IMI2

15th Call for proposals

Annex II to the 3rd amended IMI2 JU Annual Work Plan and Budget for 2018 approved by the IMI2 JU Governing Board on 13 July 2018 per Decision n° IMI2-GB-DEC-2018-23

Document reference: IMI2/INT/2018-01049

Contents

Introduction

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

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

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

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

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

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

The initiative should therefore seek to involve a broader range of partners, including mid-sized companies[3], from different sectors e.g. biomedical imaging, medical information technology, diagnostic and/or animal health industries. Involving the wider community in this way should help to advance the development of new approaches and technologies for the prevention, diagnosis and treatment of diseases with high impact on public health.

The IMI2 Strategic Research Agenda (SRA)[4] is the main reference for the implementation of research priorities for IMI2 JU. The scientific priorities for 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.

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

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

Before submitting a proposal, applicant consortia should familiarise themselves with all Call documents such as the IMI2 JU Manual for submission, evaluation and grant award[9], and the IMI2 evaluation criteria. Applicants should refer to the specific templates and evaluation procedures associated with the topic type Research and Innovation Actions (RIA).

[5] Regulation (EU) 2016/679 of the European Parliament and of the Council of 27 April 2016 on the protection of natural persons with regard to the processing of personal data and on the free movement of such data, and repealing Directive 95/46/EC (General Data Protection Regulation) , OJ L 119, 4.5.2016, p. 1–88.

[6] Regulation (EU) No 536/2014 of the European Parliament and of the Council of 16 April 2014 on clinical trials on medicinal products for human use, and repealing Directive 2001/20/EC, OJ L 158, 27.5.2014, p. 1-76.

[7] Directive 2001/20/EC of the European Parliament and of the Council of 4 April 2001 on the approximation of the laws, regulations and administrative provisions of the Member States relating to the implementation of good clinical practice in the conduct of clinical trials on medicinal products for human use (the "Clinical Trials Directive), OJ L 121, 1.5.2001, p. 34.

[8] Directive 95/46/EC on the protection of individuals with regard to the processing of personal data and the free movement of such data and implementing national laws, OJ L 281, 23.11.1995, p. 31–50.

[9] 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.

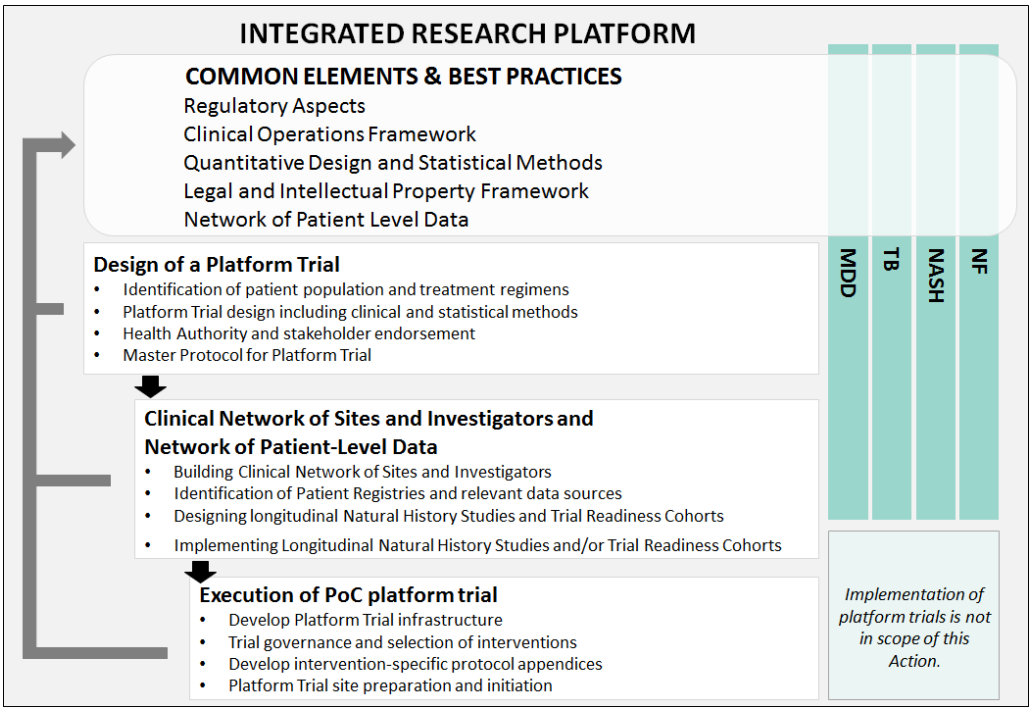

Figure 1 Schematic overview of the IRP project.

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 networks[10] 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 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.

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

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.

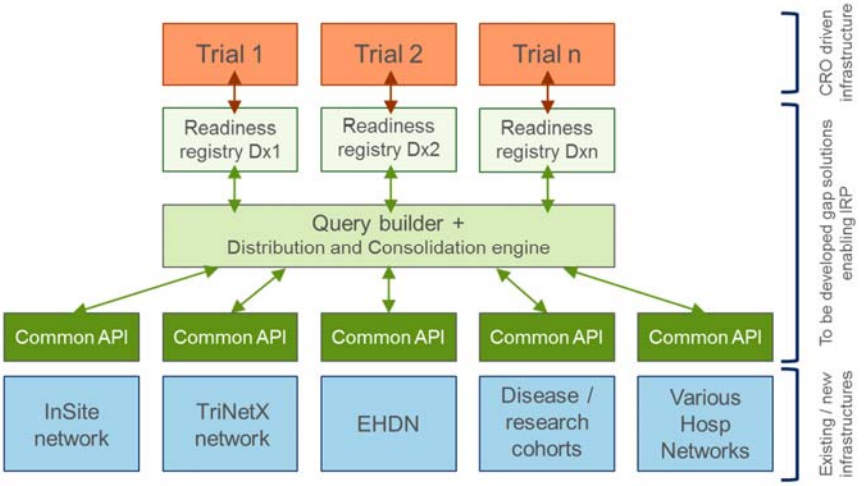

Figure 2: High-level schematic of technology components of patient-level data network

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 Nation 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 ≥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.

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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

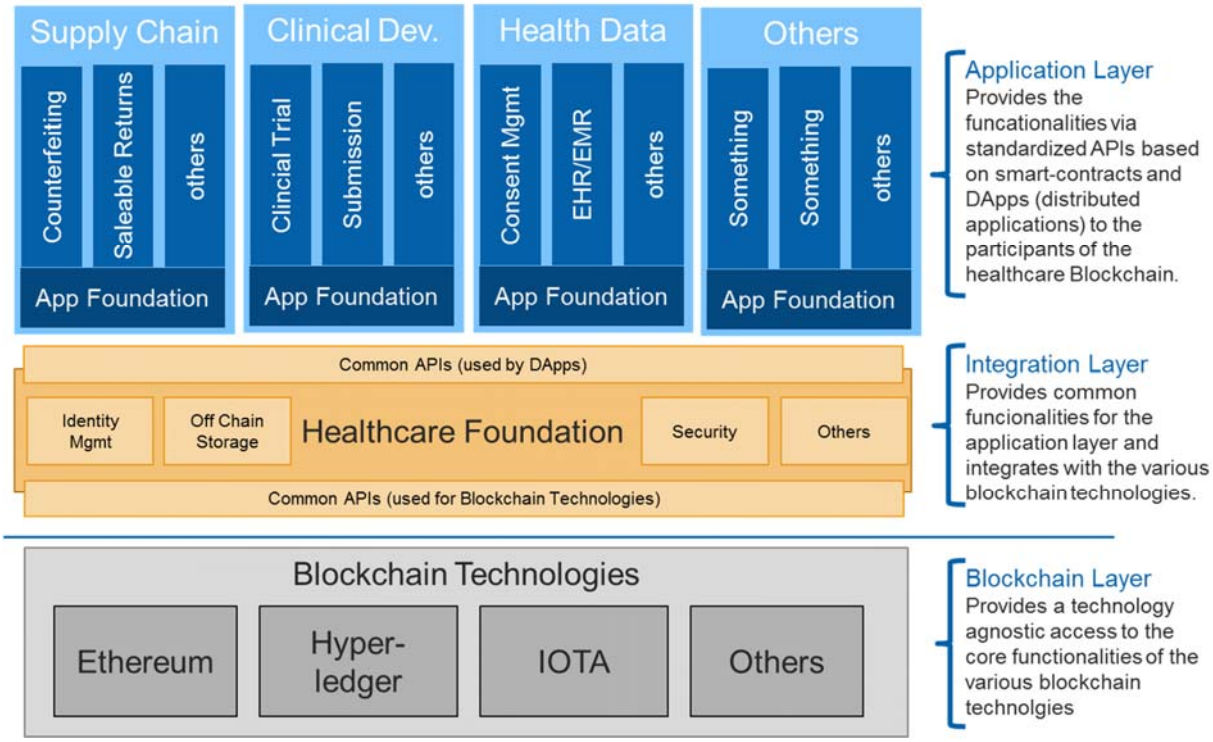
The overall objective of the agile project generated by this topic is to establish a common blockchain ecosystem for pharmaceutical development, manufacturing, and distribution that provides an incentive and serves as the basis for all participants to engage, adopt, and benefit from.

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)[11] 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:

[11] 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.

- 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 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, IEEE, 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 development[12].

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.

[12] See http://europa.eu/!ww84Xw

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.[13]

[13] 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][2].

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) Inititative (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 (ld-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 immunodulatory 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 immunodulatory 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 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;
- 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.

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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 (Aß) 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 Aß 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
- 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

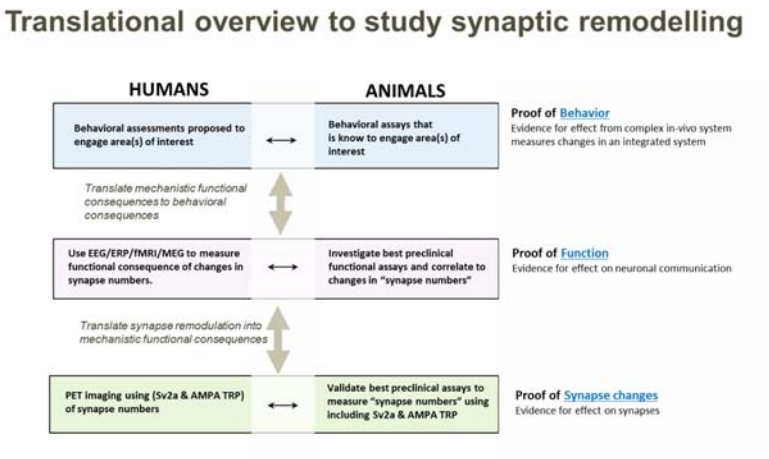
The applicant consortium should submit a short proposal which includes their suggestions for creating a full proposal architecture, taking into consideration the industry contributions and expertise provided below.

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.



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.

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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 case, 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:

1. to identify appropriate digital devices & platforms for the transformation of the standard clinical and functional endpoints into digital endpoints;
2. 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;
3. 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:

1. selection & implementation of digital platforms, devices, procedures and other technology, data processing, simulation and modelling to optimise the digital endpoint transformation process;
2. 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);
3. 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-3[14] 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.

[14] Unified Parkinson's disease rating scale

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.

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:

4. 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 beused for helping the comparative therapeutic impact among disorders of novel treatments;
5. 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 UHDRS[15] 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 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;

[15] Unified Huntington's Disease Rating Scale

- 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 FDA[16] and EMA[17] 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;
  - 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.

[16] Through, for example, C-Path
17 http://www.ema.europa.eu/ema/index.jsp?curl=pages/regulation/general/general_content_000049.jsp&mid=WC0b01ac05800229b9

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 challenge[18];
- FNIH Accelerated Medicine Partnership in PD clinical trials started in 2017[19];
- Several HD consortia are exploring the basic aspects of the disorder;
- MRC UK funded consortium: Immune-Mediated Inflammatory Disease Biobanks - UK.[20]

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)[21] 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.eunethta.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.

18 https://www.michaeljfox.org/research/levodopa-data-challenge.html
19 https://fnih.org/what-we-do/current-research-programs/accelerating-medicines-partnership-parkinsons
20 www.imidbio.co.uk
21 https://c-path.org/programs/cpp/

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 Foundation[22]

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);

[22] Its participation is subject to formalisation of its association to IMI2 JU for the present topic.

- 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 obtained[23].

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.[24]

[23] See http://europa.eu/!ww84Xw
[24] See http://ec.europa.eu/research/participants/data/ref/h2020/grants_manual/hi/oa_pilot/h2020-hi-oa-data-mgt_en.pdf

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Introduction to the IMI2 Antimicrobial Resistance (AMR) Accelerator programme

Background and problem statement

The discovery and development of new preventions and treatments to address antimicrobial resistance (AMR) is an undisputed European and global challenge 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[25]) 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[26] 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.

[25] For example, points 3 and 4 from the 'Roadmap for Progress'.
[26] http://ec.europa.eu/research/participants/data/ref/h2020/other/call_fiches/jtis/h2020-call-fiche18-16-imi2-ju_en.pdf

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)[27]. 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).

27 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 group[28]) 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 Agreement[29] 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.

28 For additional details see the topic 7 “Capability Building Network” of IMI2 JU Call 15.
29 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 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/optimise 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; 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 contribution[30].

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 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

[30] 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').

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 statement[31] 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-up[32] and a dynamic, global, multi-sectoral approach[33] is needed if the global target of eradicating tuberculosis by 2030[34] 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.

[31] http://europa.eu/rapid/press-release_STATEMENT-18-2461_en.htm
[32] https://news.un.org/en/story/2016/10/542712-massive-scale-needed-if-global-targets-tuberculosis-are-be-met-top-un-health
[33] https://news.un.org/en/story/2017/10/569592-tuberculosis-worlds-top-infectious-killer-un-health-agency-calls-political
[34] http://www.who.int/tb/strategy/en/

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.

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 grants[35].

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.

[35] 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%93AGA.pdf

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;
- 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-candidates[36] from TB portfolios from EFPIA and Associated Partners for further analysis.
- Perform preclinical development studies[37] (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;

[36] Pre-candidate studies: discovery activities from Lead optimisation to selection of a molecule as preclinical candidate
[37] Preclinical development: studies performed between preclinical candidate and first time in human.

- 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 heathy 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.

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.[38]

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;

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

- 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);
- 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 heathy volunteers to determine key pharmacokinetic parameters in humans (half-life, volume of distribution, clearance and potential for accumulation under extensive repeated doses) and to asses 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 be 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.

IMI2-2018-15-03 **Microenvironment imposed signatures in tissue and liquid biopsies in immune-mediated diseases**	The indicative contribution from EFPIA companies is EUR 15 500 000 The financial contribution from IMI2 JU is a maximum of EUR 15 500 000	Research and Innovation Action (RIA) Two-stage submission and evaluation process. Only the applicant consortium whose proposal is ranked first at the first stage is invited for the second stage.
IMI2-2018-15-04 **Emerging translational safety technologies and tools for interrogating human immuno-biology**	The indicative contribution from EFPIA companies is EUR 10 895 000 The indicative IMI2 JU Associated Partners contribution is EUR 105 000 The financial contribution from IMI2 JU is a maximum of EUR 11 000 000	Research and Innovation Action (RIA) Two-stage submission and evaluation process. Only the applicant consortium whose proposal is ranked first at the first stage is invited for the second stage.
IMI2-2018-15-05 **Development and validation of translational platforms in support of synaptopathy drug discovery**	The indicative contribution from EFPIA companies is EUR 6 730 500 The indicative IMI2 JU Associated Partners contribution is EUR 71 500 The financial contribution from IMI2 JU is a maximum of EUR 6 210 862	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.
IMI2-2018-15-06 **Digital endpoints in neurodegenerative and immune-mediated diseases**	The indicative contribution from EFPIA companies is EUR 19 400 000 The indicative IMI2 JU Associated Partners contribution is EUR 1 900 000 The financial contribution from IMI2 JU is a maximum of EUR 21 000 000	Research and Innovation Action (RIA) Two-stage submission and evaluation process. Only the applicant consortium whose proposal is ranked first at the first stage is invited for the second stage.
IMI2-2018-15-07 **AMR Accelerator programme Pillar A: Capability Building Network to accelerate and validate scientific discoveries**	The indicative contribution from EFPIA companies is EUR 17 300 000 The financial contribution from IMI2 JU is a maximum of EUR 8 000 000	Research and Innovation Action (RIA) Two-stage submission and evaluation process. Only the applicant consortium whose proposal is ranked first at the first stage is invited for the second stage.
IMI2-2018-15-08 **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**	The indicative contribution from EFPIA companies is EUR 53 900 000 The indicative IMI2 JU Associated Partners contribution is EUR 67 000 000 The financial contribution from IMI2 JU is a maximum of EUR 89 830 000	Research and Innovation Action (RIA) Two-stage submission and evaluation process. Only the applicant consortium whose proposal is ranked first at the first stage is invited for the second stage.

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 2018-2020[39].

LIST OF COUNTRIES AND APPLICABLE RULES FOR FUNDING

By way of derogation[40] from Article 10(1) of Regulation (EU) No 1290/2013, only the following participants shall be eligible for funding from the Innovative Medicines Initiative 2 Joint Undertaking:

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

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

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

(ii) secondary and higher education establishments;

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

(c) the Joint Research Centre;

(d) international European interest organisations.

Participating legal entities listed in (b) above established in a third country may receive funding from the IMI 2 JU provided their participation is deemed essential for carrying out the action by the IMI 2 JU or when such funding is provided for under a bilateral scientific and technological agreement or any other arrangement between the Union and the country in which the legal entity is established[41].

STANDARD ADMISSIBILITY CONDITIONS, PAGES LIMITS AND SUPPORTING DOCUMENTS

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

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

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

For stage 2 of a two-stage call, the limit for RIA/IA full proposals is 70 pages.

STANDARD ELIGIBILITY CONDITIONS

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

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

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

[39] http://ec.europa.eu/research/participants/data/ref/h2020/other/wp/2018-2020/annexes/h2020-wp1820-annex-ga_en.pdf
[40] 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
[41] 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 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.[42]

TYPES OF ACTION: SPECIFIC PROVISIONS AND FUNDING RATES

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

TECHNOLOGY READINESS LEVELS (TRL)

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

EVALUATION RULES

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

Award criteria and scores:

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

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

[42] 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
	innovation potential, and is beyond the state of the art; Mobilisation of the necessary expertise to achieve the objectives of the topic, ensure engagement of all relevant key stakeholders	contribute to the IMI2 objectives[43].	including manageability of the consortium.
RIA and IA Single stage, and 2nd stage evaluation	The following aspects will be taken into account, to the extent that the proposed work corresponds to the topic description in the call for proposals and referred to in the IMI2 Annual Work plan and is consistent with the stage 1 proposal: Clarity and pertinence of the proposal to meet all key objectives of the topic; Credibility of the proposed approach; Soundness of the concept, including trans-disciplinary considerations, where relevant; Extent that proposed work is ambitious, has innovation potential, and is beyond the state of the art; Mobilisation of the necessary expertise to achieve the objectives of the topic, ensure engagement of all relevant key stakeholders.	The following aspects will be taken into account, to the extent to which the outputs of the project should contribute at the European and/or International level: The expected impacts of the proposed approach as mentioned in the call for proposals; Added value from the public private partnership approach on R&D, regulatory, clinical and healthcare practice as relevant; Enhancing innovation capacity and integration of new knowledge; Strengthening the competitiveness and industrial leadership and/or addressing specific societal challenges; Improving European citizens' health and wellbeing and contribute to the IMI2 objectives;[43] Any other environmental and socially important impacts; Effectiveness of the proposed measures to exploit and disseminate the project results (including management of IPR), to communicate the project, and to manage research data where relevant.	The following aspects will be taken into account: Coherence and effectiveness of the project work plan, including appropriateness of the roles and allocation of tasks, resources, timelines and budget; Complementarity of the participants within the consortium (where relevant); Clearly defined contribution to the project plan of the industrial partners (where relevant); Appropriateness of the management structures and procedures, including manageability of the consortium, risk and innovation management and sustainability plan.

[43] 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)

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

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

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

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.[44]

Under the two-stage evaluation procedure, and on the basis of the outcome of the first stage evaluation, the applicant consortium of the highest ranked short proposal (first stage) for each topic[45] 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.

INDICATIVE TIMETABLE FOR EVALUATION AND GRANT AGREEMENT

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

[44] http://www.imi.europa.eu/sites/default/files/uploads/documents/apply-for-funding/call-documents/imi2/IMI2_ManualForSubmission_v1.6_October2017.pdf
[45] 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

BUDGET FLEXIBILITY

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

ACTIONS INVOLVING FINANCIAL SUPPORT TO THIRD PARTIES

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

CONDITIONS RELATED TO OPEN ACCESS TO RESEARCH DATA

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

However, should a project "opt-out" of these provisions, a Data Management Plan must still be prepared. A template for the Data Management Plan is available under:

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

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

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

Ethical issues should be duly addressed in each submitted proposal to ensure that the proposed activities comply with ethical principles and relevant national, Union and international legislation. Any proposal that contravenes ethical principles or which does not fulfil the conditions set out in the H2020 Rules for Participation, or in the IMI2 JU Call for proposals shall not be selected.[46]

In order to ensure excellence in data and knowledge management consortia will be requested to Disseminate scientific publications on the basis of open access[47] (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

[46] Article 19 of Horizon 2020 Framework Programme and Articles 13 and 14 of the Horizon 2020 Rules for Participation.
[47] 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

consortia must have agreed upon a consortium agreement, i.e. the internal arrangements regarding their operation and co-ordination.

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

Applicants intending to submit a proposal in response to the IMI2 JU Calls should also read the topic text, the IMI2 JU Manual for submission, evaluation and grant award, and other relevant documents[48] (e.g. IMI2 JU model Grant Agreement).

[48] http://www.imi.europa.eu/apply-funding/call-documents/imi2-call-documents

LIST OF ACRONYMS

Acronym	Meaning
ACTG	AIDS Clinical Trial Group
AD	Alzheimer's disease
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
AWP2018	Annual Work Plan 2018
BMGF	Bill and Melinda Gates Foundation
BSL3	Biosafety Level 3
CBN	Capability Building Network
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
ChIP	Chromatin Immunoprecipitation
CNS	Central Nervous System
C-Path	Critical Path Institute
CPD	Continuing professional development
CPP	Critical Path Parkinson
CPTR	Critical Path to TB Drug Regimens initiative
CRO	Contract research organisation
CRO	Clinical Research organisation
CSA	Coordination and Support Action
CSC	Common Support Centre
CTA	Clinical Trial Application
CTF	Children's Tumour FoundationDR – Drug Resistant
CTTI	Clinical Trials Transformation Initiative
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
DMP	Data Management Plan

Acronym	Meaning
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
EDPS	European Data Protection Supervisor
EEG	Electroencephalograph
EEG	Electroencephalogram
EFPIA	European Federation of Pharmaceutical Industries and Associations
EHR	Electronic Health Record
ELF	Enhanced Liver Fibrosis
EMA	European Medicines Agency
EMIF	European Medical Information Framework
EMVO	European Medicines Verification Organisation
ERP's	Event Related Potential
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
FFPE	Formalin Fixed Paraffin Embedded
FIH	first-in-human
fMRI	functional Magnetic Resonance Imaging
FP	Full Proposal
FP7	Seventh Framework Programme
FTE	Full Time Equivalent
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
GDP	Good Distribution Practice
GDPR	General Data Protection Regulation
GIRP	Groupement International De La Repartition Pharmaceutique
GLP	Good Laboratory Practice

Acronym	Meaning
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
HCT	Human challenge trials
HD	Huntington's Disease
HECOR	Health Economics & Outcomes Research
Helmsley Charitable Trust	Leona M. and Harry B. Helmsley Charitable Trust
hiPS cells	Human Induced Pluripotent Stem cells
HIV	Human Immunodeficiency Virus
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
IBD	Inflammatory Bowel Disease
ICC	Internal Control Coordinator
ICHOM	International Consortium for Health Outcome Measurement
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 1Joint Undertaking
IMI2 JU	Innovative Medicines Initiative 2Joint 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

Acronym	Meaning
IRPs	Integrated Research Platforms
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
JU	Joint Undertaking
KM	Knowledge Management
KOLs	Key Opinion Leaders
KPI	Key Performance Indicator
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
MDR	Multi-drug resistance
MEAs	Multielectrode Arrays
MEG	MagnetoEncephaloGraphy
MEP	Member of the European Parliament
MJFF	Michael J Fox Foundation
MoA	modes of action
MoU	Memorandum of Understanding
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

Acronym	Meaning
NFTs	Neurofibrillary Tangles
NIMBL	Non-Invasive Biomarkers for Metabolic Liver Disease
NIMH	National Institute of Mental Health
NMD	Neurodegenerative Movement Disorders
NTM	Non-tubercular mycobacteria
PA	Payment Appropriation
PanAACEA	Programa Argentino para Niños, Adolescentes y Adultos con Condiciones del Espectro Autista
PBNs	Company-specific Portfolio Building Networks
PD	Pharmacodynamics
PD	Parkinson's Disease
PDFF	Proton Density Fat Fraction
PGEU	Pharmaceutical Group of European Union
PMDA	Pharmaceuticals and Medical Devices Agency
PnSEP	Primary and secondary Endpoints
POC	Proof of Concept
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
RIA	Research and Innovation Action
ResER	Residual error rate
RoI	Return on investment
RWD	Real Word Data
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
SNAP-25	Synaptosomal Associated Protein 25
SOFIA	Submission of Information Application
SP	Short Proposal

Acronym	Meaning
SRA	Strategic Research Agenda
SRG	States Representatives Group
SV2A	Synaptic Vesicle Glycoprotein 2A
SZ	Schizophrenia
T1D	Type 1 diabetes
T2D	Type 2 diabetes
T2DM	Type 2 Diabetes Mellitus
TB	Tuberculosis
TBA	TB Alliance (Global Alliance for Tuberculosis Drug Development)
TBDA	TB Drug Accelerator
TBDDN	Tuberculosis Drug Development Network
TBRU-N	Tuberculosis Research Units Network
TBTC	Tuberculosis Trial Consortium
TI	therapeutic index
TRD	Treatment Refractory Depression
TRL	Technology Readiness Level
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
WHO	World Health Organisation
WP	Work package
XDR-TB	Extensively-drug resistant
18F-FDG	Fludeoxyglucose (18F)
2-DG	2-Deoxy-D-Glucose