Topic: Integrated Research Platforms enabling Patient-Centric Drug Development

All information regarding future IMI Call topics is indicative and subject to change. Final information about future IMI Calls will be communicated after approval by the IMI Governing Board.

Topic details

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, (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;
- *Health care providers, investigators and hospitals* contribute disease and healthcare (delivery) expertise, expertise in ethics (ethics committees) and facilitate access 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).

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 full implementation of platform trials; however, this is out of scope in this Call topic.

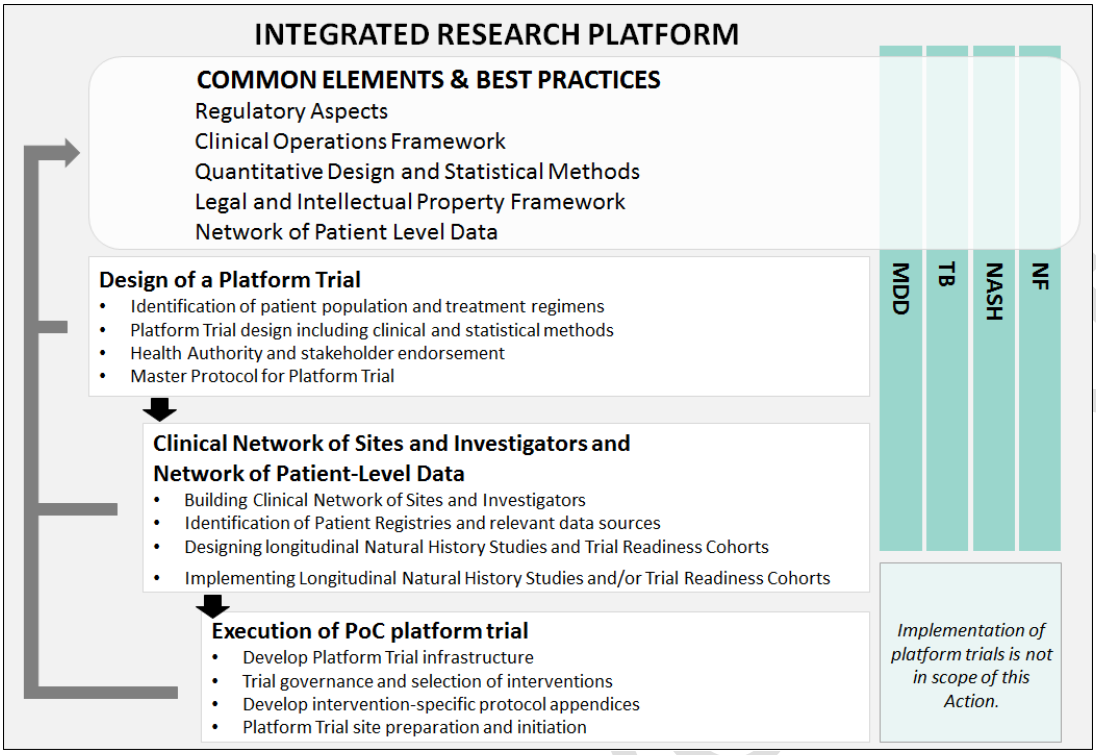

Figure 1 Schematic overview of the IRP Project.

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.

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 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. 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 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 in this project. Experience and best practices from prior platform studies across indications will be analysed and structured into template master protocols and Intervention Specific Appendices (ISAs) that support IRPs for different indications. Table 1 presents the overall content of the master protocol and the ISA.

General platform trial Design Features	
Master protocol	Intervention specific appendix
The overall *study design* *Study population* inclusion and exclusion criteria *Randomisation scheme* Primary, secondary and other *outcomes* *Statistical methodology*, and the planned analyses that are common across all interventions. *Disease specific elements* common for all interventions, e.g, safety assessments *Standard methodology* for clinical trials and administrative sections, e.g. safety reporting	*A summary of product characteristics*, including mechanism of action and rationale for use in the disease to be studied *A summary of available preclinical and clinical data* including pharmacokinetic /pharmacodynamic, target engagement, biomarker data, drug-drug interactions, and safety data *A summary of the dose rationale***,** including information for either a single or multiple doses as appropriate and the inclusion of a long-term safety extension when appropriate. *Specific endpoints and biomarker pharmacodynamic assessments*, which are compound-specific to the proposed mechanism of action of the intervention *Intervention-specific inclusion or exclusion criteria, concomitant medication usage, and safety assessments* related to known toxicology, drug-drug interactions, or potential safety risks *Intervention-specific statistical assessments***,** such as the sample size, randomisation method/ratio, and the decision rules

Table 1: General platform trial design features

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 the preparation of and for execution of platform trials. When fully implemented, these networks will have two main components, both with common-foundational and disease-specific dimensions:

a) Clinical network of sites and investigators

For full IRP and platform trial implementation, enduring multinational networks[1] 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.

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 enabling faster recruitment in platform trials.

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

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).

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.

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.

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 practices documents and be freely available for creation of future networks of patient-level data.

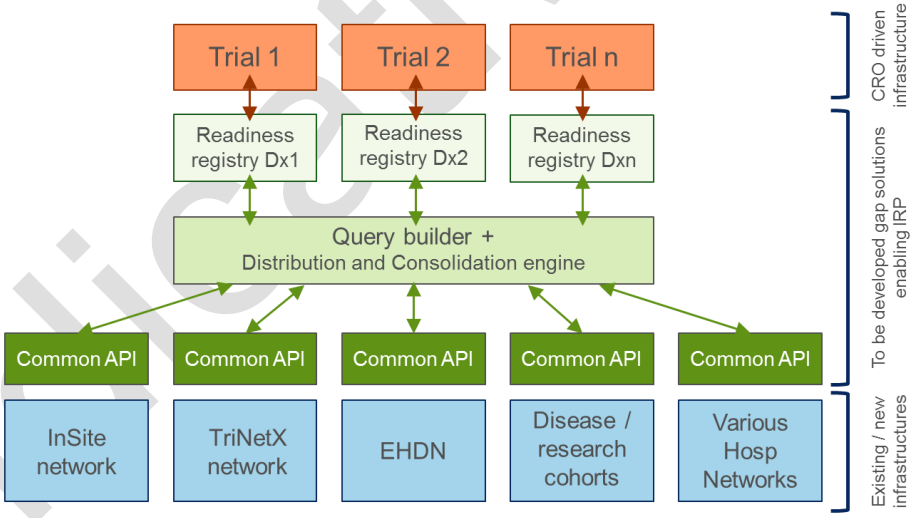

Figure 2: High level schematic of technology component of network of patient-level data

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 full implementation 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 full implementation. 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 full implementation. 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 Invesitgational 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 stakeholders 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 foundational elements work stream and a disease-specific work stream, or via another communication mechanism 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 and process for design of platform trials with multiple companies and public stakeholders, including general framework for the definition of trial sponsorship and responsibilities for oversight and compliance;
    - Compound selection procedure for inclusion in platform trials;
    - clinical network: include the necessary legal, contractual processes, tools and accountability instruments;
    - 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 with national health authorities including the role of the sponsor and management of specific roles and responsibilities in the context of IRPs with multiple products, different manufacturers and company confidential information. Among others, 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. (linking to proposals developed within the statistical methodology domain);
  - evaluation of applicability of existing and emerging regulatory guidance for specific diseases or populations and an evaluation of the need for additional guidance applicable to broader diseases / populations to be studied in a platform trial;
  - use of investigational product combinations in the context of IRPs;
  - scientific advice from health authorities and HTA bodies on prognostic and predictive biomarkers and potential diagnostic tests in the context of IRPs;
  - privacy and ethical questions arising from new approaches, et al; linking to proposals developed within the legal and clinical operations domains;
  - mechanisms for frequent, timely and collaborative engagement with stakeholders e.g. medicines & device regulators and ethic committees, beyond existing scientific advice procedures.
- 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 (eg. contractual considerations/language to enable two or more compound 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, in particular for performance and execution IRPs, and for evaluating the long-term impact of the Action on clinical development paradigm, platform trials in particular, and on innovative new treatments reaching patients.
4. Communication strategy and engagement with Key Opinion Leaders (KOLs) and competent authorities (including health authorities, HTA bodies, ethics committees) to enhance acceptance and promote future 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 and standards, and/or guidance documents (when 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 be included in platform trial design;
  - Identification of potential treatment regimens to be foreseen in platform trial design;
  - Platform trial design (created by simulation guided clinical trial design, evaluation of operating characteristics; statistical analysis plan) following common methodologies which will 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 (eg. 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 trials, (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. An overarching sustainability plan for the governance, maintenance, expansion and improvement of the common foundational elements and of the frameworks for clinical networks and networks of patient level data.

Expected impact

The objectives, deliverables and anticipated impact of the resulting Action are well aligned with the mission and goals of IMI2 JU. Most importantly, it will deliver a transformational new approach, standards and tools to accelerate the development of innovative medicines for diseases of high unmet medical need, including diseases that are within 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 and implementing the proposed reusable IRP and platform trial approach in Europe will deliver to the region a tangible advantage for developing innovative new medicines, and for advancing fundamental and applied medicines research in general, in academia and industry. 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 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.

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

Industry consortium

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 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 36 months.

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:

- clinical and research and development expertise in the disease areas identified in this proposal, including biomarker and clinical endpoint expertise;
- leadership or access to clinical site consortia and/or networks in the four targeted disease areas in scope: MDD, TB, NASH and NF;
- experience and know-how in clinical trials including clinical operations, clinical programme management and clinical trial regulations;
- know-how and experience with clinical trial sponsorship and GCP responsibilities;
- statistical expertise for the design of platform trials and longitudinal natural history studies, statistical methods, modelling and simulation;
- regulatory expertise;
- 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; data standards
- legal expertise;
- ethics expertise;
- business model expertise for consortia of companies and organisations working together;
- expertise in project management and programme management services;
- communication expertise, preferably for alliance management of large-scale consortia;
- grant administration and compliance;
- capability to perform clinical trial sponsor duties for platform trials.

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, health care providers, investigators and hospitals, academic research groups, health authorities and HTA groups, and SMEs.

While preparing their proposals, Applicant Consortia should 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 below architecture for the full proposal is a suggestion; different innovative project designs are welcome, if properly justified.

The final architecture of the full proposal will be defined by the participants in compliance with the IMI2 rules and with a view to the achievement of the project objectives. In the spirit of the partnership, and to reflect how IMI2 Call topics are built on identified scientific priorities agreed together with EFPIA beneficiaries/large industrial beneficiaries, it is envisaged that IMI2 proposals and projects may allocate a leading role within the consortium to an EFPIA beneficiary/large industrial beneficiary. Within an applicant consortium discussing the full proposal to be submitted at stage 2, it is expected that one of the EFPIA beneficiaries/large industrial beneficiaries may elect to become the coordinator or the project leader. Therefore, to facilitate the formation of the final consortium, all beneficiaries are encouraged to discuss the weighting of responsibilities and priorities therein. Until the roles are formally appointed through a Consortium Agreement the proposed project leader shall facilitate an efficient negotiation of project content and required agreements.

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 and will ensure investments and deliverables of all project components and ensure delivery on the primary objectives of the Action. Professional programme and project management approaches will be deployed to achieve synergies between the common foundational elements, clinical networks and networks of data, and disease-specific integrated research platforms.

This work package includes:

- Project management and communication (within the consortium, with relevant external collaborators/stakeholders, and with the public);

- Grant administration;
- Dissemination of scientific results, research data and common 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;
- Overall sustainability plan facilitating continuation beyond the duration of the action;
- Establish collaborations with ongoing initiatives.

Industry contribution:

- experience in leading and managing large scale public-private partnerships;
- expertise in programme/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);
- experience in workshop/ conference organisation.

Expected applicant consortium contribution: all of above with

- exceptional expertise in programme/project management and communication;
- proven experience in leading and managing large scale public-private partnerships from a public-sector perspective;
- clinical and research expertise in all disease areas of this proposal;
- expertise in Cochrane-type or other meta-analysis reviews to identify 'best practices' and standardisation of practice;
- experience in public-private partnerships to help define KPIs for public parties.

Work package 2 – Common foundational elements

The goals of this work package will be as follows:

Referring to the scope described earlier, this work package includes at least:

- Best practices compiled and published throughout the project life;
- Regulatory: precedence of HA interactions to support IRP/platform trials of a particular design. The project will benefit from pressure testing proposals via Regulatory Authority and patient organisation input in the form of their participation in advisory bodies;
- Quantitative Sciences: statistical methodology and trial simulation tools (e.g. computer software, codes) that will enable the efficient design and execution of disease-specific IRPs and future IRPs;
- Clinical operations: best practices (processes, guidance documents, et al) will enable the efficient setup and execution of IRPs;
- Legal: legal frameworks and agreement templates/language that will enable the efficient setup and execution of IRPs.

Industry contribution:

- resources with expertise in statistical and quantitative modelling and simulation methodologies related to adaptive clinical trial designs and platform trials;
- 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, track record of strategic approach to collaborate with health authorities to introduce innovative methodologies;
- legal expertise related to IP and cross-company collaboration;
- expertise in clinical operations, clinical programme management, medical writing, data privacy;
- access to KOLs;
- experience in workshop/ conference organisation.

Expected applicant consortium contribution:

- leadership in statistical methodology i.e. Bayesian statistics, modelling methodologies, adaptive trial designs;
- leadership in RWD related to nesting clinical research within existing hospital infrastructures;
- experience in operationalising the execution of platform trials;
- regulatory expertise: where possible contributions from regulatory experts or funds set aside by the consortium members to support consultation with highly experienced regulatory experts. In addition, extensive experience with providing input and scientific advice on platform trials or complex adaptive designs, including guidance on the acceptability, from a regulatory perspective, to support subsequent regulatory submissions including marketing authorisation would be required;
- ethics committee expertise: extensive experience leading ethics committees with responsibility for approving platform clinical trials or other complex adaptive clinical trial designs; deep understanding of complex innovative study designs; expert knowledge of privacy laws, regulations and related 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;
- expertise in project management;
- capability to perform clinical trial sponsor duties for platform trials.

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

The goals of this work package will be as follows:

The work stream 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 different layers and modules needed for this work package are:

- Developing an approach and interoperability networks components for efficiently interrogating the existing networks such that potential candidate-patients for the trial readiness cohorts can be identified. The development of a common API for integration with the various pre-existing networks is anticipated;
- Setting up a common query workbench that includes distributing the search queries over the different relevant data networks and which can consolidate results. Local data owners should also be able to run these queries and validate the results;
- A common informed consent (probably eConsent) solution to be identified that can be used across IRPs for the recruitment of patients;

- Sharing a common underlying technical solution across disease registries with disease specific aspects and sufficiently common and modular elements to allow for support of registries in multiple different disease areas. Given this is expected to be a centralised database(s), with information from consented participants, data security is of the utmost importance. Hosting partners for this will need to show the highest standards of data privacy protection, logical and physical data security;
- Usage of "eResearch" platforms that conform to the required regulatory validation. This platform should allow for Electronic Data Capture and support other necessary functionalities for trial execution. Similar to the solution for the trial readiness cohorts, this eResearch platform should be modular and able to support trials across different disease areas;
- Patient driven trial participation, e.g. structures / solutions in which patients as holders of their personal health data decide with whom to share their data. Equally, solutions in which patients can provide additional outcomes related data (patient reported outcomes) or in which connected devices can capture and deliver data (e.g. activity trackers for MDD);
- Governance bodies for overall data management and security, patient privacy (adherence to General Data Protection Regulation [GDPR]) and consent, data quality, etc. Further, implementation of such infrastructures in participating hospitals / data providers will require support and change management in those participating data providers. Additionally, it is critical to ensure sufficient capture the "voice of the customer", i.e. get the input and collaboration from the various stakeholders, from patients to healthcare providers and data custodians.

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

Industry contribution:

- resources with 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;
- interpretation of clinical information and project management;
- leadership in building sites and hospital networks to support clinical Phase 0-4 studies;
- technologies to utilise EHRs.

Expected applicant consortium contribution:

- experiences 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;
- necessary 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 etc), as well in secure hosting of patient level data;
- provide input and solutions for patient centric trial participation;
- connectivity/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)

The goals of this work package will be as follows:

Unmet need and drug development challenge

Major depressive disorder (MDD) is the leading cause of disability in the world. Its prevalence is increasing and it strikes people of all ages, affecting ability to work and straining family and social relationships.

Most antidepressants work through the monoamine system with only a few distinct classes of medications. From large naturalistic studies, only 50% of patients have at least a 50% response to initial treatments. In addition, there is increased recognition of ongoing impact of residual symptoms and of the need to shift focus from symptom response to remission of depressive symptoms. Remission is achieved in only 20-30% of patients while on treatment. For partially responsive patients, the options are to switch antidepressants, add a second antidepressant, or augment with another agent. Many patients with MDD inadequately respond to any treatment and develop treatment refractory depression (TRD). For TRD patients, only invasive therapies such as electroconvulsive therapy or the use of experimental pharmacological treatments are available. For augmentation in partially responsive patients, only atypical antipsychotics are approved but these medications have significant tolerability issues and do not help many patients.

Therefore, a clear need exists to develop additional medications with new mechanisms of action for patients with TRD and patients who do not have TRD but require augmentation of antidepressant treatment.

This work package will design and prepare for implementation of an MDD IRP and platform trial.

Patient population

The population will be patients with MDD who fail to adequately respond to an antidepressant treatment. This includes partial responders as well as those with full TRD. The work package will achieve a consensus definition of lack of adequate response as well as the definition of a TRD patient. In addition, an adequate duration and dose of an antidepressant needs to be defined.

Clinical network

The work package will plan, design and initiate a clinical network. Conceptually, the clinical network will consist of primary care sites working with mental health referral centres. Through this referral process, a pool of well characterised patients meeting the consensus disease definition will be identified.
Tasks will include:

- identify requirements for participating primary care and referral centres;
- identify and engage primary care and referral centres to the clinical network and evaluate their overall operational readiness;
- develop an initial coordination plan between the primary care sites and referral centres;
  define the process to establish standardised assessments;
- evaluate the privacy issues that will allow recruitment from the clinical network to the longitudinal natural history study and/or platform trial.

The feasibility of using EHRs will be assessed from regulatory and ethical perspectives. Methods will be developed to efficiently extract the required information and identify potential patients. For future implementation, multiple clinical networks may be established that feed into the longitudinal natural history study and/or platform trial.

Longitudinal natural history study

From the clinical network, once live, potential subjects can be identified to participate in a longitudinal natural history study. This work package will design a study to better understand the clinical course of patients who are partial responders or lack an adequate response to treatment, with the goal to identify and validate clinical and biomarker characteristics for early identification of patients who are likely to develop TRD. In addition, through the

longitudinal natural history study, patients can be identified for enrolment into the platform trial. Since mechanism of actions may be specific to either TRD or MDD with partial response, this determination will be important in the initial screening process within the longitudinal natural history study.

Key deliverables include the design and associated protocol for the longitudinal natural history study and defining the key operational components that will be required to allow identification of patients for the IRP.

Platform trial

A key deliverable is the development of the master protocol for a platform trial. The focus will be on two regulatory pathways: TRD (primary) and adjunctive MDD (secondary). The platform trial will have multiple arms, adaptive design, and a shared placebo group across interventions. There will be appendices for each compound's specific requirements (e.g., dose/dose regimens, relevant biomarker collection) enabling entry into the platform trial. The primary outcome for the platform trial will be improvements in symptoms of MDD compared to placebo. Placebo issues associated with MDD trials will need to be addressed (e.g. expectation bias, double-blind placebo lead ins, sequential parallel comparison designs).

Details of the design will be a focus of the work package. Current thinking is that the design will focus on a proof of concept study of 4-6 weeks of active treatment after a 4-week screening period. Patients will be followed for 1-2 weeks after discontinuation to identify withdrawal symptoms and/or persistence of effect. Intervention would be after initial treatment for at least 4 weeks with antidepressant medication. Patients in their first episode of MDD will be included. There will be the potential of long-term extension of treatment determined by both the consortium and specific drug developer.

Feasibility and sustainability

Execution of the platform trial and the related longitudinal natural history study are not within scope. However, feasibility assessments to conduct this programme are an expected deliverable. This will include initiation of a clinical network, assessment of the feasibility for patients and investigators to participate in this programme, overall evaluation of site readiness and identification of common gaps, and obtaining regulatory endorsement for the platform trial.

Finally, a sustainability plan will be developed that addresses moving from planning to full implementation of the IRP and execution of the platform trial, including full funding for sustaining the platform.

Industry contribution:

- expertise in MDD drug development and clinical testing of candidate compounds;
- expertise in setting up clinical network of sites and investigators;
- leadership in building hospital networks to support clinical studies, and technologies to utilise EHRs;
- expertise in designing and implementing disease registries and trial readiness cohorts;
- expertise in patient recruitment, site start-up and clinical operations;
- expertise in drug development and experience in compound selection for clinical studies.

Expected applicant consortium contribution:

- expertise in MDD trials and enabling identification of suitable patients in MDD;
- ability to develop a clinical network, connecting primary and specialty providers;
- expertise in establishing network of patient-level Data (EHRs);
- expertise in platform design;
- expertise in designing and implementing disease registries;
- expertise in clinical operations, including design and implementation of a clinical database;

- experience in interactions with health authorities to obtain input into study design;
- experience in obtaining ethical approvals.

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

The goals of this work package will be as follows:

Unmet need and drug development challenge

Tuberculosis (TB) prevalence and deaths between 1990 and 2014 were reduced by 42% and 47%, respectively [8]. Nonetheless, TB remains a deadly communicable disease with 1.8 million deaths in 2016, 10.4 million cases reported and 600,000 cases resistant to first line drugs. TB disproportionately affects the world's poorest and most vulnerable, including children, people co-infected with HIV, and individuals without access to healthcare [9]. Also in the developed world, TB remains a significant medical and societal problem.

The *WHO End TB Strategy* calls for a response to meet the 2035 targets and the need to "focus on ensuring availability of new tools from the research pipeline, in particular:

- a new vaccine that is effective pre- and post-exposure;
- a safer and more effective treatment for latent TB infection;
- better diagnostics, including new point of care tests;
- and safer and easier treatment including shorter drug regiments for TB disease.

The TB R&D community rallied around the overall goals to accelerate the decline in global TB incidence, and to champion the development of new 3-4 drug regimens for both drug sensitive (DS) and drug resistant (DR) cases. International consortia, such as the CEO Roundtable, the TB Drug Accelerator (TBDA), and CPTR, are established to advance this global research agenda and the pipeline for TB drugs shows significant promise to deliver phase 2 ready clinical candidates over the next 3 years [10].

This work package will design and prepare for implementation of a TB IRP and platform trial to efficiently test new combinations of 3-4 drug therapies, comprised of existing and novel compounds.

Patient population

The population will be patients with drug sensitive (DS) and drug resistant (DR) TB.

Platform trial

Two major outputs are envisioned for this module: (i) a master protocol and (ii) a set of selection criteria that will qualify drug combinations to enter this platform.

The design requirements of the master protocol are anticipated to include:

- a learn phase to test efficacy of compound combinations after a 2-month treatment (e.g. based on culture conversion);
- a confirm phase testing a longer treatment duration and suitable efficacy endpoints that can result in a data package to support eventual registration;
- decision criteria that will allow a combination to advance from the learn to the confirm phase;
- potential accommodation of both DS and DR patient populations;
- entry of compound combinations at different time points of the learn and confirm phases;
- sample size optimised to test each combination at each phase, taking into consideration the limited funding available for TB R&D and the range of drug combinations suitable for inclusion;
- criteria and a decision-making system to progress newer, shorter regimens into the learn and confirm phases and allow shorter, more effective regimens to replace control arms when confirmed.

The master protocol should be designed leveraging the outputs of work package 2. Clinical trial simulations will identify the optimal design parameters and rules at each decision point. Regulatory inputs should be obtained to ensure the acceptance for registration.

The second output is a set of selection criteria and data requirements that will qualify drug combinations to be tested in the platform trial. These criteria and data requirements will be informed by the global TB development pipeline and access to (data on) well-documented TB specimens from public- and philanthropically-funded biorepositories, in association with early testing efforts supported by individual compound owners and public- and philanthropically-funded TB initiatives.

Implementation planning

As most TB patients reside in developing countries, the planning and supportive preparation of the TB platform trial must be tailored. Potential trial sites in TB-endemic countries will be identified from ongoing projects (AIDS Clinical Trial Group (ACTG), Tuberculosis Trial Consortium (TBTC), Programa Argentino para Niños, Adolescentes y Adultos con Condiciones del Espectro Autista (PanACEA), The Union, TB Alliance, CEO Roundtable, etc). Outputs of external TB capability-building efforts will be leveraged to (i) develop plans for evaluating readiness of such sites and investigators to participate in the platform trial, (ii)define requirements and assessment procedures for the standardisation of microbiology laboratories and specialised laboratory setup (such as BSL3 microbiology capability), and (iii) fill in any gaps in operational readiness.

In addition, the feasibility of using technologies such as EHR equivalents and patient tracking/contact methods through community health workers to shorten the time gap between patient screening, diagnosis and enrolment will be assessed. Efforts will be directed to integrate public data networks and existing hospital/regional/national health records systems.

New compound combinations are expected to be ready to enter the learn phase of the platform trial around mid-2020. As the design of the master protocol progresses, coordination with consortia and individual compound owners will allow timely selection and entry of suitable compound combinations. This includes the development and non-clinical (e.g. toxicology) and early clinical (e.g. drug interaction) information required before entry to support the desired treatment combination and duration. While such studies will be funded outside this IMI2 IRP proposal, strong coordination with the compound/combination owners will be required and these activities will be an important input into this programme.

Finally, to move from planning to implementation, a detailed sustainability plan for the TB platform trial will be developed to ensure governance of the IRP and platform trial, identification and selection, retention or graduation of (combinations of) novel and existing compounds, and full funding for sustaining the platform.

Industry and IMI2 JU Associated Partners contribution: In addition to expertise from the common foundational elements work packages:

- clinical expertise in TB disease and TB drug development expertise;
- expertise in conduct of large scale studies to test compound combinations;
- expertise in the microbiology technologies to support trial conduct;
- experience and access to validated assays to support TB drug development;
- regulatory expertise in TB;
- organisational experience and connections with existing TB R&D consortia such as TBDA, CEO roundtable, and CPTR, as well as new and expected future consortia such as PanACEA, ACTG/TBTC, the future projects resulting from AMR accelerator, in particular pillar B (Call 15), IMI-PreDICT-TB and the future IMI EHDN project.

Expected applicant consortium contribution:

- expertise in TB regimen development paradigms in low resource settings and varying resistance profiles;

- expertise in rapid and low-cost diagnostic capabilities and validated assays, to enable identification and recruitment of TB drug-sensitive and resistant- patients;
- a partner that could serve as, or be able to identify, a trial sponsor for the platform trial once entering the implementation phase;
- clinical trial execution experience in TB-endemic countries, including experience in medical education and clinical capacity building, BSL3 microbiology laboratory setup, and experience recruiting drug-sensitive and drug resistant patients;
- experience working with healthcare systems and infrastructures in resource limited settings;
- expertise and/or knowledge of patient-level data networks in TB prevalent countries;
- clinical operations experience, ideally direct experience with implementing platform trials.

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)

The goals of this work package will be as follows:

Unmet need and drug development challenge

Non-alcoholic fatty liver disease (NAFLD) is the most common liver disorder in Western industrialised countries, impacting 20-30% of adults, with major risk factors including central obesity, type 2 diabetes mellitus (T2DM), dyslipidemia, and the metabolic syndrome. Approximately 20% of patients with NAFLD have more significant disease, called non-alcoholic steatohepatitis (NASH), which is associated with liver inflammation and fibrosis and, long-term can result in an increased risk of cirrhosis, hepatocellular carcinoma, other cancers, and death (typically from cardiovascular disease) [11]. NASH is expected to soon surpass hepatitis C as the primary indication for liver transplantation [12]. Consistent with the associated obesity and diabetes epidemics, the prevalence of NASH is anticipated to increase significantly over time [13].

Current treatments for NASH include weight loss, on-label use of pioglitazone in patients with T2DM, and Vitamin E in patients without T2DM [14]. None of these is adequately addressing the medical need due to difficulties in achieving and sustaining the necessary weight loss and due to drug treatment-related adverse events and long-term safety risks. Importantly, no studies have been done to assess the impact of the histologic changes seen with these interventions on clinically meaningful outcomes.

Many biotechnology and pharmaceutical companies are developing therapies to treat NASH, with a few such compounds (obeticholic acid [15], elafibranor [16], cenicriviroc [17], and selonsertib [18]) currently in Phase 3. However, given the requirement for liver biopsies for diagnosis and prognosis of NASH, the limited number of patients with recent existing liver biopsies, and the myriad of companies looking to evaluate new treatments for this disease, a progressively worsening recruitment bottleneck leads to numerous delays in the completion of NASH studies.

This work package will design and prepare for implementation of a NASH IRP and platform trial that can efficiently test (combinations of) new treatments for the interception and treatment of NASH.

Patient population

The population will be patients with NASH on a continuum of disease with well-characterised biomarkers and clinical phenotypes for inclusion in a platform trial.

Platform trial

The platform trial could consider evaluating compounds in Phase 2b, Phase 3/4, or both, potentially in a seamless way. A similar study population and design is proposed for Phase 2b and Phase 3 to provide replicative efficacy data and a larger safety database. Until non-invasive diagnostic and prognostic tests that can accurately substitute

for liver biopsy are available, a liver biopsy would serve as the primary diagnostic and prognostic assessment of NASH in clinical studies. Phase 2 would likely have a 52- or 72-week treatment duration, and patients in Phase 3 will continue on study therapy for at least 4 years with continued follow-up to assess for NASH outcomes (i.e. cirrhosis and all-cause mortality). The NASH platform trial will also allow for the systematic and efficient evaluation of monotherapies and combination therapies to help ensure the most appropriate therapies are given to the appropriate patients at the appropriate time in their disease.

Status of biomarker development and opportunity

The diagnosis and prognosis of NASH currently requires a liver biopsy, an imperfect gold standard that is invasive (associated with both morbidity and mortality), subject to sampling bias (samples a very small fraction of a heterogeneous liver), and variability in its performance (operator dependence) [19]. Given aforementioned limitations of liver biopsy and the absence of any approved drug therapies for NASH, most patients with NASH go undiagnosed and untreated. As a result, the true prevalence of NASH and its natural history are incompletely characterised and likely under-appreciate the epidemic of NASH.

Non-invasive tools are desperately needed to facilitate drug development and bring new therapies to patients with NASH, and to ensure that all patients who may benefit from these treatments receive them and can be easily followed by their physicians. Non-invasive tools can be generally grouped into imaging modalities [e.g. magnetic resonance imaging (MRI)-proton density fat fraction (PDFF), MR elastography (MRE), fibroscan and multiparametric MRI] and laboratory measures [e.g. liver transaminases, non-invasive risk scores of FIB-4 and NAFLD fibrosis score, miRNA and the enhance liver fibrosis (ELF) score] [20].

Ultimately, the diagnosis and prognosis of NASH may require new/different non-invasive tests, algorithms of existing and/or new tests, or pairing of imaging and laboratory testing to substitute for liver biopsy. The ongoing IMI-funded LITMUS consortium and FNIH-funded NIMBLE programme aim to achieve these goals. These programmes will develop repositories of non-invasive biomarkers for NASH, which leverage existing clinical data and prospective data available to each programme. Collaboration with consortia such as LITMUS or NIMBLE could enhance the efficiency of the trial design, and enable new biomarker research and validation. The systematic collection of non-invasive biomarkers within a NASH platform trial complements and facilitates the goals of programmes like the IMI LITMUS consortium.

Clinical network

The work package will determine the requirements and design for a Clinical Network of sites and investigators, identify potential sites and design and initiate such Clinical Network, and evaluate overall readiness of sites to contribute data and/or to participate in the platform trial.

The work package will also identify, evaluate and assess feasibility of networks of patient-level data (e.g. existing EHR systems) to facilitate identification and recruitment of patients.

This work package will leverage capabilities developed by the “clinical network and network of patient-level data” utilise patient-level data, including EHRs.

Finally, a sustainability plan will be developed that addresses moving from planning to full implementation of the IRP and execution of the platform trial, including full funding for sustaining the platform.

Industry contribution:

- expertise in drug development, trial design and clinical testing of candidate compounds;
- specific expertise and knowledge of the investigational treatments to be included in the IRPs;
- expertise in setting up clinical network of Sites and Investigators to enable execution of platform trials;
- expertise in designing and implementing disease registries;
- experience in creating trial readiness cohorts as part of clinical recruitment strategy;

- leadership in building sites and hospital networks to support clinical Ph0-4 studies;
- technologies to utilise EHRs; familiarity with the future IMI-EHDN project.

Expected applicant consortium contribution:

- expertise in the design and execution of clinical trials for NASH and adjacent diseases;
- appropriate expertise, sites and/or patient organisations to inform clinical trial design, including biomarker and endpoint definition, to enable identification and recruitment of suitable patients;
- expertise in designing and implementing disease registries, expertise in creating trial readiness cohorts as part of clinical recruitment strategy;
- access to large patient datasets;
- technological expertise in developing queries to patient databases;
- expertise in drug development policy and regulatory decision making.

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

The goals of this work package will be as follows:

Unmet need and drug development challenge

Clinical research on rare diseases is facing many difficulties due to regulatory requirements and the high resource needs to enrol only a few patients. The therapeutic options for rare diseases are often limited and usually it is difficult for patients to have access to diagnostic tools and proper care. In addition to addressing the high medical need in neurofibromatosis, development of an IRP for neurofibromatosis is included as a case model applicable to a variety of other rare diseases.

Neurofibromatosis type 1 (NF1), neurofibromatosis type 2 (NF2), and Schwannomatosis (SWN) are distinct neurogenetic syndromes caused by mutations in tumor suppressor genes that manifest with multiple tumors throughout the central and peripheral nervous system. All three syndromes are rare, with NF2 and SWN estimated to affect between 1/25,000 and 1/40,000 births [21] and NF1 being the more common, with an estimated incidence of 1/2,500–1/3,000 births [21][22]. Although it is unclear whether there is an increased risk for malignancy in NF2 and Schwannomatosis, the risk for malignancy in NF1 has been widely described.

The main morbidities for NF1 are benign tumors (neurofibromas) that can grow very large. NF1 patients are also at risk of developing brain and optic pathway tumors, malignant peripheral nerve sheath tumors, and juvenile myelomonocytic leukemia [23][24][25][26][27]. There are also multiple other manifestations, including vascular and bone malformations, altered neurocognitive development, and endocrine system tumors.

The hallmark of NF2 is the growth of bilateral vestibular schwannomas on the vestibular nerves and also meningiomas are predominant. NF2 has a significant level of morbidity and early mortality [28][29].

The main symptom of Schwannomatosis is chronic excruciating pain, either local or diffuse [30].

The diverse presentation and variable progression of NF may have relevance for the selection of patient treatments. Together with the small size of the patient populations, this makes NF a good candidate for building an IRP to study natural progression and identify predictive and informative biomarkers, and for designing a platform trial to test multiple (combinations of) potential treatments tailored to individual patient profiles.

This work package is composed of two main modules: (i) design of a platform trial and (ii) development of a clinical network. This work package will also identify potential treatments to be included in the platform trial and will assess the potential of combination treatments to enter into the trial.

Patient population

The differential diagnosis of NF and its subtypes is mainly driven by sets of clinical criteria used and codified in

multiple diagnostic criteria papers and by confirmatory genetic testing. The Children's Tumor Foundation (CTF) is sponsoring an international workshop in June 2018 to revise the diagnostic criteria.

The scope of the overall IRP will include NF1 and NF2 patient populations of all ages and other subtypes that are less well defined. The platform trial, however, may be designed to include NF patients below the age of 18, taking into account the difference in incidence and expected enrolment of the two types of NF.

Platform trial

The work package includes the full design and development of the master protocol for a platform trial in NF that can efficiently test new combinations of multiple drug therapies for the different NF manifestations. This module includes the planning for implementation of the platform trial, but does not include full execution. Included in the implementation planning is the development of a detailed sustainability plan with the objective to establish well defined mechanisms for governance of the IRP and platform trial, for identification and selection of (combinations of) novel and existing compounds, for retention or graduation of compounds for futility or success, and for full funding for sustaining the platform beyond the period of this Action.

Clinical network

Building on expertise, ongoing efforts and registry data of CTF, a clinical network of sites and investigators will be designed and initiated with the objectives to:

- access relevant patient registries and existing patient level data;
- identify clinical sites to be qualified for execution of the platform trial;
- plan for and design a longitudinal natural history study. The aim of the latter is to investigate disease progression and to identify biomarkers for diagnosis and disease characterisation, prediction of disease progression, and selection of most promising (combination of) treatments for individual patients eligible to enrol in the platform trial.

Overall, operational readiness of the sites in scope for the clinical network will be assessed and common gaps will be identified.

This work package will leverage the general framework for clinical networks and networks of patient-level data and leverage experience and data from concerted efforts in the diagnosis and treatment of NF.

Industry and IMI2 JU Associated Partners contribution:

- expertise in drug development, trial design and clinical testing of candidate compounds;
- specific clinical expertise in oncology and NF in particular;
- leadership in building hospital networks to support clinical studies, and technologies to utilise EHRs;
- regulatory expertise;
- organisational experience and connections with NF clinical consortia;
- advocacy to expand learnings of NF experience to other rare disease communities.

Expected applicant consortium contribution:

- clinical expertise and knowledge of NF and currently used and investigational treatments;
- expertise in the design and execution of clinical trials for NF;
- expertise and access to sites and patient (caregivers) organisations to inform clinical trial design, including biomarker and endpoint definition, to enable identification and recruitment of suitable patients for inclusion in the IRP and platform trial;
- expertise in implementing Patient Registries and access to applicable NF patient registries;
- technological expertise in developing queries to patient databases;

- clinical operations experience, ideally direct experience implementing platform trials
- expertise in drug development policy and regulatory decision making.

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