

## 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 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.

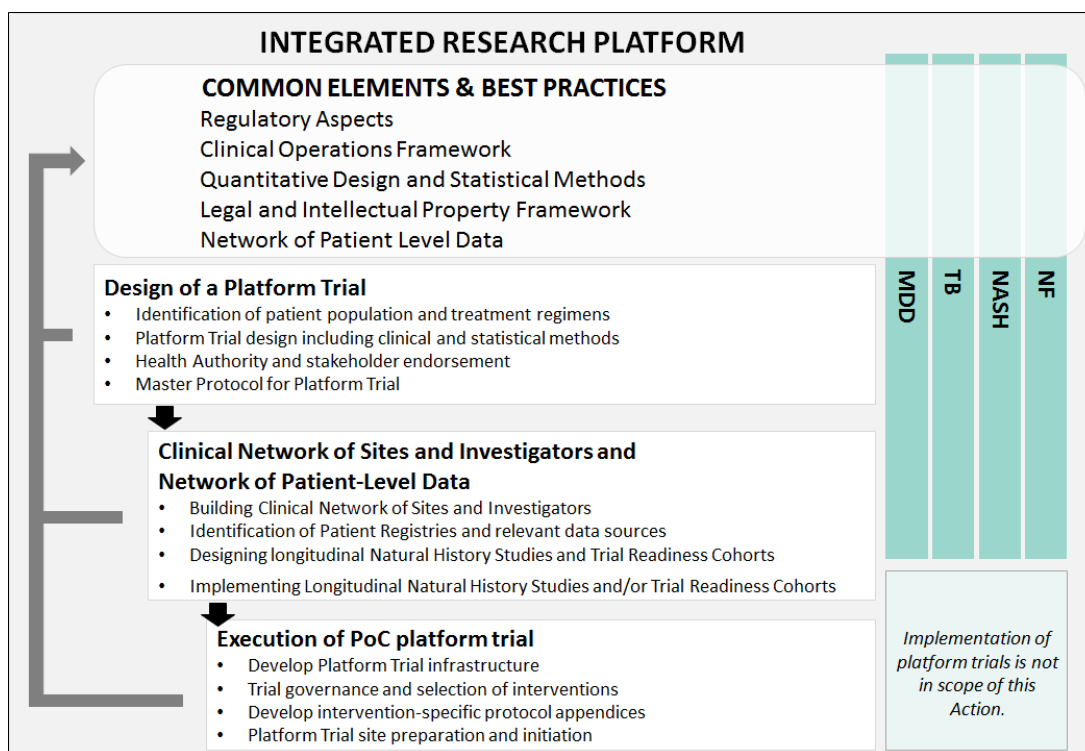


Figure 1 Schematic overview of the IRP project.

## 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 treatment 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<sup>1</sup> 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

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

coordinating centres. The international clinical networks would be set up as a permanent disease-specific, trial-ready infrastructure, able to engage with both patient organisations (patient advocacy groups) and medical community to support research programmes.

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

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

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

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

## **b) Network of patient-level data**

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

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

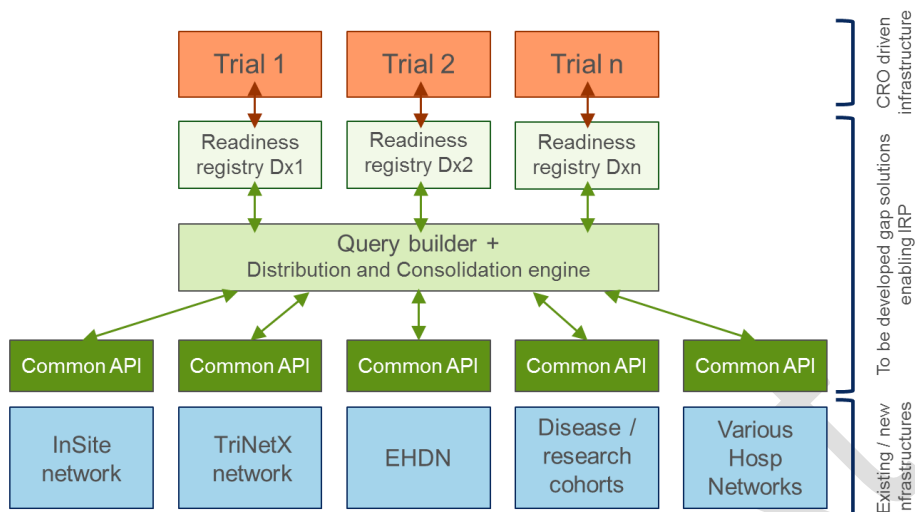
Ongoing efforts to expand the network of connected hospitals to EHR platforms will need to be amplified, when possible, to include centres that will form the clinical network, described in section 2a) above, from both hospital sectors as well as from primary care sectors.

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

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

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

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



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

### 3. Disease-specific integrated research platforms

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

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

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

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

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

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

### Expected key deliverables

The common foundational elements work stream will provide common solutions to the disease-specific work streams, and integrate learnings and feedback obtained from the disease-specific work streams to enhance and extend the collection of common solutions. This process will iterate throughout the life of the project resulting in a collection of published, endorsed common



methodology, standards and best practices, templates and/or guidance documents. This may be achieved by overlapping participation of members in the common and disease-specific work streams, or mechanisms established by the project consortium.

Specific key deliverables to achieve this are:

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

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



- obtaining regulatory endorsement for platform trial,
  - obtaining ethics endorsement for platform trial,
  - sustainability plan to include planning for transition from design to implementation, and to ensure continuation of IRP and platform trial beyond the IMI2 JU project horizon;
  - clinical network of investigators and patient-level data:
    - determine requirements and design for a clinical network of sites and investigators to contribute patients to registries, longitudinal natural history studies and/or trial readiness cohorts, and/or to participate in the platform trial,
    - identify potential sites for such clinical network of sites and investigators,
    - initiate such clinical network of sites and investigators,
    - evaluate overall readiness of sites to contribute data and/or to participate in the platform trial, and identify any common gaps,
    - evaluate site Biosafety Level 3 (BSL3) microbiology laboratory capabilities (TB only),
    - identify, evaluate and assess feasibility of networks of patient-level data (e.g. existing EHR systems or other public data networks) to facilitate identification and recruitment of patients. Leverage IMI-EHR4CR, IMI-EHDN and to-be-developed common methodologies and qualify remaining gaps to fully address this need,
    - identify existing patient registries and/or create protocol for patient registries to enrol in a longitudinal natural history study and/or trial readiness cohort,
    - design and create protocol for longitudinal natural history study (MDD, NASH and NF only),
    - developing funding model for platform trial, including sustainability plan for any activities foreseen beyond the project duration;
  - developing a disease-specific sustainability that includes at least (i) a blueprint and funding model to move from planning to implementation of the IRPs and platform trial execution, (ii) approach for retention of current and attracting new commercial and not-for-profit pharmaceutical development partners and (iii) the mechanism to fully fund and sustain platforms beyond the period of this action, including knowledge and infrastructure sustainability;
7. dissemination and publication of best practices and results;
  8. overarching sustainability plan for governance, maintenance, expansion and improvement of the common foundational elements and of the frameworks for clinical networks and networks of patient-level data;
  9. Memorandum of Understanding (MoU) with TBDDN consortium (from Call 15 topic 8) to cover collaboration and sharing of information on TB-related activities.

## Expected impact

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

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

lower burden to patients, investigators and sponsors, and the feasibility of such trials will be enhanced.

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

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

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

## Potential synergies with existing consortia

Applicants should take into consideration, while preparing their short proposal, relevant national, European, and non-European research projects and infrastructure initiatives. Synergies and complementarities should be considered in order to incorporate past achievements, available data and lessons learnt, thus avoiding unnecessary overlap, duplication of efforts and funding. Examples of relevant IMI and non-IMI projects/initiatives are:

- disease-specific biomarker initiatives such as (incomplete list, examples only):
  - IMI-EMIF (European Medical Information Framework), an IMI project integrating existing in-depth Alzheimer's Disease databases with large scale EHRs <http://www.emif.eu/>,
  - IMI-LITMUS (Liver Investigation – Testing Marker Utility in Steatohepatitis) <https://www.imi.europa.eu/projects-results/project-factsheets/litmus>,
  - complementary international initiatives (e.g. Foundation for National Institute of Health (FNIH)-sponsored Non-Invasive Biomarkers of Metabolic Liver Disease (NIMBL) which are focused on generating the data necessary for qualification of non-invasive NASH biomarkers);
- IMI-EPAD platform trial in Alzheimer prevention <http://ep-ad.org/>;
- relevant registries and projects ongoing at national levels;
- International Consortium for Health Outcome Measurement (ICHOM);
- IMI portfolio of knowledge management projects: eTRIKS, DDMORE, Open PHACTS, IMI-EHR4CR (and the resulting i~HD), and RADAR-CNS (<https://www.imi.europa.eu/projects-results/project-factsheets>);
- TransCelerate BioPharma bringing standardisation to trial conduct processes across sponsors <http://www.transceleratebiopharmainc.com/>;
- future IMI2 JU project resulting from the topic European Health Data Network (EHDN) IMI2 – Call 12, which will deliver an operational, federated network in order to have direct access to RWD for developing new or incremental services in healthcare area [http://www.imi.europa.eu/sites/default/files/uploads/documents/IMI2Call12/IMI2\\_Call12\\_CallText.pdf](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_en); [https://ec.europa.eu/health/ern/networks\\_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.

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

In the spirit of the partnership, and to reflect how IMI2 JU call topics are built on identified scientific priorities agreed together with EFPIA beneficiaries/large industrial beneficiaries, these beneficiaries

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

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

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

### **Work package 1 – Governance and project management**

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

This work package includes:

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

#### Industry contribution:

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



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

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

## **Work package 2 – Common foundational elements**

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

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

### Industry contribution:

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

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

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

- clinical trial sponsor duties for platform trials.

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

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

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

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

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

#### Industry contribution:

- expertise in working in federated data networks;
- expertise leveraged from prior IMI projects such as EHR4CR, EMIF and EPAD;
- expertise in RWD management, standardisation and harmonisation;
- data security methods;
- clinical trial data management and interpretation of clinical information;
- leadership in building sites and hospital networks to support clinical phase 0-4 studies;
- technologies to utilise EHRs.

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

- experience from prior relevant projects where RWD sets have been used as recruitment pool for platform or other trials, preferably within multi-stakeholder and international projects;
- leadership in RWD related to nesting clinical research within existing hospital infrastructures;
- resources to develop the technical modules to bridge the gap between the existing RWD networks and the trial platforms;

- expertise in data management, working with data standards (such as Observational Medical Outcomes Partnership common data model (OMOP CDM), CDISC, ICHOM); secure hosting of patient-level data;
- input and solutions for patient centric trial participation, including patient privacy and consent;
- connectivity and access to EHRs or other relevant data sets, with capability to support identification of patients for trial readiness cohorts and longitudinal natural history studies.

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

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

The goals of this work package are to:

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

Industry contribution:

- expertise in MDD drug development; knowledge about compounds characteristics to be potentially included in future clinical trials (note that compound testing is out of scope of the current action);
- expertise in adaptive trial design; design platform trial;
- set up clinical network of sites and investigators to enable PT execution;
- build hospital networks and technologies to utilise EHRs;
- design and implementation of disease registries and trial readiness cohorts;
- expertise in clinical operations, site start-up and patient recruitment;
- interact with health authorities;

- develop a sustainability plan for full implementation, funding and sustaining the IRP and PT.

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

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

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

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

The goals of this work package are to:

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

Industry and Associated Partner contribution:

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

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

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

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

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

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

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

The goals of this work package are to:

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

Industry contribution:

- expertise in and development of new investigational treatments for hepatic and metabolic diseases; knowledge about compound characteristics to be potentially included in future clinical trials (note that compound testing is out of scope of the current action);
- expertise in adaptive trial design; design platform trial;
- set up clinical network of sites and investigators to enable PT execution;
- build hospital networks and technologies to utilise EHRs;
- design and implementation of disease registries and trial readiness cohorts;
- expertise in clinical operations, site start-up and patient recruitment;
- interact with **health authorities**.

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

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

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

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

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

The goals of this work package are to:

- design and develop a master protocol for a seamless phase 2-3 platform trial (PT) in NF1 and NF2 patients below 18 years of age;
- design and develop a protocol for a broad longitudinal natural history study (LNHS) in NF, all types and all ages, to investigate disease progression and to identify biomarkers for disease characterisation, prediction of disease progression and selection of promising treatments for individual patients;
- define key operational components required for implementing the PT and LNHS;
- conduct feasibility assessments for patients and investigators to participate in this programme;
- obtain regulatory and ethics committee endorsement for the PT and LNHS;
- building on expertise and ongoing efforts of the Children's Tumor Foundation, design and initiate a clinical network of sites and investigators for the IRP and PT;



- evaluate overall site readiness and identification of common gaps;
- assess regulatory, ethical and technical feasibility of using existing patient registries, EHRs and other patient-level data to identify and select potential patients;
- develop a sustainability plan for full implementation, funding and sustaining the IRP and PT.

Industry and Associated Partner contribution:

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

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

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

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