disorder research, the robustness of the reported phenotypes and their translational value in supporting drug discovery efforts requires strengthening. Thus, multiple cross-site characterisation of disease models utilising both available and innovative technologies are necessary to better define and select those most appropriate for drug discovery and development efforts with a focus on the synapse. Disease models may include, but are not limited to, cell-based and transgenic mouse strains expressing risk genes for psychiatric, neurodegenerative and potentially developmental disorders and also of perturbations known to impact synaptic remodelling.

The applicants should demonstrate their strategy for the choice of the most appropriate models and tools for achieving the objectives of the topic. Technologies and platforms may include synaptic imaging markers as well as other functional correlates such as electrophysiological (multiple electrodes arrays (MEA), long term potentiation/long term depression (LTP/LTD), electroencephalograms (EEG), event related potentials (ERPs)), imaging (calcium, high content, immunohistochemical, autoradiography, 2-deoxyglucose (2-DG)), synaptic biomarker measurements (synaptosomal-associated protein 25 (SNAP-25), growth associated protein 43 (GAP-43) etc.), microdialysis, neurotransmitter sensors and optogenetics and behavioural platforms (cognitive, motor and psychosis/mood related).

Expected key deliverables

Initial phase (approx. 3 years)

1. a prioritised list of robust disease models, preclinical and clinical platforms fit for purpose for synaptopathy drug discovery;
2. *in vitro* and *vivo* synaptopathy disease models that have been characterised and validated across sites using the predefined platforms and technologies to identify those disease models and platforms most optimal for drug discovery efforts;
3. a robust clinical assessment battery able to detect synaptic alterations in relevant patient cohorts;
4. selected CNS disorder animal models that have been both behaviourally and deeply phenotyped to establish the translation between synaptic marker and behavioural endpoints;
5. initial interactions with patient groups and regulatory bodies to discuss appropriate development paths forward for novel therapies targeting synaptopathies.

Late phase (approx. 2 years)

Based on successful achievement of the above deliverables, the remaining two years should deliver:

1. a comprehensive cross-site profiling of existing and novel therapies believed to positively address synaptopathy in the defined *in vivo* disease models using the battery of preclinical platforms;
2. a definitive clinical evaluation of novel positron-emission tomography (PET) ligands targeting pre- and post-synaptic proteins, for example synaptic density protein 95 (PSD-95), vesicular glutamate transporters (VGLUT1/2), excitatory amino acid transporter-2 (EAAT2) or others to be determined;
3. the determination of the pharmacological sensitivity of the defined clinical assessment battery using existing chemical entities thought to modulate synaptic function, for example ketamine or others to be determined;
4. some conclusions, based on the discussions of the results achieved with regulatory bodies and patients, on the best development paths forward for novel therapies targeting synaptopathies.

If stage one fails to deliver on key and well defined goals, entry into stage two will not be permitted and the project will be terminated.

Expected impact

The overarching objectives of IMI2 JU are to develop the next generation vaccines, medicines and treatments to provide patients, with more efficient and effective therapies. The IMI2 JU strategic research agenda (SRA) identified four key focus areas where multi-stakeholder collaborative efforts were deemed critical for success. This topic not only aligns with 2 of the 4 strategic research agenda areas (target validation/biomarker research and innovative medicines), but also aims to address 3 of the 12 IMI2 health priority disorders (neurodegenerative, psychiatric and age-associated diseases).

The expanded knowledge base generated to define the contribution that synaptopathies play in neurodevelopmental, psychiatric and neurodegenerative disorders will lead to improved disease pathway understanding and thus better position academia, SMEs and pharmaceutical companies to identify and validate tractable drug targets. The concerted and aligned efforts will minimise duplication and redundancy. The tools, platforms and technologies will ultimately drive success in both the discovery and clinical arenas by providing robust translatable evidence of early clinical efficacy as compounds are evaluated in patient populations. These achievements will facilitate the delivery of much needed, highly effective medicines and treatments for CNS disorders.

Applicants should also indicate how they will strengthen the competitiveness and industrial leadership of Europe by, for example, engaging suitable SMEs. Solutions that are co-created with SMEs can provide an economic stimulus that can be enduring. Their involvement in the action might offer a complementary perspective to industry and the academia, and help deliver the long-term impact of the project.

Potential synergies with existing consortia

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

Potential consortia synergies include:

- Deep and Frequent Phenotyping; combinatorial biomarkers for dementia experimental medicine: [https://www.research.ed.ac.uk/portal/en/projects/deep-and-frequent-phenotyping-combinatorial-biomarkers-for-dementia-experimental-medicine\(fc7b73c2-1596-44d0-9df2-c13b9c726002\).html](https://www.research.ed.ac.uk/portal/en/projects/deep-and-frequent-phenotyping-combinatorial-biomarkers-for-dementia-experimental-medicine(fc7b73c2-1596-44d0-9df2-c13b9c726002).html)
- IMI-PRISM: <https://prism-project.eu/en/prism-study/>
- IMI-EU AIMS: <https://www.eu-aims.eu/>
- IMI-European Prevention of AD: <http://ep-ad.org/>

- European Lead Factory: <https://www.europeanleadfactory.eu/>
- MIND-MAPS “Molecular Imaging of Neurodegenerative Disease Mitochondria, Associated Proteins & Synapses) program”: <http://www.imanova.co.uk/news/imanova-receives-1m-award-from-the-mrc-to-develop-early-markers-of-dementia-the-mind-maps-study>
- The upcoming project generated by the IMI2 Call 10 topic “Personalised medicine approaches in autism spectrum disorders”: https://www.imi.europa.eu/sites/default/files/uploads/documents/apply-for-funding/call-documents/imi2/IMI2_Call10_TopicsText.pdf
- The projects selected under the Horizon 2020 ERA-NET NEURON Cofund
- SysMed PD: Systems Medicine of Mitochondrial Parkinson’s Disease (<http://sysmedpd.eu/>).

Industry Consortium

The industry consortium is composed of the following EFPIA partners:

- Janssen (lead)
- Boehringer Ingelheim
- Heptares
- H. Lundbeck A/S
- Lilly
- Psychogenics
- Servier

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

- Invicro

The industry consortium (EFPIA and Associated Partner) will contribute the following expertise and assets:

Preclinical

1. *In vitro* and *in vivo* disease models known to demonstrate synaptic dysfunction linked to neurodevelopmental, psychiatric and neurodegenerative disorders including but not exclusive to:
 - transgenic mouse strains expressing risk genes for neurodevelopmental, psychiatric and neurodegenerative disorders;
 - *in vivo* viral transduction models;
 - *in vivo* proteinopathy seeding and spreading models;
 - *in vitro* cell culture models e.g. patient derived human induced pluripotent stem (hiPS) cells
2. Access to technologies, know-how and protocols including but not limited to:
 - rodent PET;
 - electrophysiological (MEA, LTP/LTD, EEG, ERP’s);
 - imaging (calcium, high content, immunohistochemical, autoradiography, 2-DG);
 - synaptic fluid biomarkers measurements (SNAP-25, GAP-43, lysosome-associated membrane protein 2 (LAMP-2) for example);
 - microdialysis, neurotransmitter sensors and optogenetics;
 - behavioural platforms (cognitive, motor and psychosis/mood related).
3. Commercially available and development tool compounds
 - PET ligands for synaptic markers;
 - pharmacological modulators of synaptic architecture.

Clinical

1. Clinic ready PET ligands (SV2A and AMPA TARP) in addition to PET chemistry support for novel ligand development.
2. Clinical expertise in trial design, implementation and regulatory support.

The industry consortium may also support communication/dissemination and project management activities.

Indicative duration of the action

The indicative duration of the action is 60 months.

Indicative budget

The indicative industry in-kind contribution is EUR 6 802 000.

This contribution comprises an indicative EFPIA in-kind contribution of EUR 6 730 500 and an indicative IMI2 JU Associated Partner in kind contribution of EUR 71 500.

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.

The financial contribution from IMI2 JU is a maximum of EUR 6 210 862.

Applicant Consortium

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

The applicant consortium is expected to address all the research objectives (please refer carefully in particular the sections '**Scope**', '**Deliverables**' and '**Suggested architecture of the full proposal**') and make key contributions to the defined deliverables in synergy with the industry consortium, which will join the selected applicant consortium in preparation of the full proposal for stage 2. This may require mobilising, as appropriate, the following expertise:

- basic neuroscientists with disease understanding of neurodevelopmental, psychiatric and neurodegenerative disorders;
- clinical and disease area experts with access to patient cohorts;
- PET ligand development experts;
- imaging, electrophysiology and fluid biomarker experts;
- expertise in clinical data management and clinical statistics;
- expertise in patient advocacy and engagement, privacy and ethical considerations;
- regulatory expertise and experience in development and qualification of novel end-points.

The participation of SMEs with the following expertise is highly encouraged:

- PET ligand development;
- imaging and image analysis technologies;
- clinical trial operation and execution;
- targeted mass spectrometry based proteome analysis;
- data and knowledge management;
- project management with expertise and experience relevant to IMI2 JU/H2020 projects.

Addressing successfully the objectives of the topic may also require mobilising, as appropriate, the following resources (please refer carefully in particular the sections '**Scope**', '**Deliverables**' and '**Suggested architecture of the full proposal**'):

- patient cohorts;
- patient and regulatory bodies.

Suggested architecture of the full proposal

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

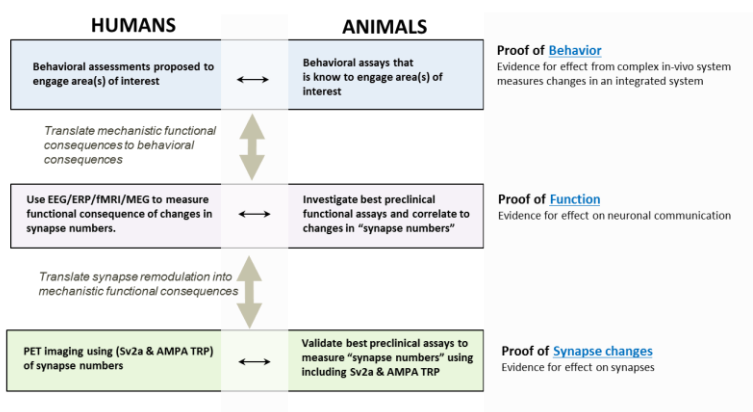
In the spirit of the partnership, and to reflect how IMI2 JU call topics are built on identified scientific priorities agreed together with EFPIA beneficiaries/large industrial beneficiaries, these beneficiaries intend to significantly contribute to the programme and project leadership as well as project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

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

The work plan should enable the construction of a precompetitive research platform focused on furthering our scientific understanding on how synaptopathies can elicit or contribute to brain disorders. It should focus on the development and validation of both existing and innovative translational tools and platforms to facilitate drug-discovery-targeted synaptic health. If successful, the plan should deliver knowledge and validated technologies to facilitate the delivery of promising pharmaceutical therapies for the treatment of CNS disorders linked to deficits in synapse function. All deliverables should be achieved using scientifically robust experimental studies, agreed upon with the consortium partners, and conducted across multiple sites employing both existing and novel experimental models of synapse dysfunction together with deep clinical phenotyping of defined patient populations.

The work plan must reflect the pooling of resources and expertise from academia, SMEs and industry in a fully integrated public-private partnership that will ultimately deliver a heightened understanding of the contribution of synapse dysfunction to CNS disorders together with a battery of robust, validated, decision-making preclinical and clinical platforms to facilitate drug development.

Translational overview to study synaptic remodelling



Applicants should suggest the most suitable project architecture to implement the activities below within two phases, an initial phase and a late phase of action.

Initial phase (approx. 3 years)

1. The consortium partners should undertake an early appraisal of all available disease models, preclinical and clinical platforms together with selected patient cohorts to prioritise activities and ensure the most effective delivery of the project objectives.
2. Cross-site characterisation of *in vivo* synaptopathy disease models using the predefined platforms and technologies will be initiated and derived data will be used to identify those disease models and platforms most optimal for drug discovery efforts. Potential disease models may include but should not be limited to transgenic mouse strains expressing risk genes for psychiatric, neurodegenerative and developmental disorders.
3. Clinical protocols will be composed and regulatory/ethical approvals gained to permit initiation of recruitment for the synaptopathy phenotyping of defined patient cohorts. Recruitment will be initiated and an *ad interim* analysis conducted for signal detection and power analysis determination. These assessments can include but may not be limited to:
 - demonstration of the grade of usefulness of existing PET ligands (made available from the industry consortium, namely SV2A and AMPA TARP), and 18F-FDG as markers of synapse integrity/function;
 - development and assessment of synaptic PET tracers, for example novel ligands targeting post synaptic density protein 95 (PSD-95), vesicular glutamate transporters (VGLUT1/2), excitatory amino acid transporter-2 (EAAT2) or others to be determined;
 - assessment of clinical imaging modalities such as functional magnetic resonance imaging, magnetoencephalography and diffusion tensor imaging for relevance and suitability to detect synaptic alterations in patient cohorts and correlation of these readouts with above synaptic function PET tracers;
 - assessments of clinical EEG measurements employing a battery of paradigms that induce cognitive or other functional event-related brain potentials or coherence;
 - developing behavioural and synaptic imaging marker phenotyping for selected CNS disorder animal models to be able to establish translation between synaptic marker and behavioural endpoint.
4. Interactions with patient groups and regulatory bodies will be initiated to discuss appropriate development paths forward for novel therapies targeting synaptopathies.

Late phase (approx. 2 years)

Based on successful implementation of the above activities, the remaining two years will focus on:

1. cross-site profiling of existing and novel therapies believed to address positively synaptopathy in the defined *in vivo* disease models using the battery of preclinical platforms;
2. clinical evaluation of novel PET ligands targeting pre- and post-synaptic proteins, for example synaptic density protein 95 (PSD-95), vesicular glutamate transporters (VGLUT1/2), excitatory amino acid transporter-2 (EAAT2) or others to be determined;
3. determination of pharmacological sensitivity of defined clinical assessment battery using existing chemical entities thought to modulate synaptic function, for example ketamine or others to be determined.

Work package 1 – Clinical work streams

The goals of this work package will be as follows:

- Characterisation of existing PET ligands, namely SV2A and AMPA TARP and 18F-FDG, which may prove to be useful markers of synapse integrity/function. This work package could also be extended to the development of novel PET ligands targeting PSD-95, VGLUT1/2, EAAT2 for example. Other imaging modalities such as functional magnetic resonance imaging, magnetoencephalography and diffusion tensor imaging should also be considered based on their relevance and suitability to detect synaptic alterations.
- Development of novel behavioural assessments (cognitive, motor and psychosis/mood related) and EEG measurements, that better reflect synaptic function and alterations as defined by translatable synaptic PET markers.

Industry consortium contribution:

- clinical and disease area experts with access to patient cohorts;
- clinic ready PET ligands (synaptic vesicle glycoprotein 2A (SV2A) and α -amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid transmembrane regulatory proteins (AMPA TARP)) in addition to PET chemistry support for novel ligand development;
- clinical expertise in trial design, implementation and regulatory support;
- access to preclinical synaptopathy models (AD, PD, MDD, schizophrenia, autism).

Expected applicant consortium contribution:

- clinical and disease area experts with access to patient cohorts;
- PET ligand development expertise;
- rodent PET capabilities;
- imaging experts;
- clinical trial operation and execution;
- expertise in clinical data management and clinical statistics;
- expertise in patient advocacy and engagement, privacy and ethical considerations;
- regulatory expertise and experience in development and qualification of novel end-points;
- data management.

Work package 2 – Preclinical work streams

The goals of this work package will be as follows:

- Cross-site characterisation of *in vitro* and *in vivo* synaptopathy disease models using the predefined platforms and technologies. Potential disease models may include, but should not be limited to, *in vitro* cell culture models e.g. patient-derived hiPS cells and transgenic mouse strains expressing risk genes for psychiatric, neurodegenerative and developmental disorders.
- Technology and platform development and assessment: these may include but should not be limited to electrophysiological, imaging, synaptic fluid biomarkers measurements, minimally invasive biomarkers improving early diagnostics and patient stratification, neurotransmitter sensors, optogenetics and behavioural platforms (cognitive, motor and psychosis/mood related).

Industry consortium contribution:

- Disease models known to demonstrate synaptic dysfunction linked to neurodevelopmental, psychiatric and neurodegenerative disorders including, but not exclusive to, transgenic mouse strains expressing risk genes for neurodevelopmental, psychiatric and neurodegenerative disorders.
- Access to technologies, know-how and protocols including but not limited to:
 - electrophysiological (MEA, LTP/LTD, EEG, ERPs);
 - imaging (calcium, high content, immunohistochemical, autoradiography, 2-DG);
 - synaptic fluid biomarkers measurements (SNAP-25, GAP-43, LAMP-2 for example);
 - microdialysis, neurotransmitter sensors and optogenetics;
 - behavioural platforms (cognitive, motor and psychosis/mood related).
- Commercially available and development tool compounds.

Expected applicant consortium contribution:

- academics and SMEs with disease understanding of neurodevelopmental, psychiatric and neurodegenerative disorders;
- expertise in disease model generations and characterisation;
- preclinical imaging, electrophysiology and fluid biomarker experts.

Work package 3 – Management, dissemination, stakeholder interaction, data & knowledge management and sustainability

The goals of this work package will be as follows:

- management & coordination
- communication and dissemination.

Please see the Call conditions for further details. In particular, applicants are reminded that full proposals must contain a draft plan for the exploitation and dissemination of the results.

- Interaction with stakeholders including regulators

The applicants are expected to have a strategy for the translation of the relevant project outputs into regulatory practices, and regulatory, clinical and healthcare practice. A plan for interactions with regulatory agencies/health technology assessment bodies with relevant milestones and resources allocated should be proposed to ensure this e.g. qualification advice on the proposed methods for novel methodologies for drug development, qualification opinion.

A guidance document has been developed jointly by EFPIA and IMI that summarises the services offered by regulators and is intended for use by researchers who wish to have a better understanding of these opportunities:

<http://www.imi.europa.eu/sites/default/files/uploads/documents/apply-for-funding/call-documents/imi2/RegulatoryRequirementsGuide.pdf>

- Data and knowledge management

To ensure adherence to the legislation concerning protection of personal data, controlled access digital repositories and data governance need to be considered. Proposals should use well-established data formats and content standards for data collection and data management in order to ensure interoperability to quality standards and optimal use of IMI resources. Preferably existing standards should be adopted. Should no such standards exist, consideration should be given to adapt existing standards in collaboration with a data standards organisation (e.g. CDISC, the Clinical Data Interchange Standards Consortium). Only if no existing useable standards exist in any format should consideration be given to developing new standards in collaboration with relevant bodies to ensure that any new standards are planned to become the de facto standard for any relevant future projects.

In addition, technical solutions (tools, data repositories, etc.) for data storage, management, analysis or visualisation should always re-use existing solutions where possible in preference to the development of new resources. For instance, many scientific data needs are now well served by well-established open source or commercial solutions, which should be identified in the application, with appropriate budget projections. This could include such areas as (but not limited to): electronic lab notebooks, biological assay data analysis tools, 'omics data storage and analysis, etc.

The applicants should provide in their short proposals a brief description of the data and knowledge management plan that will be further detailed in the data management plan in the full proposal. They should also ensure resources and budgetary planning for data management and include a deliverable for an initial data management plan (DMP) by month 6 at the latest into their proposal (see guidelines of FAIR (findable, accessible, interoperable, and reusable) data management in H2020

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

- Sustainability

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

Industry consortium contribution:

Support to communication/dissemination and project management activities.

Expected applicant consortium contribution:

Applicants are expected to contribute to the implementation of all of the above activities.

References

- [1] J. Olesen, A. Gustavsson, M. Svensson, H.U. Wittchen, B. Jönsson (2012) The economic cost of brain disorders in Europe. *European Journal of Neurology* 19: 155–162
- [2] Li J.Y., Plomann M., Brundin P. (2003) Huntington's disease: a synaptopathy? *Trends Mol. Med.* 9, 414–420.
- [3] Huguet G., Ey E. and Bourgeron T. (2013) The genetic landscapes of autism spectrum disorders. *Annu. Rev. Genomics Hum. Genet.* 14, 191–213.
- [4] Hardy J. A. and Higgins G. A. (1992) Alzheimer's disease: the amyloid cascade hypothesis. *Science* 256, 184–185
- [5] Hardy J. and Selkoe D. J. (2002) The amyloid hypothesis of Alzheimer's disease: progress and problems on the road to therapeutics. *Science* 297, 353–356
- [6] Gray E. G., Paula-Barbosa M. and Roher A. (1987) Alzheimer's disease: paired helical filaments and cytomembranes. *Neuropathol. Appl. Neurobiol.*, 13, 91–110
- [7] Terry R. D., Masliah E., Salmon D. P., Butters N., DeTeresa R., Hill R., Hansen L. A. and Katzman R. (1991) Physical basis of cognitive alterations in Alzheimer's disease: synapse loss is the major correlate of cognitive impairment. *Ann. Neurol.* 30, 572–580
- [8] Nagy Z., Esiri M. M., Jobst K. A. et al (1995) Relative roles of plaques and tangles in the dementia of Alzheimer's disease: correlations using three sets of neuropathological criteria. *Dementia* 6, 21–31
- [9] Kril J. J., Patel S., Harding A. J. and Halliday G. M. (2002) Neuron loss from the hippocampus of Alzheimer's disease exceeds extracellular neurofibrillary tangle formation. *Acta Neuropathol.* 103, 370–376
- [10] Duman RS, Aghajanian GK, Sanacora G, Krystal JH (2016) Synaptic plasticity and depression: new insights from stress and rapid-acting antidepressants. *Nat Med.* 22: 38-49
- [11] Selemon, L.D. & Goldman-Rakic, P.S. (1999) The reduced neuropil hypothesis: a circuit based model of schizophrenia. *Biol. Psychiatry* 45: 17–25

Topic 6: Digital endpoints in neurodegenerative and immune-mediated diseases

Topic details

Topic code	IMI2-2018-15-06
Action type	Research and Innovation Action (RIA)
Submission and evaluation process	2 stages

Part of IMI2 JU Digital Transformation of Clinical Trial Endpoints programme

Introduction to the IMI2 JU Programme on Digital Transformation of Clinical Trial Endpoints and problem statement

The development of novel treatments requires reliable and sensitive measurements of patients' clinical conditions and, when possible, functional capacity in daily living. The current clinical assessments, based on subjective clinical scoring systems, are characterised by low sensitivity, high variability, low sampling frequency (i.e. monthly assessments) and, in some cases, insufficient detection of the patient's actual needs. The consequences of these limitations for the development of novel treatments are significant, leading to increased probability of failed clinical trials, higher costs and excessive complexity in study management, often increasing patient burden for no real benefit.

The recent invention and diffusion of affordable digital technologies is offering the possibility to detect and monitor the progression of clinical conditions and their impact on daily living activities in patients in a cost-effective manner. The advantages for this digital transformation are impressive and have been well-reviewed in several articles. However, while more and more medical devices are receiving regulatory approval as diagnostic supports, very few digital procedures (that require a combination of particular digital devices, performance on tasks, passive data collection and algorithmic data extraction) have gained a qualification to be used as a clinical trial endpoint. If qualified, these endpoints could also allow for the possibility to rapidly scale-up to a very large number of patients, thereby driving a change in how clinical trials are implemented.

In this programme, we propose to identify, profile and validate digital devices, platforms and procedures based on mobile or residential technology for remote assessment of health-related parameters that could effectively substitute for the currently used clinical endpoints and functional outcomes required for obtaining regulatory approval and facilitate health technology assessment (HTA) relevance for novel treatments.

Need and opportunity for public-private collaborative research

Several pharmaceutical companies are exploring ways to apply digital technology to clinical development programmes and in post-marketing authorisation assessments of drug efficacy, tolerability and safety. One key aspect of this progress is the regulatory recognition of such endpoints, which requires proper validation. To achieve this objective, a wide variety of expertise across a number of stakeholders is needed:

- clinical trial expertise from pharmaceutical companies;
- patient advocacy groups to ensure the technologies developed are aligned with patients' needs;
- small and medium-sized enterprises (SMEs), larger technology companies and academic groups with expertise in digital devices, digital device implementation, digital data collection and analysis, including artificial intelligence (AI) approaches;
- academic groups with an in-depth clinical understanding of patients' conditions;
- regulators to advise on the requirements for validation.

By working together to jointly tackle this problem using an interdisciplinary, precompetitive and transparent approach, solutions can be developed that should align with the main regulatory requirements as well as with

the societal goals of addressing the key health challenges recognised by the World Health Organisation (WHO) and other institutions. A critical point of the programme will also be the openness towards the contribution from other programmes running in Europe, USA or in other part of the world.

Overall objectives of the programme

The key objectives of the programme are:

- to identify appropriate digital devices & platforms for the transformation of the standard clinical and functional endpoints into digital endpoints;
- to experimentally test the validity of the proposed digital endpoints in clinical trials, with the final aim to select a few endpoints and progress them to obtain qualification from regulatory agencies;
- to progress towards the validation of digital procedures to profile activities of daily living (ADL) / disabilities/ health related quality of life (HRQOL) measures whose ecological validity is recognised by patients and payers.

Structure of the programme

The programme is divided in three main activities:

- selection & implementation of digital platforms, devices, procedures and other technology, data processing, simulation and modelling to optimise the digital endpoint transformation process;
- initial focus on delivering the digital transformation for a specific group of patients with progressive disorders affecting movements and activities of daily living with therapeutic unmet needs described in the first topic of this programme, i.e., with neurodegenerative movement disorders (NMD) and immune mediated inflammatory disorders (IMID);
- design of a clinical & regulatory plan, with appropriate data analysis leading to a scientific validation for the proposed digital endpoint and consequent progression of the most promising solutions into a regulatory path for qualification, including assessment on how policy-makers, HTA bodies and payers can take into account the proposed digital endpoints in their decision process.

The validation plan for digital endpoints and outcomes measures should be aligned with Clinical Trials Transformation Initiative (CTTI) guidelines (<https://www.ctti-clinicaltrials.org/files/detailedsteps.pdf>).

Data management platform, digital sensors & procedures

An efficient generic data management digital platform that has already been partially developed for health care use will be selected as part of topic 1. This platform should allow the use of different standardised datasets, the plug in of several devices and data-streams, be flexible and easy to adapt for use in clinical trials.

The projects will focus on the latest advances in biosensors and mobile technologies to develop and validate novel clinical and real world endpoints while building on work that is already being done in this area. Therefore, it is critical that the platform has the possibility to integrate already standardized data. For example, in the first topic of this programme, it is likely that within the next 2-3 years a digital transformation of motor sign measurements currently delivered by UPDRS-3⁷⁷ will be available [1]. Therefore, this first topic will focus on developing the non-motor sign and symptoms, of relevance for activities of daily living (ADL), i.e., those captured by UPDRS-2.

This platform will be made publicly available for other future digital transformation topics and elsewhere, while the specific IP for all plug-in for proprietary technologies and solutions will be protected.

Future topics in the programme will focus on other indications and where possible use the platform already implemented for the first topic of this programme, if successful. However, these future topics may also select other platforms and technologies to suit their particular objectives.

⁷⁷ Unified Parkinson's disease rating scale

Collaboration agreements

To maximise the overall impact of the programme, and ensure synergies and learnings are fully shared, the projects in the programme will be expected to sign collaboration agreements with each other. The collaboration agreements should allow for the sharing of the technology platforms, learnings on device selection, development and the implementation during the clinical studies and any other relevant activities.

The respective options of Article 2, Article 31.6 and Article 41.4 of the [IMI2 Model Grant Agreement](#) will be applied.

Specific challenges to be addressed

Neurodegenerative movement disorders (NMD) and immune mediated inflammatory diseases (IMID) can cause considerable disability and morbidity in spite of the availability of approved treatments. Recent estimates suggest that neurodegenerative disorders are becoming one of the fastest growing costs for healthcare systems [2]. Movement disorders, in particular Parkinson's disease (PD), affect about 1.2 million European citizens, a number set to double by 2050 [3]. While rarer, the burden of Huntington's disease can be up to 5 times higher than that of PD patients [4].

The socio-economic burden of IMID is well known [5]. An estimated 2.5–3 million people in Europe are affected by inflammatory bowel disease (IBD), with a direct healthcare cost of EUR 4.6–5.6 billion per year. Recent studies have suggested that more than 2.3 million individuals are diagnosed with rheumatoid arthritis (RA) in Europe, generating annual direct and indirect costs of management of over EUR 45 billion [6].

The continuous progress in the understanding of neurodegenerative processes and immunopathology are building hope that breakthroughs will soon be made and new agents will enter clinical development in the next few years. However, most of the current clinical endpoints used in trials for neurodegenerative or autoimmune-mediated disorders are based on 'scores' and focus on assessing the severity of disorder-specific signs & symptoms at a given stage of the disease progression. These values may vary in degree or intensity among different patients, suggesting a relevant biologic variability, as well as in the training and capacity of the 'rater' in scoring the symptoms or in self-assessing the disabilities, in case of direct response of the patients. The consequences of these limitations for drug development are significant, leading to increased probability of failed trials, higher costs and excessive management complexity and lost opportunities for patients. Therefore, it is imperative to improve the efficiency of clinical trials to maximise the chances for delivering novel therapies for patients with unmet needs within the next 5-10 years.

Digital technology, in particular remote monitoring systems, if properly implemented and validated, could provide a critical help in improving measurements of efficacy by increasing sensitivity and precision, reducing variability, and enhancing their ecological validity making them closer to the actual unmet needs of patients. This project will develop a technology platform to collect and analyse sensor/generated datasets, principally high resolution passively and actively collected digital measurements, i.e. actigraphy, socialisation parameters and momentary self-reported assessments, mainly using (but not limited to) wearables and smartphone sensors and apps. The project will also seek to engage the European Medicines Agency (EMA) in providing scientific advice and give the direction for its validation and, eventually, acceptance of at least one digital endpoint to be used in future clinical trials of drug development.

Need and opportunity for public-private collaborative research

As stated in the introduction to the programme, pharmaceutical companies are exploring ways to apply digital technology to clinical development and in post-marketing authorisation assessments of drug efficacy, tolerability and safety. One key aspect of this progress is the regulatory recognition of such endpoints, which requires proper validation.

To address these challenges and deliver the digital transformation of endpoints in neurodegenerative and autoimmune mediated diseases, a range of different expertise is required to work effectively together. This includes technical expertise in device development such as that found in digital technology companies, SMEs and academic groups, as well as strong technical, statistical, analytical and data management expertise to integrate the data from the devices with existing data from academia, the pharmaceutical industry and other consortia for developing and updating the endpoint & disease models. By combining this expertise with clinical scientists (both industry and academic) and patients in a public-private partnership, the best digital technologies can be adapted and optimised to the specific features of the clinical /functional endpoints.

Finally, regulatory knowledge is essential to ensure the technologies can receive regulatory validation and therefore have maximum long-term impact.

An additional critical point will also be the openness towards the contribution of data from other private-public partnerships running in Europe, USA or in other parts of the world, so to leverage all available knowledge.

Scope

Subtle impairments in accomplishing daily activities are sometimes reported among the first signs of a disorder that will progressively develop towards more severe disabilities for individuals affected with NDD and IMID. Identifying the ADLs that first or more consistently are affected by the disorders and tracing their progression using original digital solution is a key aspect of the present project. In fact, advances in micro-sensors and mobile technologies have the potential to enable seamless, continuous, objective measurements of symptoms and disabilities, providing more precise and higher frequency data collection. The early identification of impairment and the possibility to follow its worsening with precision and reliability are essential tools for assessing the effects of novel treatments that should target the disorder in its early phases. In fact, if the disorders progress beyond a certain point, the disabilities may not be reversible, justifying early interventions.

The focus of this programme is to provide an effective digital transformation of clinical endpoints for the following disease clusters.

The NMD cluster:

- Parkinson's disease (PD)
- Huntington's Disease (HD)

The IMID cluster:

- Rheumatoid arthritis (RA) or systemic lupus erythematosus (SLE)
- Inflammatory bowel disease (IBD).

The main objectives of this project will be:

- the identification and characterisation of subtle disabilities in the activities of daily living (ADL) that worsen over time, that are either common or partially shared among the NDD and IMID hereby considered, so to represent a patient related outcome that can be used for assessing the effects of treatment in the real world and also be used for helping the comparative therapeutic impact among disorders of novel treatments;
- the identification of digital solutions that appropriately measure clinical and behavioural signs & symptoms related to ADLs that are specific for each one of the disorders mentioned below, so as to obtain better standards than the current clinical scales and that can be considered of relevance by regulatory authorities in clinical development trials for novel treatments.

In the case of PD and HD, the focus will be on a set of signs & symptoms that can be optimally measured by a selected series of sensors, devices, platforms and procedures to provide a proper correlation with scores of the UPDRS for PD and UHDRS⁷⁸ for HD (or equivalent clinical scales) that would satisfy regulatory standards. As other programmes are targeting the motor aspect of PD patients, the aim of this project is to target other ADL and behavioural aspects of the disorders that are often very early complaints from patients.

For patients with all disorders, i.e. NMD and IMID, critical ADL related to quality of life (QoL) measures will need to be prioritised within the context of the global condition as patients, so as to identify digital solutions whose precision, reliability and ecological relevance are relevant to patients, clinicians, regulators and payers

The selected ADLs should be evaluated in both NMD and IMID patients, in order to test if the use of the proposed technology is sensitive enough to assess the levels of disability across disorders, but also specific enough in identifying the underlying primary drivers (e.g. fatigue, pain, anxiety, etc.) that contribute to

⁷⁸ Unified Huntington's Disease Rating Scale

determining the disability in the various groups of input of both patient associations (advocacy and research foundations) and clinical experts in supporting the choice of specific ADL/disabilities to be profiled.

The project is suggested to be divided temporally in 2 parts.

Part A is an approximately 1.5-year long period for digital technology initial implementation and validation using modelling and beta-testing in a small group of patients, aimed at selecting the best technologies that establish a reasonable relationship with the targeted clinical endpoints.

Part B is an approximately 3.5-year long validation programme aimed at demonstrating that the selected digital procedures properly represent the rating scale-based clinical endpoint and ADL, and are sensitive to pharmacologic treatments. Data will be analysed with modern algorithmic approaches, engaging expertise of all consortium members also during this period.

Expected key deliverables

Part A: The first 1.5 years

- identification of the digital data management platform;
- prioritised list of sign & symptom-based clinical endpoints for NMD that are amenable for digitisation and selection of the most promising device and procedure;
- prioritised list of ADLs/disabilities/HRQOL measures amenable to original digital solutions in NMD and IMID, possibly using the same digital devices proposed for clinical endpoints;
- Public release of the adapted digital data management platform with appropriate privacy protection assurances and seamless integration to EMR systems to enable e.g. monitoring protocol compliance, for quality assurance, data integration, and ensuring data integrity;
- introduction of some existing digital solutions that have already been successfully used i.e. from the literature (anchoring dataset);
- development of novel methods to probe the ADLs or other endpoints not previously addressed in the literature (innovative dataset);
- initial test of feasibility, acceptability and utility with some volunteers;
- collection of available data from project members and external sources; initial proposal of models for the diseases (starting with PD and HD), establishment of clinical trial simulation package to test the expected digital technology data delivery and their impact on different clinical trial designs;
- pilot study synopsis in NMD: exploration in a small group of patients with PD and HD of the various devices for acceptability, feasibility and utility, to be possibly run in one or two clinical centres for clinical endpoints. At least two ADL/disabilities digital devices will be tested among those that have been discussed as common or partially common with IMID;
- pilot study synopsis in IMID exploration in a small group of IMID of the various devices for acceptability, feasibility and utility, to be possibly run in one or two clinical centres for clinical endpoints. At least 2 ADL/disabilities digital design will be tested among those that have been discussed as common or partially common with NMD;
- Scientific advice from the regulatory agencies, including FDA⁷⁹ and EMA⁸⁰ on the proposal for the longitudinal study in part B.

Part B: The last 3.5 years

- Longitudinal study in digital mobility and clinical outcome assessment over 2.5 years in PD, HD and IMID populations for assessing clinical endpoints and ADL/ disabilities:
 - development of clinical protocols and IRB, ethics committee approval;

⁷⁹ Through, for example, C-Path

⁸⁰ http://www.ema.europa.eu/ema/index.jsp?curl=pages/regulation/general/general_content_000049.jsp&mid=WC0b01ac05800229b9

- a clinical observational part of the study to establish correlations of digital endpoint with clinical endpoints for PD and HD and for ADL/disabilities/HRQOL across both NMD and IMID patient populations;
 - the adaptive nature of the study should help to include possible changes based on the scientific advice from EMA, possibly FDA and HTA agencies based on data from the interim analysis and associated clinical trial simulation scenarios (e.g., after one year).
- Data analysis:
 - digital data management plan, including digital data format and standardisation, alignment with legal requirements, privacy aspects, storage backups and cybersecurity;
 - performance of algorithm-delivered recognition of digital endpoints and ADL/disabilities/HRQOL patterns for automatic detection;
 - assessment of the precision and sensitivity of digital endpoints vs. clinical scales and their effects on sample size and effect size in simulated clinical trials;
 - assessment of the precision and sensitivity of ADL/disability/HRQOL digital sequences to estimate ADL/HRQOL scores and their effects on sample size and effect size in simulated clinical trials across the different disease populations;
 - interim assessment after one year (or another duration) to provide a robust dataset for engaging in a second round of EMA Scientific Advice;
 - final analysis package to support a request for the qualification of the use of the novel digital endpoints via EMA scientific advice, early HTA consultation and, possibly, FDA.
 - Overview and position paper as well as a series of scientific articles on digital transformation on clinical trials.
 - Final public event to showcase the results of the project.

Expected impact

Digital transformation of clinical and real-world measures of ADL / quality of life measures relevant to patients and care-givers will give deeper and more detailed insights into how diseases progress and cause disabilities in patients, which, in turn, will enable development of interventions that better address these clinical deficits and disabilities.

Digital endpoints when combined with patient self-reported outcomes and other traditional clinical measures will provide a more valid and complete assessment of patient and care-giver impact of disease and their treatments.

Digital transformation of clinical and real-world endpoints will enable larger and more inclusive clinical trials and reduce patient burden thus allowing assessment of interventions in more diverse and representative populations.

Use of passive digital technologies will increase the efficiency of clinical trials, enabling faster clinical development and a reduction in the time taken to bring new therapies to patients. These technology enabled endpoints with passive data collection will make larger and longer follow-on studies to assess real world impact of therapies on patients possible, thus enabling more effective value driven health care decision making.

It is expected that, in the long run, this project will enable the development and evaluation of more effective therapies for patients thus improving outcomes for patients and reducing cost for all stakeholders.

Applicants should also demonstrate how they will impact on the competitiveness and industrial leadership of Europe by, for example, engaging suitable SMEs.

Potential synergies with existing consortia

Applicants should take into consideration, while preparing their proposal, other relevant initiatives (national, European - both research projects as well as research infrastructure initiatives - and non-European initiatives) in particular those in the pre-competitive space. Synergies and complementarities should be considered to incorporate past achievements, available data and lessons learnt where possible, thus avoiding unnecessary overlap and duplication of efforts and funding, but at the same time to open up a dialogue for best-practice and actual data sharing, so as to cross-fertilise the present project.

For example, other initiatives are addressing to the selected diseases, as such:

- MJFF Parkinson Disease Digital Biomarker DREAM challenge⁸¹;
- FNIH Accelerated Medicine Partnership in PD clinical trials started in 2017⁸²;
- Several HD consortia are exploring the basic aspects of the disorder;
- MRC UK funded consortium: Immune-Mediated Inflammatory Disease Biobanks - UK.⁸³

There is potential synergy with other IMI projects that focus on digital medicines such as **RADAR-CNS** (www.radar-cns.org) in patients affected by epilepsy, depression, multiple sclerosis, related to reuse of parts of the tech platform, sharing challenges in designing and operationalising clinical studies. Other projects are: **EMIF** (www.emif.eu), **eTRIKS** (www.etriks.org), **EHR4CR** (www.ehr4cr.eu), and the other relevant programmes, especially in regard to learnings about data management, privacy, transfer, data analysis and definition of clinical outcomes.

An additional synergy could be via interactions /collaboration with Critical Path Parkinson (CPP)⁸⁴ initiative for the regulatory approval of digital endpoints for PD and possibly HD.

Collaboration with EUnetHTA Joint Action 3 (European network for Health Technology Assessment – www.eunetha.eu/) should be considered given the technological expertise related to digital platforms with high flexibility and to ensure acceptability of the results by the HTA community.

Collaboration with ECRIN, which is a not-for-profit infrastructure supporting multinational clinical research projects in Europe will be also considered. ECRIN provides information, consulting and services to investigators and sponsors in the preparation and in the conduct of multinational clinical studies.

Finally, consideration should be given to collaborating with the CTTI project 'Developing Novel Endpoints Generated by Mobile Technology for Use in Clinical Trials' (<https://www.ctti-clinicaltrials.org/projects/novel-endpoints>). Such agreements would enhance the ability of various types of digital data to be captured, analysed, and shared with greater efficiency, and would be an additional boon to the field.

Industry consortium

The industry consortium is composed of the following EFPIA companies:

- Janssen (lead)
- Takeda (co-lead)
- AbbVie
- Astra Zeneca
- Biogen
- Eli Lilly
- Orion Pharma
- Pfizer
- Roche
- Sanofi
- UCB

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

- Parkinson's UK
- CHDI Foundation⁸⁵

81 <https://www.michaeljfox.org/research/levodopa-data-challenge.html>

82 <https://fnihi.org/what-we-do/current-research-programs/accelerating-medicines-partnership-parkinsons>

83 www.imidbio.co.uk

84 <https://c-path.org/programs/cpp/>

85 Its participation is subject to formalisation of its association to IMI2 JU for the present topic.

Expected contribution by industry participants

EPFIA companies will contribute personnel with specific competences that will either complement or add and extend to those requested of the applicants.

The EPFIA personnel competences that will complement those of the applicants are:

- expertise in regulatory activity;
- expertise in patient reported outcomes;
- expertise in relations with HTA, insurance and payers;
- expertise in patient association, legal and ethical aspects;
- expertise in digital data standardisation for regulatory application;
- expertise in patient-centric approaches working with vocational groups.

Other competences will be made available to align and extend those of the applicants:

- expertise in legal and financial and project management;
- expertise in clinical study design, biostatistics, expertise in assessment of clinical domains;
- expertise in disease modelling and longitudinal analysis of cognition, function, biomarker and clinical data;
- expertise in functional assessments, including activities of daily living (ADL);
- expertise in digital data management and platform use, as well as device and sensor characterisation
- therapeutic area expertise along with years of digital and clinical endpoint strategy knowledge.

During the project, members of the industry consortium will contribute relevant data generated in prospective activities that are part of broader clinical studies independent from, but related to the project. Relevant data generated in such activities are deemed necessary for the project to achieve its objectives, and the introduction of the data to the project constitutes an in kind contribution which entails access rights to these project results in line with IMI2 JU IP rules. The prospective activities to generate these data subject to the above are as follows.

- Janssen's prospective data will come from primary and secondary endpoints (PnSEP) and exploratory endpoints (ExpEP): self reports and actigraphy data from an IMID (RA and/or IBD and/or SLE) clinical study with an in-kind relevant data generation value estimated at EUR 5 300 000.
- Takeda's (and the associated Oshi Health) prospective data will come from an observational trial in PD for validating various technologies and possibly also from some asset studies (baseline and/or placebo data). Also, some IBD placebo data will be shared. The in kind data generation value is estimated at EUR 2 500 000.
- Sanofi will share actigraphy data which can be used to infer sleep quality and serve as a marker of fatigue, and also PD data from prospective clinical studies with value estimated at EUR 3 000 000.
- CHDI will bring HD datasets to be reviewed for potential endpoints such as longitudinal observational, single time-point, imaging, biofluids, or data modelling results with an in-kind relevant generation value estimated at EUR 1 000 000.
- Pfizer will contribute data related to quality of life measurements with an estimated relevant generation value of EUR 125 000.
- AbbVie will provide data from Ph0 studies in PD patients having an estimated relevant generation value of EUR 800 000 as follows:
 - provide data contributions in CDISC standards once those are defined for digital;
 - provide data passively collected from a Phase 0 study to assess specific motor deficits (bradykinesia and tremor) - via a medical grade digital watch before and after treatment;
 - provide sleep data passively collected from the Phase 0 study along with measures of general activity (steps) and digital measures of cognition.
- Biogen will bring data from a validation study in the PD area.

Such activities, despite being part of broader independent clinical studies, will be integrated in the action as part of relevant work packages and deliverables. The introduction of these data is considered highly important and directly relevant for the project because they will contribute to achieving meaningful results in developing digital endpoints for the disease areas included in this topic: PD, HD and IMID.

Furthermore, some companies (such as Astra Zeneca, Orion Pharma, Eli Lilly) will also provide, as background of the action (Article 24 of the [IMI2 Model Grant Agreement](#)), historical data from other patient cohorts and use the work involved in transferring these data to the project as part of their in kind contribution.

Indicative duration of the action

The indicative duration of the action is 60 months.

Indicative budget

The indicative in-kind and financial contribution from EFPIA partners and IMI2 JU Associated Partners is EUR 21 300 000.

This contribution comprises an indicative EFPIA in-kind contribution of EUR 19 400 000 and an indicative IMI2 JU Associated Partners in kind contribution EUR 1 900 000.

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

The financial contribution from IMI2 JU is a maximum of EUR 21 000 000.

Applicant consortium

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

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

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

- clinical and disease area experts with specific knowledge of the disorders in focus;
- clinicians and psychologists with expertise in the critical aspects of ADL and HRQOL, including psychological aspects of the assessment of the personal perceived disabilities as well as of caregivers and attending staff or physicians to corroborate the patient profile;
- clinical and statistical experts with demonstrated knowledge of the design and conduct of clinical studies;
- expertise in clinical data management, algorithmic and statistics;
- expertise in patient advocacy and engagement, privacy and ethical considerations;
- expertise in legal aspect of data privacy with particular reference to the capture of data of potential sensitivity related to personal activities;
- expertise in device and sensor development (including SMEs): latest remote assessment technologies (wearable, off-body) that could be further developed or modified for use in the consortium;
- IT/analytics partners (including SMEs): data management architecture, hardware/software platform, state-of-the-art algorithms to process and analyse time-series data from sensors/devices, expertise in data privacy and security;
- expertise in the development and regulatory qualification of novel digital technologies, in particular if applied to health care problems
- some expertise in HECOR and patient outcome research

Applicants should bring an existing data management platform as part of their proposal. An assessment of performance, versatility, data access, sustainability, and security explaining the reasons for the selection should be included.

Applicants should include a mix between already validated digital tools and some novel methods (Technology Readiness Level 5-9) to probe the ADLs or other endpoints not fully addressed in the literature.

In addition, in their proposal, applicants should:

- identify and engage existing longitudinal cohort studies in the four relevant populations;
- design a statistically powered clinical trial to validate the digital solution to measure ADL and show capacity to detect treatment effects with higher precision;
- demonstrate access to sufficient clinical trial subjects and a proven track of clinical trial recruitment and management expertise for NMD and IMID;
- allocate funding for EMA scientific advice and to access HTA expertise;
- allocate funding for a final public conference (additional dissemination activity);
- allocate funding to interact in joint meetings with future topics.

Suggested architecture of the full proposal

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

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

Regulatory strategy

As indicated above, the consortium is expected to have a strategy for the translation of the relevant project outputs into regulatory, clinical and healthcare practice. A plan for interactions with regulatory agencies/health technology assessment bodies with relevant milestones and sufficient resources should be proposed to ensure that advice on the proposed methods for using novel digital methodologies in clinical trials and, possibly, qualification opinion can be obtained⁸⁶.

Sustainability

A draft plan for aspects related to sustainability, facilitating continuation beyond the duration of the project should be provided in the short proposal and further detailed in the full proposal.

Dissemination

A draft 'plan for the dissemination and exploitation of the project's results' should be provided in the short proposal and further detailed in the full proposal.

Data management plan

A draft data management plan (DMP) outlining how research data will be handled and made available during the project, and after it is completed, should be provided in the short proposal and further detailed as part of the full proposal.⁸⁷

⁸⁶ See <http://europa.eu/!ww84Xw>

⁸⁷ See http://ec.europa.eu/research/participants/data/ref/h2020/grants_manual/hi/oa_pilot/h2020-hi-oa-data-mgt_en.pdf

References

- [1] Zhan A, Mohan S, Tarolli C, Schneider RB, Adams JL, et al. Using Smartphones and Machine Learning to Quantify Parkinson Disease Severity: The Mobile Parkinson Disease Score. *JAMA Neurol*. <https://doi.org/10.1001/jamaneurol.2018.0809>
- [2] Gooch CL *et al*. The burden of neurological disease in the United States: A summary report and call to action. <https://doi.org/10.1002/ana.24897>
- [3] Bach JP *et al*. Projected numbers of people with movement disorders in the years 2030 and 2050. <https://doi.org/10.1002/mds.23878>. Mateus C *et al*. Health economics and cost of illness in Parkinson's disease <http://doi.org/10.17925/ENR.2013.08.01.6>
- [4] Pringsheim T *et al*. The incidence and prevalence of Huntington's disease: a systematic review and meta-analysis. <https://doi.org/10.1002/mds.25075>. Jones C *et al*. The societal cost of Huntington's Disease: are we underestimating the burden? <https://doi.org/10.1111/ene.13107>
- [5] Jacobs P *et al*. Socioeconomic burden of immune-mediated inflammatory diseases--focusing on work productivity and disability. <https://doi.org/10.3899/jrheum.110901>
- [6] Burisch J *et al*. ECCO -EpiCom. The burden of inflammatory bowel disease in Europe. <https://doi.org/10.1016/j.crohns.2013.01.010>. O'Hara J *et al*. The Burden of Rheumatoid Arthritis across Europe:a Socioeconomic Survey (BRASS). NRAS, www.nras.org.uk, Apr 26, 2017.

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 that 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), the largest single contributor to AMR health, mortality, and economic impact, is scheduled to be discussed by heads of state at the UN General Assembly (September 2018).

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 novel mechanism antibiotics 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 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 learnings 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 roughly six-year period.

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, 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, progress potential new treatments through phase 1-3 clinical trials, and 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 as 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>⁸⁸) 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 of '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 consist 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 two-stage IMI2 JU Call 15 includes two topics (topic 7 and topic 8) to launch Pillar A and Pillar B of the AMR Accelerator, respectively. The single-stage IMI2 JU Call 16 includes seven topics under Pillar C.

Applicants may submit a proposal to any of the topics under the different pillars and are not obliged to apply for all. If applicants wish to submit for more than one topic under the same or different pillars, separate proposals should be submitted.

For the two topics for Pillars A and B, launched as part of IMI2 JU Call 15:

- the indicative EFPIA in-kind contribution will be EUR 71 200 000
- the indicative Associated Partner in-kind contribution will be EUR 67 000 000.

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.

The overall IMI2 JU financial contribution to the AMR Accelerator topics under Pillars A, B and C of IMI2 JU Call 15 and IMI2 JU Call 16 will be a maximum of EUR 144 730 000.

Future call 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.

⁸⁸ For example, points 3 and 4 from the 'Roadmap for Progress'.

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 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 an action that will create 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).

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)⁸⁹. 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 available budget. A total of at least 8-10 grant agreements are anticipated in the PBN (indicative number only).

⁸⁹ 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 (selected under Pillar A from IMI2 JU Call 15 topic 7, and containing the coordination and support group⁹⁰) will be complementary to all the grant agreements of actions selected under Pillars B and C (via IMI2 JU Call 15 topic 8 and IMI2 JU Call 16 topics, and potential future additional calls for proposals), as well as probable future grant agreements from actions selected under Pillar A. In addition, grant agreements of actions under pillar B, if more than one, will be complementary between them. The respective options of Article 2, Article 31.6 and Article 41.4 of the IMI2 JU Model Grant Agreement⁹¹ will be applied. Accordingly, the consortia selected under Pillars A, B, and C will conclude collaboration agreements with the CBN consortium selected from IMI2 JU Call 15 topic 7. These collaboration agreements will provide the framework for the CBN 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 action(s) and the Integrated Research Platforms (IRP) action of IMI2 JU Call 15 topic 1 to cover collaboration and sharing of information on TB-related activities. The MoU should constitute one deliverable of the action resulting from topic 8 of IMI2 JU Call 15. 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 action(s), as well as the IRP action of IMI2 JU Call 15 topic 1, with appropriate provisions to protect confidentiality and intellectual property of the interactions between those consortia.

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 have been the 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 of 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 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.

⁹⁰ For additional details see the topic 7 "Capability Building Network" of IMI2 JU Call 15.

⁹¹ See: https://www.imi.europa.eu/sites/default/files/uploads/documents/reference-documents/h2020-mga-imi_en_v5.pdf

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 key role in a EU AMR programme with connectivity into the broader global agenda on AMR;
 - enable SME, and/or academic groups to progress pre-competitive basic science project in the AMR field;
 - 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 project 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;
 - opportunity to work within a broad network on researchers focused on TB drug discovery.
- Portfolio Building Network:
 - 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 7: AMR Accelerator programme Pillar A: Capability Building Network to accelerate and validate scientific discoveries

Part of IMI2 AMR Accelerator programme

Topic details

Topic code	IMI2-2018-15-07
Action type	Research and Innovation Action (RIA)
Submission and evaluation process	2 stages

Specific challenges to be addressed

The Capability Building Network (CBN), Pillar A of the IMI2 AMR Accelerator programme, will work to address the innovation gap in the AMR space by enabling pre-competitive research in the treatment and prevention of multi-drug resistant infections.

The success of the overall Accelerator relies on a coordinated approach to ensure efficient implementation, management, and strategic alignment across a broad range of topics, partners, and stakeholders. Expert operational support for the programme, via a centralised coordination and support group will address this need and will allow all Accelerator projects to focus on delivering scientific advancements for the field and progressing medicines and therapies to patients. This coordination and support group will also provide a unique opportunity to coordinate large-scale efforts in the AMR space in collaboration with industry and public partners and will be part of the first project in the CBN.

Scope

The dual aim of this first call for the CBN will be to:

- create an operational group to support the delivery of projects across the Accelerator, specifically:
 - support the project coordinators in horizontal administration of projects, including project and alliance management,
 - centrally source and implement IT infrastructures for projects in the Accelerator (e.g. information-sharing portals or databases, such as the framework created for the New Drugs for Bad Bugs (ND4BB) Information Centre, electronic notebooks),
 - act as an interface with stakeholders in the AMR field to explore synergies and collaboration with other initiatives and contribute to coordinating the broader AMR strategy on a global scale;
- conduct pre-competitive research aimed to:
 - provide learnings derived from shared vaccine and/or antibacterial clinical trial data,
 - improve understanding of variability and translatability of animal models of bacterial infection.

An advisory and communications board, (containing independent external experts to be selected by the CBN consortium and representatives from all the actions running in the AMR Accelerator) will be created as part of the coordination and support group within the CBN. This group will meet regularly to share summary-level, non-confidential progress reports on projects and where appropriate make recommendations to the AMR Accelerator overall including on potential future call topics.

Expected key deliverables

Deliverable 1: Operationalisation of the entire AMR Accelerator portfolio of projects, including:

- framework established for rigorous programme management and coordination of support of all actions in the Accelerator;
- secretariat role established for Accelerator committees as needed;
- interactions between the Accelerator and IMI2 Infection Control Strategic Governing Group, EFPIA, and other key stakeholders supported;
- interactions between Accelerator actions and IMI2 JU streamlined, facilitated, and supported, including support with financial and scientific reporting;
- ethical guidance and data governance and privacy standards facilitated across Accelerator as appropriate;
- sustainability of results of projects within the Accelerator ensured;
- note that some operational support will also be present in the action resulting from IMI2 JU Call 15 topic 8 (Tuberculosis Drug Development Network (TBDDN), pillar B of the Accelerator) and that the coordination and support group established by this action will work collaboratively with TBDDN in many of these areas.

Deliverable 2: Guidelines and tools for collection, integration, and dissemination of knowledge from Accelerator projects:

- IT infrastructure (e.g. information-sharing portals or databases, such as the framework created for the ND4BB Information Centre, electronic notebooks) to be used across projects in the Accelerator; for example, datasets could include:
 - clinical trial data,
 - microbiology data,
 - preclinical screening/profiling data,
 - chemical structures and descriptors,
 - animal infection model data;
- streamlined and appropriate processes for aggregation and sharing of AMR data established;
- historical AMR data to be fed into other Accelerator projects collected as needed;
- plan for distillation of findings and synthesis of key learnings across the Accelerator programme established.

Deliverable 3: Communication and collaboration across AMR funding landscape:

- mechanism for sharing information and strategies across the global AMR funding community to maximise awareness and synergy and minimise redundancy;
- plans for networking and communications across the Accelerator;
- assistance delivered in the implementation of the EU AMR agenda;
- coordination with other stakeholders on the broader AMR strategy on a global scale;
- the action resulting from IMI2 JU Call 15 topic 8 (Tuberculosis Drug Development Network (TBDDN), Pillar B of the Accelerator) and the CBN (this action) will work together to ensure the efficient communication and dissemination of information between these pillars.

Deliverable 4: Learnings derived from shared AMR clinical trial data (e.g. phase 1-3 vaccines trials, and/or antibacterial trials) and associated enabling studies:

- generation and collation of clinical trial data allow for analysis and the translation of preclinical to clinical data with respect to, for example, safety, tolerability, dose prediction, animal models of infection and efficacy, and greater disease understanding.

Deliverable 5: Improved understanding of animal infection model reproducibility and translation to clinical efficacy:

- establishment of a collection of new and/or 'control' bacterial strains to demonstrate virulence and growth *in vivo*;
- validation of rodent pneumonia and pyelonephritis models using benchmarked control compounds;

- more standardised methods of conducting these studies as ‘best practices’ identified by comparing data, sharing common practices and experiences between different investigators;
- a data set of benchmark control compounds and bacterial isolates to determine, for example:
 - reproducibility (study-to-study and lab-to-lab),
 - improve/optimize translation to clinical efficacy,
 - predictability of PK/PD targets,
 - identify optimal study conditions and practices for minimising variability.

Expected impact

The expected impact of the CBN will be to:

- contribute to the development of a vibrant AMR research environment in the EU and strengthening the competitiveness and industrial leadership of Europe;
- contribute to EU’s ambition of being a ‘best practice region’ for addressing AMR;
- with other elements of the AMR Accelerator, enhance the overall pipeline of medicines for patients with AMR infections;
- strengthen interaction of AMR stakeholders from across EU and globally;
- strengthen the scientific basis on AMR research.

Applicants should indicate how their proposals will impact and strengthen the competitiveness and industrial leadership of Europe by, for example, engaging suitable SMEs.

Potential synergies with existing consortia

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

Example of relevant IMI/IMI2 JU and non-IMI projects include:

- aspects of the research of ND4BB TRANSLOCATION (<http://www.nd4bb.eu/>) (e.g. the ND4BB Information Centre as a possible framework for data sharing);
- ND4BB ENABLE project (<http://nd4bb-enable.eu/>);
- ND4BB COMBACTE projects and iABC Programme, ([https://www.combacte.com](https://www.combacte.com;); <http://www.iabcproject.com>) in particular, in relation to networks (CLIN-NET, LAB-NET, STAT-NET and EPI-NET);
- projects funded by other organisations/programmes supporting AMR R&D e.g. the Global AMR R&D Hub, the EU Framework Programmes for Research and Innovation FP7 (for example FORMAP, NAREB) and Horizon 2020, the Joint Programming Initiative AMR, Wellcome Trust, Biomedical Advanced Research and Development Authority (BARDA), Medical Research Council (MRC), CARB-X, Global Antibiotic Research and Development Partnership (GARDP), National Institute of Allergy and Infectious Diseases (NIAID), TB Alliance and TB Drug Accelerator etc. to ensure synergy and avoid duplication of research.

Industry consortium

The industry consortium is composed of the following EFPIA companies:

- GSK (lead)
- AstraZeneca
- Evotec
- Janssen

The industry consortium will provide knowledge and expertise in:

- best practices on resourcing, setting milestones, and project/portfolio management;
- setting up and maintaining active and nimble governance processes;
- data and knowledge management (e.g. potential mechanisms for collection and pooling relevant data sets);
- ethical guidance and data governance and privacy standards as appropriate;
- networking and communication across large programmes such as the Accelerator.

The industry consortium will also:

- generate and share data, samples, and information from industry-sponsored clinical trials (phases 1-3) in the AMR space (e.g. resources associated with vaccine R&D for drug resistant bacteria causing major burden of disease in developing world, including but not limited to clinical trials and enabling studies, manufacturing, toxicology studies, etc. and/or for antibacterial R&D, e.g. phase 3 gepotidacin clinical trials and associated enabling studies such as but not limited to CMC activities, clinical operations);
- assist in the analysis of the output of clinical trials in the AMR space, e.g. efficacy, safety, translation of preclinical data with respect to safety, tolerability, dose prediction, animal models of infection and efficacy;
- conduct, share data, and analyse results from animal infection studies.

Indicative duration of the action

The indicative duration of the action is 72 months.

Future project expansion

Potential applicants must be aware that the Innovative Medicines Initiative 2 (IMI2) Joint Undertaking may, if exceptionally needed, publish at a later stage another call for proposals restricted to the consortium already selected under this topic, in order to enhance and progress the results and achievements by extending the duration and funding by means of another grant agreement. The consortium will be entitled to open to other beneficiaries as it sees fit. One of the purposes of pillar A is to collate data on antibiotic attrition and effectiveness. The analyses that are carried out will generate further knowledge and understanding and will generate further work streams as yet to be identified. The additional work plans will be addressed via a call for proposals restricted or not to the consortium already selected, depending on the resources required.

Indicative budget

The indicative EFPIA in-kind contribution is EUR 17 300 000.

Due to the global nature of the participating industry partners it is anticipated that some elements of the contributions will be non-EU/H2020 Associated countries in-kind contribution⁹².

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

Applicants should consider allocating a budget in the region of EUR 5 000 000 of IMI2 JU contribution to support the operational component of the CBN, given the need to support multiple projects across the Accelerator.

Applicant consortium

The applicant consortium will be selected on the basis of the submitted short proposals. The applicant consortium is expected to address all the research objectives and make key contributions to the defined deliverables in synergy with the industry consortium which will join the selected applicant consortium in

⁹² Note: This does not however constitute the justification referred to in Article 4(2) of Council Regulation (EU) No 557/2014 ('IMI 2 JU regulation').

preparation of the full proposal for stage 2. The applicant consortium is expected to mobilise expertise and proven track record in, for the operational group:

- conducting, and capacity for supporting, grant funded research, preferably with respect to working within projects established by the IMI/IMI2 JU or H2020;
- coordinating multiple discovery AMR projects;
- rigorous project and programme management and alliance management for projects of the complexity and scale of the overall AMR Accelerator, preferably with respect to working within projects established by the IMI/IMI2 JU or H2020 (including management of scientific and financial reporting, legal agreements including IP arrangements, meeting facilitation/secretariat role);
- ethics and data governance and privacy in relation to AMR;
- communications and outreach to the scientific community and public;
- collection, collation and curation of data sets and identifying, implementing, maintaining IT systems across large collaborative projects or PPPs,
- business development as applied to large collaborative projects or PPPs;

and in, for the scientific group:

- analysis of preclinical and clinical trial data in the AMR space in relation to e.g. efficacy, safety, translation of preclinical data with respect to safety, tolerability, dose prediction, animal models of infection and efficacy;
- conducting and analysing animal infection models to generate reference data of benchmarked control compounds and bacterial isolates.

It is suggested that, to minimise complexity, maximise stability, and maintain a lean and effective group, the number of participants directly related to the operational objectives described above be minimal in size.

Suggested architecture of the full proposal

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

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 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.

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.

Sustainability

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

Topic 8: AMR Accelerator programme Pillar B: Tuberculosis drug development network to accelerate and validate scientific discoveries and advance the R&D pipeline of new and innovative agents to address the global tuberculosis epidemic

Part of the IMI2 AMR Accelerator programme

Topic details

Topic code	IMI2-2018-15-08
Action type	Research and Innovation Action (RIA)
Submission and evaluation process	2 stages

Specific challenges to be addressed

On the eve of World tuberculosis (TB) Day 2018, the EU Commissioners for Health & Food Safety; Research, Science & Innovation; Employment, Social Affairs, Skills and Labour Mobility; and International Development and Cooperation issued a joint statement⁹³ highlighting the EU's commitment to eradicating TB and the crucial role research and product development plays in this. TB is the leading cause of death from a single infectious agent worldwide. An estimated 10.4 million people contracted TB in 2016. The lack of efficiency of current TB drugs is emphasised by the nearly 1.8 million annual deaths reported by World Health Organisation (WHO). Of these, 200 000 were confirmed cases of drug resistant TB, although real estimates could be much higher.

The majority of the 1.8 million annual TB deaths are caused by drug-susceptible TB (DS-TB). The current standard of care (SOC), namely HRZE (H=Isoniazid, R=Rifampin, Z=Pyrazinamide, E=Ethambutol) has an efficacy (favourable outcome) in clinical trials of 90-95 %, yet effectiveness in the field in high incident countries is merely ~75 %. The spread of resistant forms of TB is a continuum, with multi-drug resistant (MDR)-TB cases having already been detected in every country where there is an existing TB surveillance programme. Treatment options for MDR-TB are very poor; only 20 % of patients receive an effective treatment which is excessively long and complex (combination treatment of 7-10 drugs given for 18-24 months for a total of 20 000 pills and 240 painful injections). The lack of adequate compliance and the limited efficacy further reduces the success rate of MDR treatments to only 50 %.

Although significant efforts have been made during the last decade, only two novel drugs have been approved by the Food and Drug Administration (FDA) and European Medicines Agency (EMA) since 1975 (Sirturo® from Janssen and Delamanid® from Otsuka). Additionally, the lack of new drug candidates to combine with makes it challenging to impossible to develop a fully new combination.

As expressed by the United Nations (UN), a massive scale-up⁹⁴ and a dynamic, global, multi-sectoral approach⁹⁵ is needed if the global target of eradicating tuberculosis by 2030⁹⁶ is to be met. At present, there is a strong consensus both in private and public research sectors working on TB that having a large number of new drug candidates, which are ready to enter into clinical combination studies, is the most critical step to achieving this aspirational goal that will have a tremendous impact on global health. These new candidates should be: 1) highly efficacious against all forms of TB; 2) safe for long-term administration to all TB patients; and 3) orally bioavailable. There is currently a lack of compounds that would be active against all forms of drug-resistant TB with no cross resistance and no drug-drug-interaction liability with existing gold standard drugs. Cost of goods that allow a cheap and easy production should also be factored in to prioritise compounds as appropriate.

⁹³ http://europa.eu/rapid/press-release_STATEMENT-18-2461_en.htm

⁹⁴ <https://news.un.org/en/story/2016/10/542712-massive-scale-needed-if-global-targets-tuberculosis-are-be-met-top-un-health>

⁹⁵ <https://news.un.org/en/story/2017/10/569592-tuberculosis-worlds-top-infectious-killer-un-health-agency-calls-political>

⁹⁶ <http://www.who.int/tb/strategy/en/>

The sum of initiatives financed by the European Union and IMI (New Drugs for Bad Bugs (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 National Institutes of Health (Tuberculosis Research Units Network, TBRU-N), the Bill and Melinda Gates Foundation (TB Drug accelerator, TBDA), together with the Global Alliance for TB, have worked to create the framework and infrastructure required to support and accelerate the development of new drug candidates in TB. Bringing forward a new generation of candidates through good laboratory practice (GLP) toxicity studies and first time in human (FTIH) and performing early combination studies to explore drug-drug interactions, efficacy and safety will accelerate the discovery of novel combination regimens with a higher probability of success. The TB drug development Network (TBDDN) within the AMR Accelerator brings together the collective will of all pharmaceutical companies involved in TB in a European initiative carefully conceived to be synergistic with other initiatives such as the TBDA platform.

The TB drug development Network (TBDDN), pillar B of the IMI2 AMR Accelerator programme, will function as a platform based on the principles of open innovation to advance discovery, preclinical and early clinical projects in the field of TB and MDR-TB. This component of the Accelerator will work to address the innovation gap in the discovery and early development of a pan-TB regimen by enabling access to both novel drug candidates and innovative tools to accelerate the discovery of new combination regimens for the treatment of TB. One of the objectives of the TBDDN is to become a worldwide reference for the development of novel candidates and regimens by sharing results generated by partners and peers from small and medium-sized enterprises (SMEs), public institutions and pharmaceutical companies following the intellectual property (IP) rules set for the IMI2 JU grants⁹⁷.

Scope

The main objective of the TBDDN is to provide a unique platform where discovery, development, and clinical trial readouts will occur allowing maximal engagement across groups in the TB field. Specifically:

- coordinate, profile and progress the portfolio of anti-TB compounds existing within the industry consortium (EFPIA companies and Associated Partners) from the advanced lead stage through Phase 1 (candidates ready to enter into Ph-2 clinical studies);
- identify preferred drug partners for preclinical combination studies that will facilitate the design of combination regimens consisting of new TB drugs with an indication for the treatment of any form, including MDR, of TB (pan-TB regimen);
- create additional tools and technologies to progress anti-TB compounds, and to provide learnings derived from the analysis of shared anti-TB clinical trial data;
- develop new alternative anti-tubercular drugs (host-defence or virulence approaches);
- act as an interface with stakeholders in the TB field and explore synergies and collaboration with the action resulting from IMI2 JU Call 15, topic 7 and potential TB-focused actions from IMI2 JU Call 16 as well as other AMR initiatives.

Expected key deliverables

Deliverable 1: Development and implementation of new assays and tools to study anti-TB compounds:

- assays that can rapidly measure the efflux, outer membrane penetration, of both mycobacteria, infected macrophages, and caseum to enable the rational design of novel, pan-active anti-TB drug candidates;
- *in vitro* assays taking into account disease complexity, including host cells (foamy macrophages, granulomas, caseum medium, etc.) and relying on recent knowledge of TB pathogenesis and persistence;
- optimised animal infection models for both single drugs and combinations to i) improve / optimise translation to clinical efficacy; ii) improve reproducibility (study-to-study and lab-to-lab); iii) determine predictability of pharmacokinetic/pharmacodynamics (PK/PD) parameters; and iv) identify optimal study conditions and practices for minimising variability;

⁹⁷ See https://www.imi.europa.eu/sites/default/files/uploads/documents/reference-documents/h2020-mga-imi_en_v5.pdf and https://www.imi.europa.eu/sites/default/files/uploads/documents/apply-for-funding/call-documents/imi2/Annotated_Model_Grant_Agreement%E2%80%9393AGA.pdf

- imaging platforms (*in vitro/in vivo*) to measure pharmacodynamic responses at the sites of action, including single cell microscopy, MALDI, PET/CT, hollow-fibre;
- standardised specific PK/PD studies/models required to support approval for limited use/accelerated pathways for novel TB investigational new drug (INDs) and combinations of INDs & acceptance with EMA & FDA with a focus on human dose prediction to maximise efficacy and minimise risk of resistance;
- translational PBPK-PD models fed with preclinical and clinical data in the TB space (PBPK, PD and disease progression integrative models) to accelerate development of combination studies, associated with the development of novel biomarkers to assess treatment efficacy, disease evolution and cure at preclinical (MBL assay, CFU counting, microCT scan) and clinical (PET/CT scanning, biomarkers from urine or saliva vs blood, immunological markers) stages;
- new host-defence or virulence approaches: identify possible new targets and provide access to *in vitro* and *in vivo* translational assays to better select the next generation of anti-TB drugs.

Deliverable 2: An advanced portfolio of anti-TB compounds:

- new clinical candidates which have completed Phase 1 and are ready to enter into Phase 2 proof of concept studies in TB patients (note that Phase 2 studies are outside the scope of the TBDDN);
- new potential repurposed medicines ready to enter Phase 2;
- novel combination regimens that will be formed by combining the clinical candidates.

Deliverable 3: Learnings derived from shared TB clinical trial data (e.g. Phase 1-3 clinical trials related to TB) and associated enabling studies:

- generation and collation of clinical trial data to allow for analysis and translation of preclinical to clinical data with respect to, for example, safety, tolerability, dose prediction, animal models of infection and efficacy, and greater disease understanding.

Deliverable 4: Management of TBDDN:

- framework established for rigorous programme management and coordination of the action;
- interactions with the Pillar A action resulting from IMI2 JU Call 15, topic 7, with potential future actions under Pillar B of the Accelerator, and with IMI2 JU;
- support financial and scientific reporting for TBDDN projects;
 - collect and distribute historical preclinical and clinical TB data amongst TB projects within the AMR accelerator;
 - administrative tasks to support the TBDDN organisation, including tasks such as the organisation of consortium meetings, intra- and inter-work package meetings, preparation of minutes, progress reports, and the interaction required with the Pillar A action resulting from IMI2 JU Call 15, topic 7 that will provide operational support (particularly in legal, data sharing, communication and dissemination tasks).

Sustainability

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

Expected impact

The impact of the TBDDN will help attain the UN 2030 objective by:

- providing new tools and understandings to progress TB science for the discovery of new preclinical candidates and novel combination regimens across the TB R&D landscape;
- contributing to the development of a vibrant TB research environment in the EU and strengthening the competitiveness and industrial leadership of Europe;
- contributing to EU's ambition of being a 'best practice region' for addressing AMR;

- enabling the progression of potential new treatment solutions for TB patients worldwide using a preferential pricing approach for low- and middle-income countries, with the intent to improve the quality of life and life expectation of TB patients;
- strengthen interaction of TB R&D stakeholders from across the EU and globally.

Applicants should indicate how their proposals will impact and strengthen the competitiveness and industrial leadership of Europe by, for example, engaging suitable SMEs.

Potential synergies with existing consortia

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

The project funded under TBDDN (facilitated by the coordination and support group within the CBN) will work to maximise synergies with the following AMR projects and other public-private partnerships (PPPs):

- aspects of the research of ND4BB TRANSLOCATION (<http://www.nd4bb.eu/>) (e.g. the ND4BB Information Centre as a possible framework for data sharing);
- ND4BB ENABLE project (<http://nd4bb-enable.eu/>);
- ND4BB COMBACTE projects and iABC Programme, (<https://www.combacte.com>; <http://www.iabcproject.com>) in particular in relation to the networks CLIN-NET, LAB-NET, STAT-NET and EPI-NET;
- Projects funded by other organisations/programmes supporting AMR R&D e.g. the Global AMR R&D Hub, the EU Framework Programmes for Research and Innovation FP7 and Horizon 2020, the European & Developing Countries Clinical Trials Partnership (EDCTP) (projects such as PanACEA), Joint Programming Initiative AMR, Wellcome Trust, Biomedical Advanced Research and Development Authority (BARDA), Medical Research Council (MRC), CARB-X, Global Antibiotic Research and Development Partnership (GARDP), National Institute of Allergy and Infectious Diseases (NIAID), TB Drug Accelerator etc. to ensure synergy and avoid duplication of research.

Of note the TBDDN will ensure that:

- the current project will, where appropriate, build on the output of the IMI project PreDiCT-TB and FP7-funded projects MM4TB and ORCHID;
- complementarities with TBDA, and other global platforms in TB by involving these organisations directly as Associated Partners in the project;
- experts from the regulatory agencies (EMA) and the public and medical sector are consulted in the project so that the data generated can be used when regulatory filings will be made.

Industry consortium

The industry consortium is composed of the following EFPIA companies:

- GSK (lead)
- Evotec
- Janssen

In addition, the industry consortium includes the following IMI2 Associated Partners:

- Bill & Melinda Gates Foundation
- TB Alliance
- the University of Dundee (Drug Discovery Unit)

Please note that the IMI2 JU matching of in-kind provided by Associated Partners on a specific disease (e.g. TB) will be applied to the same disease if required by the Associated Partners.

The Associated Partners will provide novel potential products from their respective portfolios to be included in the TBDDN and scientific and project management to support their series and combinations thereof. The BMGF will also serve as an interface with the existing TB Drug Accelerator (TBDA) and the centralised hubs to access the clinical data generated in TB.

To achieve the scientific objectives of the TBDDN, the industry consortium will do the following.

- Conduct standard medicinal chemistry, microbiology, pharmacology and early ADMET optimisation programmes for novel anti-TB compounds.
- Conduct and share results and information of enabling studies such as synthesis (up-scales, fermentation), optimisation of lead molecules, computational chemistry, profiling in *in vitro* and *in vivo* models (marmoset and murine models, cell & lesion penetration, PKPD profiling and modelling, metabolomics), access to enzymology platforms (biochemical and biophysical assays and crystallography) and toxicology of novel pre-candidates⁹⁸ from TB portfolios from EFPIA and Associated Partners for further analysis.
- Perform preclinical development studies⁹⁹ (e.g. GLP toxicity studies, early pharmaceutical development, development and manufacture of clinical trial material (drug substance and drug product)).
- Where appropriate, provide compounds to support and/or validate the development of assays or approaches including potentially the generation of new natural products (fermentation, extract purification).
- Share historical TB drug discovery and development data where appropriate.
- Provide knowledge and expertise in TB drug discovery and development.
 - Capacity for multi-gram scale up synthesis of non-GMP grade of selected pre-candidates (500g), to assess therapeutic index of preclinical pre-candidates (non GLP toxicity and *in vivo* profiling into advanced TB models):
 - early pharmaceutical development including process chemistry development, pre-formulation, formulation and drug delivery techniques to maximise the evaluation of the therapeutic index of novel compound;
 - capacity for scale-up synthesis of selected candidate compounds of suitable quality (usually GMP grade) (1-5 kg) to perform GLP toxicity studies.
 - If additional throughput is needed, ability to undertake first into human studies (FTIH) on healthy volunteers to determine key pharmacokinetic parameters in humans (half-life, volume of distribution, clearance and potential for accumulation under extensive repeated doses) and to assess an indication of adverse effects (standard for any new IND with special focus on cardiovascular and hepatotoxicity).
- Generate and share data, samples, and information from industry-sponsored clinical trials (Phase 1-3) in the field of TB including drug sensitive, drug resistant, and multidrug resistant tuberculosis, of compounds (e.g. Sirturo (Bedaquiline), Pretomanid, Delamanid, Sutezolid, Leu-tRNA synthetase inhibitor, Mtb cholesterol dependent inhibitor and Mtb DprE1 inhibitors and others), including enabling studies (e.g. synthesis, profiling, and toxicology) of novel precandidates from TB portfolios from EFPIA and associated partners (DDU and TB Alliance) for further analysis.
- Assist in the analysis of the output of clinical trials in the TB space, e.g. efficacy, safety, translation of preclinical data with respect to safety, tolerability, dose prediction, animal models of infection and efficacy.

The TBDDN project will include activities from industry-sponsored studies in Phase 1-3 generating data to be shared by EFPIA with the partners of this action. Studies will be sponsored and funded by the respective contributing partner including the cost of full time equivalents (FTEs) and other expenses to run the studies, including but not limited to contract research organisation (CRO) costs, laboratory costs, and investigator and institutional grants based on respective site contracts. Payments will be based on respective agreements with trial related sites and/or trial related scientific advisory groups.

Indicative duration of the action

The indicative duration of the action is 72 months.

⁹⁸ Pre-candidate studies: discovery activities from Lead optimisation to selection of a molecule as preclinical candidate

⁹⁹ Preclinical development: studies performed between preclinical candidate and first time in human.

Indicative budget

The indicative industry in-kind contribution is EUR 120 900 000.

This contribution comprises an indicative EFPIA in kind contribution of EUR 53 900 000 and an indicative IMI2 JU Associated Partner in kind contribution of EUR 67 000 000.

Due to the global nature of the participating industry and Associated Partners, it is anticipated that some elements of the contributions will be non-EU/ H2020 Associated Countries in kind contribution.¹⁰⁰

The financial contribution from IMI2 JU contribution will be a maximum of EUR 89 830 000.

Applicant consortium

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

To achieve the scientific objectives of the TBDDN, the applicant consortium is expected to mobilise, as appropriate, expertise and capabilities in the following areas:

- analysis of preclinical and clinical trial data in the TB space in relation to e.g. efficacy, safety, translation of preclinical data with respect to safety, tolerability, dose prediction, animal models of infection and efficacy;
- collection, collation and curation of TB-specific data sets and identifying, implementing, maintaining IT systems (e.g. information sharing portals or databases) across large collaborative projects or PPPs, for example datasets could include:
 - clinical trial data;
 - microbiology data;
 - preclinical screening / profiling data;
 - chemical structures and descriptors;
 - animal infection model data;
- development of assays that can rapidly measure the efflux, outer membrane penetration, of both mycobacteria, infected macrophages, and caseum to enable rational design of novel pan-active anti-TB drug candidates;
- translation of PK/PD and regulatory knowledge to support the development of limited use/accelerated pathways for anti-tubercular drugs;
- conducting and analysing TB-animal infection models for single drugs and combinations;
- imaging platforms to measure pharmacodynamic responses at the sites of action;
- translational PBPK-PD models fed with preclinical data in the TB space (PBPK, PD and disease progression integrative models), expertise in preclinical and clinical TB biomarkers;
- drug discovery optimisation activities, e.g. medicinal chemistry, microbiology, scale up, pharmaceutical formulation, DMPK, toxicology, etc;
- development of *in vitro* and *in vivo* tools to identify, characterise and progress molecules from host-defence or virulence approaches;
- multi-gram scale up synthesis of non-GMP grade of selected pre-candidates (500g), to assess therapeutic index of preclinical pre-candidates (non GLP toxicity and *in vivo* profiling into advanced TB models);

¹⁰⁰ Note: This does not however constitute the justification referred to in Article 4(2) of the IMI 2 JU regulation.

- pharmaceutical development techniques to maximise the evaluation of the therapeutic index of novel compound;
- scale up synthesis of selected candidate compounds of GMP grade (1-5 kg) of active product ingredients of GMP grade to perform GLP toxicity studies;
- ability to conduct in parallel several first into human studies (FTIH) on healthy volunteers to determine key pharmacokinetic parameters in humans (half-life, volume of distribution, clearance and potential for accumulation under extensive repeated doses) and to assess an indication of adverse effects (standard for any new IND with special focus on cardiovascular and hepatotoxicity).

In view of the complexity and size of the action, the applicant consortium must bring expertise and consider appropriate resources to deal with the scientific coordination and daily project management, undertake financial tasks (distribution of budget, cost reporting, etc.), and deal with administrative tasks. In addition, operational support will be provided by the coordination and support group formed in the CBN through IMI2 JU Call 15 topic 7 (particularly in legal, data sharing, communication and dissemination tasks).

In addition, representatives from the selected project will contribute to an advisory and communications board (containing independent experts and representatives from all the projects running in the AMR Accelerator) created as part of the coordination and support group within the CBN. This group will meet regularly to share summary level, non-confidential progress reports on projects and where appropriate make recommendations to the AMR Accelerator overall.

Suggested architecture of the full proposal

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

The consortium is expected to have a strategy on the translation of the relevant project outputs into regulatory practices, regulatory, clinical and healthcare practice. These strategies aim to ensure 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 e.g. qualification advice on the proposed methods for novel methodologies for drug development.

Note that overall plans and go/no-go milestones for progression of different molecules or approaches in the project will need to be established during the full project proposal phase of the application and should be included in full proposals. These milestones will then assist in the decision-making process to help ensure that the overall TBDDN portfolio remains dynamic and work on compounds is prioritised across the portfolio appropriately. Therefore, applicants should be aware that resources dedicated to a specific phase or piece of work may increase or decrease during the project.

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 molecules or approaches. Such decisions would be made by a committee that includes representatives from all project partners, e.g. including from the Associated Partners (BMGF, TB Alliance and Dundee Drug Discovery Unit (DDU), the contributing EFPIA partners, and the public 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 e.g. quarterly, streamlined, single-meeting process. For the avoidance of doubt, any decisions directly affecting an existing compound asset (such as an investigational medicinal product from one of the participants), shall always require consent of the participant who owns the existing compound asset. 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, i.e., 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/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.

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.

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 15 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-IMI2-2018-15-two-stage
Type of actions	Research and Innovation Action (RIA)
Publication Date	18 July 2018
Stage 1 Submission start date	18 July 2018
Stage 1 Submission deadline	24 October 2018 (17:00:00 Brussels time)
Stage 2 Submission deadline	15 May 2019 (17:00:00 Brussels time)
Indicative Budget	
From EFPIA companies and IMI2 JU Associated Partners	EUR 214 847 000
From the IMI2 JU	EUR 171 875 862

Call Topics

IMI2-2018-15-01 Integrated research platforms enabling patient-centric drug development	The indicative contribution from EFPIA companies is EUR 10 190 000 The indicative IMI2 JU Associated Partners contribution is EUR 2 175 000 The financial contribution from IMI2 JU is a maximum of EUR 12 005 000	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.
IMI2-2018-15-02 Blockchain Enabled Healthcare	The indicative contribution from EFPIA companies is EUR 9 680 000 The financial contribution from IMI2 JU is a maximum of EUR 8 330 000	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.

<p>IMI2-2018-15-03</p> <p>Microenvironment imposed signatures in tissue and liquid biopsies in immune-mediated diseases</p>	<p>The indicative contribution from EFPIA companies is EUR 15 500 000</p> <p>The financial contribution from IMI2 JU is a maximum of EUR 15 500 000</p>	<p>Research and Innovation Action (RIA)</p> <p>Two-stage submission and evaluation process.</p> <p>Only the applicant consortium whose proposal is ranked first at the first stage is invited for the second stage.</p>
<p>IMI2-2018-15-04</p> <p>Emerging translational safety technologies and tools for interrogating human immuno-biology</p>	<p>The indicative contribution from EFPIA companies is EUR 10 895 000</p> <p>The indicative IMI2 JU Associated Partners contribution is EUR 105 000</p> <p>The financial contribution from IMI2 JU is a maximum of EUR 11 000 000</p>	<p>Research and Innovation Action (RIA)</p> <p>Two-stage submission and evaluation process.</p> <p>Only the applicant consortium whose proposal is ranked first at the first stage is invited for the second stage.</p>
<p>IMI2-2018-15-05</p> <p>Development and validation of translational platforms in support of synaptopathy drug discovery</p>	<p>The indicative contribution from EFPIA companies is EUR 6 730 500</p> <p>The indicative IMI2 JU Associated Partners contribution is EUR 71 500</p> <p>The financial contribution from IMI2 JU is a maximum of EUR 6 210 862</p>	<p>Research and Innovation Action (RIA)</p> <p>Two-stage submission and evaluation process.</p> <p>Only the applicant consortium whose proposal is ranked first at the first stage is invited for the second stage.</p>
<p>IMI2-2018-15-06</p> <p>Digital endpoints in neurodegenerative and immune-mediated diseases</p>	<p>The indicative contribution from EFPIA companies is EUR 19 400 000</p> <p>The indicative IMI2 JU Associated Partners contribution is EUR 1 900 000</p> <p>The financial contribution from IMI2 JU is a maximum of EUR 21 000 000</p>	<p>Research and Innovation Action (RIA)</p> <p>Two-stage submission and evaluation process.</p> <p>Only the applicant consortium whose proposal is ranked first at the first stage is invited for the second stage.</p>
<p>IMI2-2018-15-07</p> <p>AMR Accelerator programme Pillar A: Capability Building Network to accelerate and validate scientific discoveries</p>	<p>The indicative contribution from EFPIA companies is EUR 17 300 000</p> <p>The financial contribution from IMI2 JU is a maximum of EUR 8 000 000</p>	<p>Research and Innovation Action (RIA)</p> <p>Two-stage submission and evaluation process.</p> <p>Only the applicant consortium whose proposal is ranked first at the first stage is invited for the second stage.</p>
<p>IMI2-2018-15-08</p> <p>AMR Accelerator programme Pillar B: Tuberculosis drug development network to accelerate and validate scientific discoveries and advance the R&D pipeline of new and innovative agents to address the global tuberculosis epidemic</p>	<p>The indicative contribution from EFPIA companies is EUR 53 900 000</p> <p>The indicative IMI2 JU Associated Partners contribution is EUR 67 000 000</p> <p>The financial contribution from IMI2 JU is a maximum of EUR 89 830 000</p>	<p>Research and Innovation Action (RIA)</p> <p>Two-stage submission and evaluation process.</p> <p>Only the applicant consortium whose proposal is ranked first at the first stage is invited for the second stage.</p>

Annex III - IMI2 Call 16 topics text

Introduction

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

The Innovative Medicines Initiative 2 Joint Undertaking (IMI2 JU) has been created¹⁰¹ 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 World¹⁰².

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 companies¹⁰³, 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)¹⁰⁴ is the main reference for the implementation of research priorities for IMI2 JU. The scientific priorities for 2018 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.

¹⁰¹ Council Regulation (EU) No 557/2014 of 6 May 2014 establishing the Innovative Medicines Initiative 2 Joint Undertaking (IMI2 JU).

¹⁰² http://www.who.int/medicines/areas/priority_medicines/en/

¹⁰³ Under IMI2 JU, mid-sized companies having an annual turnover of EUR 500 million or less not being affiliated entities of companies with an annual turnover of more than 500 million; the definition of 'affiliated entities' within the meaning of Article 2(1)(2) of Regulation (EU) No 1290/2013 applies mutatis mutandis. Where established in an EU Member State or an associated country, are eligible for funding.

¹⁰⁴ 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) 2016/679¹⁰⁵ and Clinical Trial Regulation (EU) 536/2014¹⁰⁶ (and/or Directive 2001/20/EC¹⁰⁷) and any relevant legislation¹⁰⁸.

Before submitting a proposal, applicant consortia should familiarise themselves with all Call documents such as the IMI2 JU Manual for evaluation, submission and grant award¹⁰⁹, 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).

¹⁰⁵ 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.

¹⁰⁶ 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.

¹⁰⁷ 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.

¹⁰⁸ Directive 95/46/EC on the protection of individuals with regard to the processing of personal data and the free movement of such data and implementing national laws: <http://eur-lex.europa.eu/legal-content/EN/TXT/?uri=celex:31995L0046>

¹⁰⁹ http://www.imi.europa.eu/sites/default/files/uploads/documents/apply-for-funding/call-documents/imi2/IMI2_ManualForSubmission_v1.6_October2017.pdf

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 that 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), the largest single contributor to AMR health, mortality, and economic impact, is scheduled to be discussed by heads of state at the UN General Assembly (September 2018).

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 novel mechanism antibiotics 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 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 learnings 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 roughly six-year period.

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, 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, progress potential new treatments through phase 1-3 clinical trials, and 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 as 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>¹¹⁰) 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 of '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 consist 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 two-stage IMI2 JU Call 15 includes two topics (topic 7 and topic 8) to launch Pillar A and Pillar B of the AMR Accelerator, respectively. The single-stage IMI2 JU Call 16 includes seven topics under Pillar C.

Applicants may submit a proposal to any of the topics under the different pillars and are not obliged to apply for all. If applicants wish to submit for more than one topic under the same or different pillars, separate proposals should be submitted.

For the two topics for Pillars A and B, launched as part of IMI2 JU Call 15:

- the indicative EFPIA in-kind contribution will be EUR 71 200 000
- the indicative Associated Partner in-kind contribution will be EUR 67 000 000

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.

The overall IMI2 JU financial contribution to the AMR Accelerator topics under Pillars A, B and C of IMI2 JU Call 15 and IMI2 JU Call 16 will be a maximum of EUR 144 730 000.

Future call 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.

¹¹⁰ For example, points 3 and 4 from the 'Roadmap for Progress'.

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 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 an action that will create 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).

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)¹¹¹. 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 available budget. A total of at least 8-10 grant agreements are anticipated in the PBN (indicative number only).

¹¹¹ 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 (selected under Pillar A from IMI2 JU Call 15 topic 7, and containing the coordination and support group¹¹²) will be complementary to all the grant agreements of actions selected under Pillars B and C (via IMI2 JU Call 15 topic 8 and IMI2 JU Call 16 topics, and potential future additional calls for proposals), as well as probable future grant agreements from actions selected under Pillar A. In addition, grant agreements of actions under pillar B, if more than one, will be complementary between them. The respective options of Article 2, Article 31.6 and Article 41.4 of the IMI2 JU Model Grant Agreement¹¹³ will be applied. Accordingly, the consortia selected under Pillars A, B, and C will conclude collaboration agreements with the CBN consortium selected from IMI2 JU Call 15 topic 7. These collaboration agreements will provide the framework for the CBN 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 action(s) and the Integrated Research Platforms (IRP) action of IMI2 JU Call 15 topic 1 to cover collaboration and sharing of information on TB-related activities. The MoU should constitute one deliverable of the action resulting from topic 8 of IMI2 JU Call 15. 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 action(s), as well as the IRP action of IMI2 JU Call 15 topic 1, with appropriate provisions to protect confidentiality and intellectual property of the interactions between those consortia.

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 have been the 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 of 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 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.

¹¹² For additional details see the topic 7 "Capability Building Network" of IMI2 JU Call 15.

¹¹³ See: https://www.imi.europa.eu/sites/default/files/uploads/documents/reference-documents/h2020-mga-imi_en_v5.pdf

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 key role in a EU AMR programme with connectivity into the broader global agenda on AMR;
 - enable SME, and/or academic groups to progress pre-competitive basic science project in the AMR field;
 - 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 project 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;
 - opportunity to work within a broad network on researchers focused on TB drug discovery.
- **Portfolio Building Network:**
 - 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 both 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.

AMR Accelerator Programme – Pillar C: Portfolio Building Networks to advance the R&D pipeline of new and innovative agents to address AMR Topics:

Topics:

Topic 1: Progress new assets (one pre-new molecular entity (preNME) and one first-time-in-human (FTIH) start) for tuberculosis (TB) that act synergistically with bedaquiline, cytochrome bc or cytochrome bd inhibitors

Topic 2: Progress novel assets (one FTIH start) for non-tubercular mycobacteria (NTM) that may act synergistically with bedaquiline and cytochrome bc drugs

Topic 3: Discover and progress novel assets with new mechanisms of action (one preNME for TB and one preNME for NTM) and biomarkers for TB and NTM infection

Topic 4: Determination of gepotidacin levels in tonsils and prostatic tissue

Topic 5: Infection site targeting, antibiotic encapsulated in nanoparticles for treating extracellular bacterial infections

Topic 6: Functional Ethionamide boosters: a novel combination for tuberculosis therapy

Topic 7: Intravenous treatments of serious infections (urinary tract infections (UTI), intra-abdominal infections (IAI) & hospital-acquired pneumonia/ventilator associated pneumonia (HAP/VAP)) caused by Gram(-) bacteria (Enterobacteriaceae +/- *Pseudomonas* and/or *Acinetobacter*)

Topic details

Topic code	IMI2-2018-16-01
	IMI2-2018-16-02
	IMI2-2018-16-03
	IMI2-2018-16-04
	IMI2-2018-16-05
	IMI2-2018-16-06
	IMI2-2018-16-07
Action type	Research and Innovation Action (RIA)
Submission and evaluation process	single-stage

Specific challenges to be addressed

The Portfolio Building Network (PBN), Pillar C of the IMI2 JU AMR Accelerator programme, will address the limited pipeline of treatments and preventions for AMR infections by enabling vibrant and nimble collaborations between EFPIA companies and small and medium-sized enterprises (SMEs) and/or academics that will advance the R&D pipeline of new and innovative agents to address AMR.

Scope

The PBN will provide a mechanism for partnerships between EFPIA constituent and affiliated entities and SMEs and/or academic teams for the discovery and development of new antibacterial assets to address the broad topic of AMR including Gram-positive and Gram-negative bacteria, including tuberculosis (TB) and non-tubercular mycobacteria (NTM) and prevention (vaccines/mAbs, immunoprophylaxis and others) and treatment (new antibiotics, non-antibiotic alternatives, and combinations) approaches. Assets and projects can originate from SMEs, academia, or EFPIA companies, and will be jointly progressed, including potentially pre-

clinical and clinical development work. The potential generation of new clinical pathways, or the potential contribution to regulatory pathways for pathogens such as NTM is included in the scope, as is the conduct of phase 2 TB trial(s). Consortia arising from the IMI2 JU Call 16 topics 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) (see details under the section 'Applicant consortium').

There are seven topics under the current single-stage Call topic described below. Additional single-stage Calls may be published in the future.

Topics 1-3: Advancing a portfolio of novel compounds with the potential to treat TB and NTM

The goal of these actions is to develop and advance a portfolio of anti-TB drugs that may be used in combination with bedaquiline and cytochrome bc inhibitors to shorten treatment regimens and improve safety and efficacy.

Bedaquiline, currently in Phase 3 clinical development, is a diarylquinoline antimycobacterial drug indicated as part of combination therapy in the treatment of adults with pulmonary multi drug resistant tuberculosis (MDR TB). It specifically inhibits mycobacterial ATP (adenosine 5'-triphosphate) synthase, by binding to subunit c of the enzyme that is essential for the generation of energy in *Mycobacterium tuberculosis*. The cytochrome bc inhibitor 901 is in the late lead optimisation phase.

IMI2 JU Call 16, topics 1-3 target different innovative novel assets, mechanisms and combinations for TB.

Topic 1: Progress new assets (one preNME and one FTIH start) for TB that act synergistically with bedaquiline, cytochrome bc or cytochrome bd inhibitors

These compounds can target any stage of energy metabolism, including ATP synthase, cytochrome bc and bd, NDH-2, menaquinone synthesis, but also glycolysis and the citric acid cycle, or any other metabolic pathway. Other assets, targeting the host cell instead of the bacilli itself, are also potentially interesting to combine with energy metabolism inhibitors.

The scope of this topic will be to identify and progress novel lead compounds towards design and implementation of phase 1.

As part of the project objectives, several models and tools are needed to further profile the targets of the respiratory chain and evaluate the effect of the combinations, that include but are not limited to:

Evaluation in several *in vitro* and *in vivo* models including but not limited to dormancy models, models to characterise the response to the antibiotic in real time, models to study the interaction between *M. tuberculosis* and human bronchial epithelial cells, evaluation of infected macrophage models and animal zebrafish larvae pharmacokinetics / pharmacodynamics (PK/PD), animal mouse infection models as follows:

- perform structural characterisation of cytochrome bd and bc targets;
- generation/access to a library of MTB mutants to profile cytochrome bc and bd inhibitors;
- progress assets to FTIH by evaluation of the toxicology profile, performing formulation development (including exploration of long-acting formulation and fixed dose combination), screening, selection and characterisation of solid form, screening of synthetic pathways and GMP scale-up, synthesis of impurities, and performing non-GLP and GLP toxicology studies in several species (including but not limited to evaluation of mitochondrial toxicity);
- design and implementation of phase 1 studies towards the development of TB candidates.

Topic 2: Progress novel assets (one FTIH start) for non-tubercular mycobacteria (NTM) that may act synergistically with bedaquiline, and cytochrome bc drugs

The project goal is to develop and advance a portfolio of anti-NTM drugs that may be used in combination with bedaquiline and cytochrome bc inhibitors to shorten treatment regimens and improve safety and efficacy.

The EFPIA partner's internal assets as well as external compounds will be profiled alone and in combination. The scope of this topic will be to progress novel lead compounds by performing medicinal chemistry optimisation, *in vitro* and *in vivo* characterisation, as well as PK, toxicology studies, formulation and CMC (chemistry, manufacturing and controls) studies. The scope also includes implementation of phase 1 studies towards the development of novel NTM candidates. For this topic, expertise in the field of NTM is necessary. The activities of this topic include but are not limited to:

- generation/access to a library of NTM mutants and access to an extensive panel of NTM isolates to profile cytochrome bc and bd inhibitors;

- *in vitro* and *in vivo* efficacy testing (including but not limited to determination of minimal inhibitory concentration (MIC), minimal bactericidal concentration (MBC) and time-kill kinetics), animal mouse infection models, animal zebrafish larvae PK/PD, and profiling of new agents/combinations in a panel of NTM clinical isolates and in Gram negative and Gram positive bacteria;
- progress assets to FTIH by determining the toxicology profile, performing formulation development (including exploration of long-acting formulation and fixed dose combination), screening, selection and characterisation of solid form, screening of synthetic pathways and GMP scale-up, synthesis of impurities, and performing non-GLP and GLP toxicology studies in several species (including but not limited to the evaluation of mitochondrial toxicity);
- design and implementation of phase 1 studies towards the development of NTM candidates;
- expertise (key opinion leaders (KOL)) in clinical treatment of NTM and treatment outcomes is crucial.

Topic 3: Discover and progress novel assets with new mechanisms of action (one preNME for TB and one preNME for NTM) and biomarkers for TB and NTM infection

Novel assets with new mechanisms of action will be identified through high throughput screening campaigns for TB and NTM, with a special focus on *M. avium* complex. Novel screening platforms and tools are needed for this evaluation. The resulting hits will be profiled and further optimised *in vitro* and *in vivo*. In addition, a better understanding of the host-mycobacteria interaction and the impact of coexisting viral infections can provide insights about biomarkers and new targets for mycobacteria.

The objectives include, but are not limited to the following.

- The development of high throughput assays to test TB and NTM in *in vivo* relevant conditions. Target identification and characterisation including exploration of mechanism of action by transcriptomics and the generation of resistant mutants.
- *In vitro* and *in vivo* efficacy testing (including but not limited to determination of minimal inhibitory concentration (MIC), minimal bactericidal concentration (MBC) and time-kill kinetics), animal mouse infection models, animal zebrafish larvae PK/PD, and profiling of new agents and combinations in a panel of clinical isolates and in Gram negative and Gram positive bacteria as appropriate.
- Progress assets to FTIH by determining the toxicology profile, performing formulation development (including exploration of long-acting formulation and fixed dose combination), screening, selection and characterisation of solid form, screening of synthetic pathways and GMP scale-up, synthesis of impurities, and performing non-GLP and GLP toxicology studies in several species (including but not limited to the evaluation of mitochondrial toxicity).

Topic 4: Determination of gepotidacin levels in tonsils and prostatic tissue

Gepotidacin (GSK2140944) is a novel antibiotic that selectively inhibits bacterial DNA gyrase and topoisomerase IV by a unique mechanism, which is not utilised by any currently approved human therapeutic agent. Structural data with a type II topoisomerase, DNA gyrase, reveals the novel binding mode of the triazaacenaphthylene class and distinguishes it from the binding mode of the quinolone antibacterials. As a consequence of its novel mode of action, gepotidacin is active *in vitro* against most target pathogens carrying resistance determinants to established antibacterials, including fluoroquinolones. Gepotidacin has broad Gram positive activity and selective Gram negative activity.

With increasing antimicrobial resistance, there are fewer options to treat gonorrhoea (Centers for Disease Control and Prevention (CDC) and World Health Organisation (WHO) urgent need), in particular at the pharyngeal site where tissue penetration is essential to activity and extended spectrum beta-lactamases (ESBL)/MDR (CDC and WHO serious need) urological infections due to *Escherichia coli*. In addition, few orally available agents have favourable penetration characteristics which are essential to activity.

The topic goal would be to assess penetration of gepotidacin in the following groups.

- Tonsils following elective tonsillectomy in adults aged >18 years or adolescents aged 12-17 years. 20 evaluable subjects willing to participate would receive a single oral or intravenous dose of gepotidacin at defined timepoints prior to tonsillectomy. Gepotidacin levels will be measured in homogenates or extracellular fluid using validated methods that may include *ex vivo* microdialysis.
- Prostatic tissue following elective prostate biopsy or TURP in adult males. 20 evaluable subjects willing to participate would receive a single oral dose of gepotidacin at defined timepoints prior to TURP or prostate biopsy. Gepotidacin levels will be measured in homogenates or extracellular fluid using validated methods that may include *ex vivo* microdialysis.

Topic 5: Infection site targeting, antibiotic encapsulated in nanoparticles for treating extracellular bacterial infections

The topic goal would be threefold:

- to identify a bacterium or infection site targeting ligand (small molecule preferred);
- to incorporate this ligand into a nanoparticle system which can be retained selectively in infected tissues for long periods;
- to encapsulate an appropriate antibiotic into the targeted nanoparticle and confirm improved efficacy over the free antibiotic and non-targeted encapsulated antibiotic, driven by higher local concentration at the infection site, in addition to other criteria such as reduced toxicity or side effects, longer half-life, etc.

Topic 6: Functional Ethionamide Boosters: a novel combination for tuberculosis therapy

The topic goal is to generate a small molecule clinical candidate that can boost the activity of Ethionamide and revert the existing resistance to this drug, by acting on bacterial transcriptional regulators. The associated, dose dependant side effects for Ethionamide observed at the currently required human doses together with the high pre-existing levels of resistance in patients has limited the use of Ethionamide as a TB front-line agent. However, Ethionamide is considered an essential drug for MDR-TB treatment even today and could well be positioned back into first line, replacing Isoniazid as the 'fast killing' agent acting on mycolic acid synthesis, once the bio-activation of Ethionamide is optimal. This project aims at identifying novel small molecules that are capable of:

- a) increasing the level of bioactivation of Ethionamide, therefore reducing the levels of ETH required to achieve maximal efficacy both *in vitro* (>10-fold) and *in vivo* (>3-fold);
- b) revert pre-existing ETH clinical resistance using a very low oral dose.

This will make it possible to open up the scope of the ETH field of use to both drug sensitive and multi-drug-resistant (MDR) patients. This project intends to progress these new compounds from the candidate selection stage to a proof of concept as Ethionamide booster in TB patients.

Topic 7: Intravenous treatments of serious infections (urinary tract infections (UTI), intra-abdominal infections (IAI) & hospital-acquired pneumonia/ventilator associated pneumonia (HAP/VAP)) caused by Gram(-) bacteria (Enterobacteriaceae +/- *Pseudomonas* and/or *Acinetobacter*)

In the various threats encompassed in the global AMR crisis, Gram(-) bacteria and especially ESBL-producing and carbapenemases-producing *Enterobacteriaceae* consistently rank among the most problematic organisms for which novel ways of managing the infections they cause are lacking. The scope of this topic will be to progress novel lead compounds against these organisms by performing medicinal chemistry optimisation, *in vitro* and *in vivo* activity characterisation, as well as PK, ADMET, formulation and CMC studies. A particular focus will be on compounds identified from phenotypic screens of natural product extracts / libraries, and on compounds identified through non-traditional phenotypic screens (i.e. screens in non-traditional rich media and/or screens where a proxy for bacterial cell death is employed). These require specific areas of expertise in natural products (fermentation, dereplication and microbial genetics), as well as medicinal chemistry applied to natural products (including hemi-synthesis), for instance. In addition, expertise in novel approaches to de-orphan lead compounds and strong translational capabilities will be particularly useful to progress these compounds and evaluate potency as well as toxicity and resistance liabilities

Expected key deliverables

Topic 1: Progress new assets (one preNME and one FTIH start) for TB that act synergistically with bedaquiline, cytochrome bc or cytochrome bd inhibitors

- one preNME candidate for TB;
- profiling and phase 1 studies of a novel TB preclinical candidate to deliver a phase 2 ready TB asset.

Topic 2: Progress novel assets (one FTIH start) for non-tubercular mycobacteria (NTM) that may act synergistically with bedaquiline, and cytochrome bc drugs

- profiling and phase 1 studies of a novel NTM preclinical candidate to deliver a phase 2a ready NTM asset.

Topic 3: Discover and progress novel assets with new mechanisms of action (one preNME for TB and one preNME for NTM) and biomarkers for TB and NTM infection

- two preNME candidates, one for TB and one for NTM.

Topic 4: Determination of gepotidacin levels in tonsils and prostatic tissue

- plasma samples, tissues homogenates and possibly extracellular unbound levels of novel antibacterial in the tonsils following oral or intravenous dosing;
- pharmacokinetic analysis to evaluate penetration and exposure in the tonsils;
- plasma samples, tissue homogenates and possibly extracellular unbound levels of novel antibacterial in the prostate following oral dosing;
- pharmacokinetic analysis to evaluate penetration and exposure in the prostate.

Topic 5: Infection site targeting, antibiotic encapsulated nanoparticles for treating extracellular bacterial infections

- one candidate-selection of an infection site targeting, antibiotic encapsulated nanoparticle system for treatment of extracellular bacterial infections.

Topic 6: Functional Ethionamide boosters: a novel combination for TB therapy

- clinical candidate ready to enter into phase 2 for the treatment of tuberculosis;
- preclinical candidate backup on a different chemical series.

Topic 7: Intravenous treatments of serious infections (UTI, IAI & HAP/VAP) caused by Gram(-) bacteria (Enterobacteriaceae +/- Pseudomonas and/or Acinetobacter

- up to two NMEs having completed preclinical profiling, including GLP toxicity studies so as to be ready to enter into phase 1 studies;
- up to four NMEs having completed lead optimisation process (showing acceptable *in vitro* and *in vivo* activities and toxicity/resistance profiles) so as to be ready to enter phase 1 enabling studies such as GLP toxicity studies.

Expected impact

The expected impact of actions selected under this Call will be to:

- contribute to the development of a vibrant AMR research environment in the EU and strengthen the competitiveness and industrial leadership of Europe;
- contribute to the EU's ambition of being a 'best practice region' for addressing AMR;
- enhance the overall pipeline of medicines for patients with AMR infections and advance new and innovative agents.

Potential synergies with existing consortia

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

Example of relevant IMI/IMI2 JU and non-IMI projects include:

- aspects of the research of ND4BB TRANSLOCATION (<http://www.nd4bb.eu/>) (e.g. the ND4BB Information Centre as a possible framework for data sharing);
- ND4BB ENABLE project (<http://nd4bb-enable.eu/>);
- ND4BB COMBACTE projects and iABC Programme, (<https://www.combacte.com>; <http://www.iabcproject.com>) in particular in relation to networks (CLIN-NET, LAB-NET, STAT-NET and EPI-NET);
- projects funded by other organisations/programmes supporting AMR R&D e.g. the EU Framework Programmes for Research and Innovation FP7 and Horizon 2020, the Joint Programming Initiative AMR, Wellcome Trust, Biomedical Advanced Research and Development Authority (BARDA), Medical Research Council (MRC), CARB-X, Global Antibiotic Research and Development Partnership (GARDP),

National Institute of Allergy and Infectious Diseases (NIAID), TB Alliance and TB Drug Accelerator etc. to ensure synergy and avoid duplication of research.

Indicative duration of the actions

The indicative duration of the actions under the different topics is shown below. Due to the uncertain nature of drug discovery and development, a shorter duration could be envisioned depending on the scientific progress of the project.

Topic 1: 72 months

Future project expansion: Potential applicants must be aware that the Innovative Medicines Initiative 2 (IMI2) Joint Undertaking may, if exceptionally needed, publish at a later stage another Call for proposals restricted to the consortium already selected under this topic, in order to enhance and progress the results and achievements by extending the duration and funding by means of another grant agreement. The consortium will be entitled to open to other beneficiaries as it sees fit. The scope of such potential future extension would be to develop further an agent/ combination successful in phase 1.

Topic 2: 72 months

Future project expansion: Potential applicants must be aware that the Innovative Medicines Initiative 2 (IMI2) Joint Undertaking may, if exceptionally needed, publish at a later stage another Call for proposals restricted to the consortium already selected under this topic, in order to enhance and progress the results and achievements by extending the duration and funding by means of another grant agreement. The consortium will be entitled to open to other beneficiaries as it sees fit. The scope of such potential future extension would be to develop further an agent/ combination successful in phase 1.

Topic 3: 72 months

Future project expansion: Potential applicants must be aware that the Innovative Medicines Initiative 2 (IMI2) Joint Undertaking may, if exceptionally needed, publish at a later stage another Call for proposals restricted to the consortium already selected under this topic, in order to enhance and progress the results and achievements by extending the duration and funding by means of another grant agreement. The consortium will be entitled to open to other beneficiaries as it sees fit. The scope of such potential future extension would be to develop further an agent/ combination successful in phase 1.

Topic 4: 18 months

Topic 5: 36 months

Topic 6: 48 months

Topic 7: 72 months

Indicative budget

The IMI2 JU financial contribution is a maximum of EUR 46 900 000 for this Call. The IMI2 JU maximum financial contribution for each topic is:

Topic 1: EUR 6 840 000

Topic 2: EUR 5 690 000

Topic 3: EUR 1 770 000

Topic 4: EUR 7 300 000

Topic 5: EUR 6 000 000

Topic 6: EUR 7 000 000

Topic 7: EUR 12 300 000

Proposals will be ranked under each topic separately. Under each topic, only the top ranked proposal will be selected for funding within the budget available under each topic.

Applicant consortia

The applicant consortia will be selected based on submitted proposals. Each applicant consortium must include at least one EFPIA constituent or affiliated entity, i.e. EFPIA company. This requirement is justified by the particular nature of the scientific challenge to be addressed under these topics. One of the goals of the European One Health Action Plan against AMR is 'to increase the development and availability of new effective antimicrobials inside and outside the EU'. EFPIA companies are uniquely placed to have the capability to ensure that during the rapid progression of new compounds and candidate drugs and vaccines in the projects to be selected, all the relevant regulatory and other requirements from jurisdictions around the world are appropriately considered, so that the data generated can be used when regulatory filings will be made.

The applicant consortia (e.g. EFPIA company + SME) may be limited in size but they must involve at least two independent legal entities established in different EU Member States, or countries associated to Horizon 2020¹¹⁴, while addressing all of the objectives and having the necessary expertise to produce the deliverables and ensure the expected impact of the topic they are applying to. The condition for having a minimum of two legal entities is justified by the specificity of the AMR return on investment (RoI) where small consortia are sufficient to rapidly progress towards the development of new compounds while maintaining the agility of operations.

Applicants are expected to take advantage of and exploit support from different stakeholders with the necessary expertise, including the mobilisation of funds through the inclusion of contributing partners under the IMI2 JU framework of public-private consortia. Such contributing partners may include, in addition to EFPIA companies (i.e. its constituent or affiliated entities), Associated Partners to IMI2 JU.

Topics 1-3: Advancing a portfolio of novel compounds with potential to treat TB and NTM

To achieve the scientific objectives of topics 1-3, each applicant consortium is expected to mobilise as appropriate, and taking into account the scope of the different topics as described above, the following capabilities:

- Discovery capabilities including but not limited to:
 - development of animal infection models, to improve reproducibility and predictability for both single drugs and combinations;
 - development of dormancy models, such as RPF-dependent mycobacteria, low-oxygen recovery assay, nutrient starvation;
 - development of *in vitro* models to characterise the response to antibiotics in real time, such as reported-based growth inhibition and time-kill kinetics, and real-time single-cell analysis in a microfluidic device;
 - development of infected macrophage models to study the effect of single drugs and combinations, including direct antibacterials and host-directed compounds, as well as exploration of the secretome of lung epithelial cells upon interaction with mycobacteria to identify new targets and biomarkers;
 - exploration of mechanism of action, transcriptomics, generation of resistant mutants and characterisation of targets: purification, crystallisation and modelling;
 - profiling new inhibitors/ combinations in a panel of clinical isolates, and in Gram negative and Gram positive bacteria;
- Expertise in high throughput screening campaigns.
- Basic preclinical research capabilities to be able to develop and conduct specific PK/PD studies/models and tolerability studies including toxicology profiling, non-GLP and GLP toxicology profiling.
- PDMS (GMP manufacturing and formulation development) including capacity for long acting formulations of agents and combinations, and also including scale-up synthesis of non GMP and GMP selected candidates.
- In addition, applicants should have access to a network of patients of different socio-economic backgrounds on mycobacterial therapy and/or paediatric patients with underlying lung disease and carrying a mycobacterial infection.
- In depth infectious disease (TB, NTM) expertise, operational and quality capabilities required to design, implement, conduct, collect and analyse full data (bio, microbiology and clinical), and draft/finalise clinical

¹¹⁴ http://ec.europa.eu/research/participants/data/ref/h2020/grants_manual/hi/3cpart/h2020-hi-list-ac_en.pdf

study reports. Significant documented track record on the conduct of registrational phase 1 clinical studies in healthy volunteers, TB and/or NTM patients is mandatory.

- To achieve the objectives of topics 1-3, bedaquiline and cytochrome bc/bd inhibitors could be brought to the combination, as well as expertise in discovery and development activities.
- Access to compounds in the field of TB/NTM.

Topic 4: Determination of gepotidacin levels in tonsils and prostatic tissue

To achieve the scientific objectives of the topic, each applicant consortium is expected to mobilise as appropriate, the following capabilities:

- access to patients undergoing tonsillectomy;
- access to patients undergoing TURP or prostate biopsy;
- experience with clinical trials;
- training in International Council of Harmonisation (ICH) guidelines and good clinical practice (GCP);
- expertise and capacity to perform PK analysis.

Topic 5: Infection site targeting, antibiotic encapsulated nanoparticles for treating extracellular bacterial infections

To achieve the scientific objectives of the topic, each applicant consortium is expected to mobilise as appropriate, the following capabilities:

- experience with bacterial or infection site targeting;
- experience with nanoparticles with clear regulatory path, e.g. nanoparticles that have reached suitable levels of drug development (e.g. phase 3 or marketed, for any indication, not necessarily for infectious disease) as a demonstration that there are no insurmountable technical or regulatory challenges;
- experience with the incorporation of surface modifications of nanoparticles;
- experience in production, characterisation, and scale-up of nanoparticles, including preferably GMP-production;
- experience and capacity to run *in vivo* animal models of infection;
- experience in running rodent toxicology studies, including immunotoxicology, with nanoparticle agents;
- experience with preclinical PET imaging;
- experience working with regulators.

Topic 6: Functional Ethionamide boosters: a novel combination for TB therapy

To achieve the scientific objectives of the topic, each applicant consortium is expected to mobilise as appropriate, the following capabilities:

- experience with the use of bacterial transcriptional regulators;
- experience with bacterial or infection site targeting;
- experience setting up, validating, and running *In vitro* biochemistry assays;
- experience in using HPLC/mass spectrometry for the identification of metabolites;
- experience and capacity to run *Mycobacterium tuberculosis* animal models of infection including PK/PD;
- experience in running toxicology, pharmacokinetics and pharmaceutical development studies, including human dose projection;
- experience with preclinical PET imaging;
- experience in active pharmaceutical ingredient (API) production;
- experience working with regulators;
- GMP manufacturing / CMC / clinical experience;
- medicinal chemistry experience.

Topic 7: Intravenous treatments of serious infections (UTI, IAI & HAP/VAP) caused by Gram(-) bacteria (Enterobacteriaceae +/- Pseudomonas and/or Acinetobacter)

To achieve the scientific objectives of the topic, each applicant consortium is expected to mobilise as appropriate, the following capabilities:

- compounds and expertise in novel phenotypic screening assays, including the expertise in new natural products (fermentation, extract purification, dereplication);
- expertise in technologies necessary to quickly de-orphan hits from phenotypic screens;
- expertise in approaches and techniques to translationally validate novel mode of action to the clinical situation; expertise and capacity in medicinal chemistry, microbiology, pharmacology and early ADMET optimisation programmes as well as pharmaceutical development techniques to maximise the evaluation of the therapeutic index of novel compound;
- expertise in innovative PK/PD approaches, including hollow-fibre models;
- expertise in development of companion diagnostics and biomarkers, enabling special stratification and/or monitoring of treatment response such as, for instance, antibody-focused and/or broader immune profiling of patients.
- ability to perform preclinical development studies (e. g. GLP toxicity studies, formulation, synthesis of material of clinical degree);
- ability to undertake first into human studies (FTIH) on healthy volunteers to determine key pharmacokinetic parameters in humans.

Note that, as stated above, the scope of this topic will be to progress novel lead compounds. These lead compounds should be proposed by the applicant consortium and might come either from the EFPIA company or from any other partner of the consortium. Thus, in addition to or in place of novel compound(s), novelty brought in by the applicant consortium might be new tools, new competence and/or specific knowledge in a novel targeted pathway that are applicable to the progression of an EFPIA compound.

Note regarding all topics

Note that for all topics, most day-to-day management such as rigorous project, programme, and alliance management (including but not limited to supporting the coordinator in the management of scientific and financial reporting, prosecution of legal agreements such as confidentiality agreements (CDA), material transfer agreements (MTA), meeting facilitation and secretariat) of projects across the Accelerator will be supported by the coordination and support group within the CBN (established through the IMI2 JU Call 15, topic 7 action). Therefore only minimal project and financial management capabilities will be required from the applicant consortium in the PBN.

In addition, representatives from all selected projects will contribute to an advisory and communications board (containing independent experts and representatives from all the projects running in the AMR Accelerator) created as part of the coordination and support group within the CBN. This group will meet regularly to share summary level, non-confidential progress reports on projects and where appropriate make recommendations to the AMR Accelerator overall.

Suggested architecture of the full proposal

The applicant consortia should suggest complete architectures in the submitted proposals.

Decision making: Each applicant consortium must agree on a fair and robust go/no-go decision-making process to ensure that only the most promising compounds or approaches are pursued. Note that go / no go milestones will need to be proposed in each proposal and later formalised in the relevant Annex 1 of the Grant Agreement, and consortium agreement. These milestones will then assist in the decision-making process to help ensure that projects funded under the PBN remain dynamic.

Each consortium's decision making would be governed by a committee whose makeup will take into account the nature and scope of the work planned, and be detailed in the respective consortium agreement and agreed to by all partners. The committee must include at least one independent expert to be selected by a process established by the full consortium and to be detailed in the consortium agreement. This committee will track the progress of the project against its own internal milestones and will be empowered (as outlined in each project's consortium agreement) to make recommendations for progression/stopping tasks based on each consortium's pre-agreed go / no go milestones in an e.g. quarterly, streamlined, single-meeting process. It is anticipated that the consortium agreements will be structured such that independent experts can recommend termination or continuation of a project, but they cannot force a project to continue if all partners suggest termination. The decision-making process by the committee may result, in case of '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 IMI2 JU MGA. The final decision about the project continuation or termination will be taken by the 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, i.e., even without the aforementioned recommendation.

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.

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 proposal in response to the IMI2 Call 16 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-IMI2-2018-16-single-stage
Type of actions	Research and Innovation Action (RIA)
Publication Date	18 July 2018
Submission start date	18 July 2018
Submission deadline	24 October 2018 (17:00:00 Brussels time)

Indicative Budget

From EFPIA companies and IMI2 JU Associated Partners	To be defined based upon submitted proposals
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From the IMI2 JU	EUR 46 900 000
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Call Topics

IMI2-2018-16-01 Progress new assets (one pre-new molecular entity (preNME) and one first-time-in-human (FTIH) start) for TB that act synergistically with bedaquiline, cytochrome bc or cytochrome bd inhibitors	The indicative contribution from EFPIA companies is to be defined based upon submitted proposals The financial contribution from IMI2 JU for is EUR 6 840 000	Research and Innovation Action (RIA) Single-stage submission and evaluation process. Under each topic, proposals submitted will be evaluated and ranked in one single list.
IMI2-2018-16-02 Progress novel assets (one FTIH start) for non-tubercular mycobacteria (NTM) that may act synergistically with bedaquiline and cytochrome bc drugs	The indicative contribution from EFPIA companies is to be defined based upon submitted proposals The financial contribution from IMI2 JU for is EUR 5 690 000	Research and Innovation Action (RIA) Single-stage submission and evaluation process. Under each topic, proposals submitted will be evaluated and ranked in one single list.
IMI2-2018-16-03 Discover and progress novel assets with new mechanisms of action (one preNME for TB and one preNME for NTM) and biomarkers for TB and NTM infection	The indicative contribution from EFPIA companies is to be defined based upon submitted proposals The financial contribution from IMI2 JU for is EUR 1 770 000	Research and Innovation Action (RIA) Single-stage submission and evaluation process. Under each topic, proposals submitted will be evaluated and ranked in one single list.

<p>IMI2-2018-16-04</p> <p>Determination of gepotidacin levels in tonsils and prostatic tissue</p>	<p>The indicative contribution from EFPIA companies is to be defined based upon submitted proposals</p> <p>The financial contribution from IMI2 JU for is EUR 7 300 000</p>	<p>Research and Innovation Action (RIA)</p> <p>Single-stage submission and evaluation process.</p> <p>Under each topic, proposals submitted will be evaluated and ranked in one single list.</p>
<p>IMI2-2018-16-05</p> <p>Infection site targeting, antibiotic encapsulated in nanoparticles for treating extracellular bacterial infections</p>	<p>The indicative contribution from EFPIA companies is to be defined based upon submitted proposals</p> <p>The financial contribution from IMI2 JU for is EUR 6 000 000</p>	<p>Research and Innovation Action (RIA)</p> <p>Single-stage submission and evaluation process.</p> <p>Under each topic, proposals submitted will be evaluated and ranked in one single list.</p>
<p>IMI2-2018-16-06</p> <p>Functional Ethionamide boosters: a novel combination for tuberculosis therapy</p>	<p>The indicative contribution from EFPIA companies is to be defined based upon submitted proposals</p> <p>The financial contribution from IMI2 JU for is EUR 7 000 000</p>	<p>Research and Innovation Action (RIA)</p> <p>Single-stage submission and evaluation process.</p> <p>Under each topic, proposals submitted will be evaluated and ranked in one single list.</p>
<p>IMI2-2018-16-07</p> <p>Intravenous treatments of serious infections (urinary tract infections (UTI), intra-abdominal infections (IAI) & hospital-acquired pneumonia/ventilator associated pneumonia (HAP/VAP)) caused by Gram(-) bacteria (Enterobacteriaceae +/- Pseudomonas and/or Acinetobacter)</p>	<p>The indicative contribution from EFPIA companies is to be defined based upon submitted proposals</p> <p>The financial contribution from IMI2 JU for is EUR 12 300 000</p>	<p>Research and Innovation Action (RIA)</p> <p>Single-stage submission and evaluation process.</p> <p>Under each topic, proposals submitted will be evaluated and ranked in one single list.</p>

LIST OF ACRONYMS

Acronym	Meaning
ABAC	Accrual Based Accounting System
ACTG	AIDS Clinical Trial Group
AD	Alzheimer's disease
AD (HR)	Administrator
ADL	Activities of Daily
AER	Average error rate
AI	Artificial intelligence
AMPA TARP	α -amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid Transmembrane Regulatory Proteins
AMR	Antimicrobial Resistance
API	Application Programming Interface
AST	Assistant
ATAC-Seq	Assay for Transposase-Accessible Chromatin using sequencing
AUC	Area under the curve
AWP2018	Annual Work Plan 2018
BAFF	B-cell Activating Factor
BAL	Bronchoalveolar Lavage
BCR	B-cell Receptor
BMGF	Bill and Melinda Gates Foundation
BSL3	Biosafety Level 3
CA (Budget)	Commitment Appropriation
CA (HR)	Contractual Agent
CD	Cluster of differentiation
CD	Crohn's Disease
CDAI	Crohn's Disease Activity Index
CDISC	Clinical Data Interchange Standards Consortium
CDM	Common Data Model
CEOi	Global CEO Initiative
CFAST	Coalition for Accelerating Standards and Therapies
CFS	Certificates on Financial Statements
ChIP	Chromatin Immunoprecipitation
CISCRP	Center for Information and Study on Clinical Research Participation
CNS	Central Nervous System
COPD	Chronic Obstructive Pulmonary Disease
C-Path	Critical Path Institute
CPD	Continuing professional development
CPP	Critical Path Parkinson
CPTR	Critical Path to TB Drug Regimens initiative

Acronym	Meaning
CRO	Contract research organisation
CRO	Clinical Research organisation
CSA	Coordination and Support Action
CSC	Common Support Centre
CT	Computed tomography
CTA	Clinical Trial Application
CTF	Children's Tumour FoundationDR – Drug Resistant
CTTI	Clinical Trials Transformation Initiative
CytoF	Cytometry by Time of Flight
DC1	Disease cluster 1 - SLE, RA, and MS
DC2	Disease cluster 2 - UC and CD
DC3	Disease cluster 3 - Asthma and COPD
DCT	decentralised clinical trial
DDMORE	Drug Disease Model Resource
DG AGRI	Directorate-General Agriculture and Rural Development (European Commission)
DG GROW	Directorate-General for Internal Market, Industry, Entrepreneurship and SMEs (European Commission)
DG HR	Directorate-General Human Resources and Security (European Commission)
DG RTD	Directorate-General for Research and Innovation (European Commission)
DG SANTE	Directorate-General for Health and Food Safety (European Commission)
DMP	Data Management Plan
DPO	Data protection officer
DS	Drug Sensitive
E&T	Education & Training
EAAT2	Excitatory Amino Acid Transporter-2
EBiSC	European induced pluripotent stem cell
EC	European Commission
EC	Ethics Committees
ECA	European Court of Auditors
EDPS	European Data Protection Supervisor
EEG	Electroencephalograph
EEG	Electroencephalogram
EFPIA	European Federation of Pharmaceutical Industries and Associations
EHR	Electronic Health Record
EHRs	Electronic Health Records
ELF	Enhanced Liver Fibrosis
EMA	European Medicines Agency
EMIF	European Medical Information Framework
EMVO	European Medicines Verification Organisation
ERP's	Event Related Potential

Acronym	Meaning
ESFRI	European Strategy Forum on Research Infrastructures
eTRIKS	European Translational Information & Knowledge Management Services
EU	European Union
EU GDPR	EU General Data Protection Regulation
EUnetHTA	European network for Health Technology Assessment
ExpEP	Exploratory endpoints
FDA	Food and Drug Administration
FEV1	Forced expiratory Volume
FFPE	Formalin Fixed Paraffin Embedded
FG	Function Group
FIH	first-in-human
fMRI	functional Magnetic Resonance Imaging
FMT	Fecal Microbiota Transplantation
FNIH	Foundation for the National Institutes of Health
FP	Full Proposal
FP7	Seventh Framework Programme
FTE	Full Time Equivalent
FTE	Full Time Employee
FWC	Framework Contract
GA	Grant Agreement
GAMIAN	Global Alliance of Mental Illness Advocacy Networks
GAP	Global Alzheimer's Platform
GAP-43	Growth Associated Protein 43
GB	Governing Board
GBM AGILE	Glioblastoma Multiforme Adaptive Global Innovative Learning Environment
GCP	Good Clinical Practices
GDP	Good Distribution Practice
GDPR	General Data Protection Regulation
GIRP	Groupement International De La Repartition Pharmaceutique
GLP	Good Laboratory Practice
GLP	Good Lab Practice
GMP	Good Manufacturing Practice
GS1	Global Standards One
H2020	Horizon 2020 is the financial instrument implementing the Innovation Union, a Europe 2020 flagship initiative aimed at securing Europe's global competitiveness. For more information, click here: http://ec.europa.eu/programmes/horizon2020/en/what-horizon-2020
HA	Health Authority
HCP	Health Care Professionals/Providers
HCT	Human challenge trials
HD	Huntington's Disease

Acronym	Meaning
HECOR	Health Economics & Outcomes Research
Helmsley Charitable Trust	Leona M. and Harry B. Helmsley Charitable Trust
hiPS cells	Human Induced Pluripotent Stem cells
HMA	Heads of Medicines Agency
HR	Human resources
HRQOL	Health-related quality of life
HTA	Health Technology Assessment
I~HD	European Institute for Innovation through Health Data
IAC	Internal Audit Capability
IAPO	International Alliance of Patients' Organisations
IAS	Internal Audit Service of the European Commission
IBD	Inflammatory Bowel Disease
ICC	Internal Control Coordinator
ICH	International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use
ICHOM	International Consortium for Health Outcome Measurement
ICS	Internal Control Standards
ICS	Inhaled corticosteroid
ICT	Information Communications Technology
IEEE	Institute of Electrical and Electronics Engineers
IEEE BCI	Brain Computer Interface
ILG	Industry Liaison Group
IMI	Innovative Medicines Initiative
IMI1 JU	Innovative Medicines Initiative 1 Joint Undertaking
IMI2 JU	Innovative Medicines Initiative 2 Joint Undertaking
IMI EHDN	IMI European Health Data Network IMI2- Call 12
IMI EHR4CR	IMI Electronic Health Records for Clinical Research
IMI JU	Innovative Medicines Initiative Joint Undertaking
IMI PreDICT	Model-based preclinical development of anti-tuberculosis drug combinations
IMI RADAR CNS	Remote Assessment of Disease and Relapse in Central Nervous System Disorders
IMID	Immune Mediated Inflammatory diseases
IMI-EPAD	IMI European Prevention of Alzheimer's Dementia
IMP	Investigational Medicinal Product
IND	Investigational New Drug
IoT	Internet of Things
IP	Intellectual property
iPS cells	Induced pluripotent stem cells
IRB	Institutional Review Board
IRPs	Integrated Research Platforms

Acronym	Meaning
ISA	Information System for Absences
ISAs	Intervention Specific Appendices
ISO	International Standards Organization
I-SPY2	Investigation of serial Studies to Predict Your Therapeutic response with imaging and molecular analysis 2
IT	Information Technology
ITF	EMA Innovation Task Force
ITI-PF&S	Innovative therapeutic interventions against physical frailty and sarcopenia
JDRF	Juvenile Diabetes Research Foundation
JUs	Joint Undertakings
KM	Knowledge Management
KOLs	Key Opinion Leaders
KPI	Key Performance Indicator
LABA	Long-acting beta2-agonists
LAMA	Long-acting muscarinic antagonists
LITMUS	Liver Investigation Testing Marker Utility in Steatohepatitis
LAMP-2	Lysosome-Associated Membrane Protein 2
LTD	Long Term Depression
LTP	Long Term Potentiation
MABEL	minimum anticipated biological effect level
MAPPs	Medicines adaptive pathways to patients
MDD	Major Depressive Disorder
MEAs	Multielectrode Arrays
MEG	MagnetoEncephaloGraphy
MEP	Member of the European Parliament
MJFF	Michael J Fox Foundation
MoA	modes of action
mPAD	minimum pharmacologically active dose
MRC	Medical Research Council
MRE	Magnetic Resonance Elastography
MRI	Magnetic Resonance Imaging
MRSD	maximum recommended starting dose
MS	Multiple sclerosis
MTA	Material transfer agreement
NAFLD	Non-Alcoholic Fatty Liver Disease
NASH	Non-Alcoholic Steatohepatitis
ND4BB	New Drugs for Bad Bugs
NF	Neurofibromatosis
NFTs	Neurofibrillary Tangles
NIMBL	Non-Invasive Biomarkers for Metabolic Liver Disease

Acronym	Meaning
NIMH	National Institute of Mental Health
NK	Natural killer
NMD	Neurodegenerative Movement Disorders
OECD	Organisation for Economic Co-operation and Development
OLAF	European Anti-Fraud Office
PA	Payment Appropriation
PanAACEA	Programa Argentino para Niños, Adolescentes y Adultos con Condiciones del Espectro Autista
PD	Pharmacodynamics
PD	Parkinson's Disease
PDFF	Proton Density Fat Fraction
PET	Positron Emission Tomography
PGEU	Pharmaceutical Group of European Union
PHC	Personalised health care
PM	Person/month
PMDA	Pharmaceuticals and Medical Devices Agency
PnSEP	Primary and secondary Endpoints
POC	Proof of Concept
POM	Proof of mechanism
PPP	Public-private partnership
PRO	Patient reported outcomes
PSD	Platform Study Design
PSD-95	Synaptic Density Protein 95
QST	Quantitative sensory testing
R&D	Research and development
RA	Rheumatoid arthritis
RAE	Risk assessment exercise
RCSA	Risk and control self-assessment
RepER	Representative error rate
ResER	Residual error rate
RIA	Research and Innovation Action
ROC	Receiver operating characteristic
ROI	Return on investment
RWD	Real Word Data
SABA	Short-acting beta-agonists
SC	Scientific Committee
SEND	CDISC SEND Controlled Terminology
SGGs	Strategic Governing Groups
SLC	Solute carriers
SLE	Systemic Lupus Erythematosus
SME	Small and Medium-Sized Enterprise

Acronym	Meaning
SMEs	Small and Medium-sized Enterprises
SNAP-25	Synaptosomal Associated Protein 25
SNP	Single Nucleotide Polymorphism
SOFIA	Submission of Information Application
SOP	Standard operating procedure
SP	Short Proposal
SPECT	Single photon emission computed tomography
SRA	Strategic Research Agenda
SRG	States Representatives Group
SV2A	Synaptic Vesicle Glycoprotein 2A
SVM	Support vector machine
SZ	Schizophrenia
T1D	Type 1 diabetes
T2D	Type 2 diabetes
T2DM	Type 2 Diabetes Mellitus
TA	Temporary Agent
TB	Tuberculosis
TBA	TB Alliance (Global Alliance for Tuberculosis Drug Development)
TBDA	TB Drug Accelerator
TBTC	Tuberculosis Trial Consortium
TCR	T-cell Receptor
TI	therapeutic index
TNF	Tumor Necrosis Factor
TRD	Treatment Refractory Depression
TRL	Technology Readiness Level
TTG	Time to Grant
TTP	Time to Pay
UC	Ulcerative Colitis
UHDRS	Unified Huntington's Disease Rating Scale
UK	United Kingdom
UPDRS	Unified Parkinson's Disease Rating Scale
US	United States
VGLU1/2	Vesicular Glutamate Transporters 1/2
VOC	Volatile Organic Compounds
WHO	World Health Organisation
WP	Work package
WPs	Work Packages
18F-FDG	Fludeoxyglucose (18F)
2-DG	2-Deoxy-D-Glucose

