IMI2

10th Call for proposals

Approved by the IMI2 Governing Board of the Innovative Medicines Initiative 2 Joint Undertaking on 16.12.2016

Annex 1 to the Decision of the IMI2 JU Governing Board no. IMI2-GB-DEC-2016-31

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Contents

Introduction

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

- Research related to the future of medicine should be undertaken in areas where societal, public health and biomedical industry competitiveness goals are aligned and require the pooling of resources and greater collaboration between the public and private sectors, with the involvement of small and medium-sized enterprises (SMEs).
- The scope of the initiative should be expanded to all areas of life science research and innovation.
- The areas should be of public health interest, as identified by the World Health Organisation (WHO) report on priority medicines for Europe and the World[2].

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

The IMI2 Strategic Research Agenda (SRA)[4] is the main reference for the implementation of research priorities for IMI2 JU. The scientific priorities for 2016 for IMI2 JU have been prepared based on the SRA.

Applicant consortia are invited to submit a proposal for each of the topics that are relevant for them. These proposals should address all aspects of the topic to which the applicant consortia are applying. The size and composition of each consortium should be adapted so as to respond to the scientific goals and the expected key deliverables.

While preparing their proposals, applicant consortia should ensure that the needs of patients are adequately addressed and, where appropriate, patient involvement is encouraged. Applicants should ensure that gender dimensions are also considered. Synergies and complementarities with other national and international projects and initiatives should be explored in order to avoid duplication of efforts and to create collaboration at a global level to maximise European added value in health research. Where appropriate, the involvement of regulators is also strongly encouraged.

Applicant consortia shall ensure that where relevant their proposals abide by the EU legal framework on data protection[5].

Before submitting a proposal, applicant consortia should familiarise themselves with all Call documents such as the IMI2 Manual for submission, evaluation and grant award[6], and the IMI2 evaluation criteria. Applicants should refer to the specific templates and evaluation procedures associated with the topic type: Research and Innovation Action (RIA).

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[1] Council Regulation (EU) No 557/2014 of 6 May 2014 establishing the Innovative Medicines Initiative 2 Joint Undertaking (IMI2 JU).
[2] http://www.who.int/medicines/areas/priority_medicines/en/
[3] Under IMI2 JU, mid-sized companies having an annual turnover of EUR 500 million or less, not being affiliated entities of companies with an annual turnover of more than 500 million which are established in an EU Member State or an associated country, are eligible for funding. The definition of 'affiliated entities' within the meaning of Article 2(1)(2) of Regulation (EU) No 1290/2013 shall apply *mutatis mutandis*.
[4] http://www.imi.europa.eu/sites/default/files/uploads/documents/IMI2_SRA_March2014.pdf
[5] Directive 95/46/EC on the protection of individuals with regard to the processing of personal data and the free movement of such data and implementing national laws: http://eur-lex.europa.eu/legal-content/EN/TXT/?uri=celex:31995L0046
[6] http://www.imi.europa.eu/sites/default/files/uploads/documents/IMI2_CallDocs/Manual_SubEvalAward_IMI2_v1.4_Oct2016.pdf

Topic 1: Understanding hypoglycaemia: the underlying mechanisms and addressing clinical determinants as well as consequences for people with diabetes by combining databases from clinical trials

Topic details

Topic code	IMI2-2016-10-01
Action type	Research and Innovation Action (RIA)
Submission & evaluation process	2 Stages

Specific challenges to be addressed

Diabetes represents an increasing global healthcare challenge. Controlling blood glucose is a cornerstone in diabetes management aiming to reduce the increased morbidity and mortality associated with this disease. However, only around 50% of patients achieve accepted international glycaemic targets. Whilst the reasons behind this are multifactorial, it is well recognised that episodes of hypoglycaemia (low blood glucose levels) and the resulting fear of hypoglycaemia are significant barriers to achieving better glycaemic control.

Hypoglycaemia is common, and the importance of hypoglycaemia as a major concern for both healthcare professionals and patients is reflected by its impact on daily life as well as its serious consequences, including hospitalisation and mortality. The physical and cognitive effects of hypoglycaemia on the patient can include, for example, behavioural changes, memory loss, and confusion. These can lead to accidents at home, the work place and on the road; an increase in falls in the elderly resulting in fractures; and sleep disturbances, all having a major impact on quality of life. Acute hypoglycaemia is also associated with an increased risk of both cerebrovascular and cardiovascular morbidity and mortality. There are also well reported psychological and psychiatric consequences of hypoglycaemia, and the social and economic impact of these falls not only on the patient but other family members and healthcare systems.

In addition, recurrent hypoglycaemia can lead to hypoglycaemia unawareness by mechanisms which are not clearly understood. Hypoglycaemia and the fear of hypoglycaemia represent a recognised and measurable contributor to the burden of disease for people afflicted by diabetes, as well as their families, friends, and other parties – also known as ‘The Greater Patient’.

Thus, hypoglycaemia is an important clinical issue for many people with diabetes, and it constitutes a major concern for patients on glucose lowering treatment regimens, particularly insulin, sulfonylureas SUs, or glinides, who face the daily challenge of achieving accepted glucose targets safely, without increasing the risk of hypoglycaemia.

In recent years we have seen an increasing number of phase III clinical trials in type 1 and type 2 diabetes, but despite the improved accuracy of glucose measuring devices and increased patient access to continuous glucose monitoring (CGM) technology, detecting and reliably registering hypoglycaemic events in clinical trials remains a challenge. No approved guidelines or methods for how hypoglycaemia should be measured exist. Regarding hypoglycaemia, detailed monitoring of blood glucose and the recording of daily events, including physical activity and diet, are rarely carried out. Although data on severe, and in most cases symptomatic hypoglycaemia are collected during the trial period, information on other types of hypoglycaemia, particularly asymptomatic as well as episodes wherein patient outcomes are not immediately noticeable, is limited. Moreover, people with a past history of severe hypoglycaemia are often excluded from clinical trials and little if any information is routinely collected on other types of pre-trial hypoglycaemia. As a consequence, this type of information is rarely included in post-trial analyses.

The current gaps and challenges in our understanding of hypoglycaemia consequently limit the management of hypoglycaemia. Furthermore, a consensus between healthcare professionals and other professional bodies, including the regulatory authorities, on the definitions of the clinical categories of hypoglycaemia is lacking. This makes analyses of hypoglycaemic episodes difficult. **Thus the overarching objective of this Call topic is to reduce the risk and burden of hypoglycaemia and, as a consequence, ultimately improve glycaemic control in people with diabetes.** To achieve this we will focus on a number of related specific challenges including:

1. the need for a better understanding of the clinical determinants and consequences of hypoglycaemia and hypoglycaemia unawareness;
2. the need to adopt scientifically sound, robust, consistent, and clinically meaningful definitions of hypoglycaemia that will be accepted by practicing clinicians, regulators, industry and academia in order to probe clinical data;
3. the need to create standard guidelines, that will be accepted by regulators globally, on how to measure hypoglycaemic events to test glucose lowering drugs with respect to occurrence rates or severity of hypoglycaemic episodes;
4. the need for standardised collection of clinical and laboratory data within clinical trials to increase our understanding of hypoglycaemia;
5. the need to include hypoglycaemia in the current approach to determine 'value for patients' in a clinical development context;
6. the need for better insights into the underlying pathophysiology and defects in the counter-regulatory mechanisms associated with hypoglycaemia ,recurrent hypoglycaemic episodes and hypoglycaemia unawareness.

Need and opportunity for public-private collaborative research

The proposed IMI2 initiative on hypoglycaemia, based upon a public-private partnership, provides a unique scientific opportunity to address the above-mentioned challenges. The three major insulin producing pharmaceutical companies, as well as those providing continuous glucose monitors, will work together with academic partners and non-profit organisations to produce and analyse databases of anonymised patient data from pooled clinical trial programmes to address key questions in hypoglycaemia research.

In an unprecedented effort to enrich the value of controlled clinical data available for studying the determinants of hypoglycaemia, Eli Lilly, Novo Nordisk, and Sanofi will combine their anonymised clinical trial data from individuals treated with glucose lowering therapies (type 1 diabetes mellitus (T1DM) and type 2 diabetes mellitus (T2DM), age range from 18-80+ years, multiple formulations of insulin, metformin and other drugs) in a single database to test hypotheses concerning the clinical characteristics that may predict a greater likelihood of developing severe hypoglycaemia and other quantifiable forms of hypoglycaemia. A clinically informed interrogation of the database will be conducted, and in a step-wise approach, the hypotheses and correlations that arise from probing the clinical trial database will be tested using the pooled data from the glucose monitoring device companies collected in second database. Abbott, Medtronic and DexCom, will deliver real-time glucose measurements from continuous glucose monitoring. This is expected to generate information about new relationships between baseline characteristics and interventions related to hypoglycaemia, and lead to novel hypotheses that can be tested in pre-clinical studies, and hopefully lead to future evaluations of real-life data sets. The latter will also lead to studies on the social and economic impacts of the short and long term consequences of hypoglycaemia.

The assessment of hypoglycaemia for patients and society will be driven by the T1DM community represented by JDRF, Type 1D Exchange and International Diabetes Federation with support from patient relation managers but the project will also include theT2DM population as they represent a numerically larger population with a substantial burden of hypoglycaemia.

In order to achieve the objective and deliver valid conclusions, internationally recognised clinical academics, with expertise in clinical diabetes, hypoglycaemia and the handling and interpretation of clinical trial data,

including information from large clinical databases, are needed to establish and analyse the large pool of data supplied by the industry and non-profit partners.

The increased scientific and clinical understanding of hypoglycaemia will be translated and presented to regulators by academic partners together with regulatory experts from industry to facilitate a common understanding across all partners. This will support an increased understanding of the requirements for clinical trials and type of data needed to achieve benefits regarding hypoglycaemia within the treatment of diabetes that can be reflected in the regulatory language in product labels.

Therefore a strong and dedicated collaboration between the industry and academic partners will be critical to achieve the ambitious goals of this project.

Scope

To achieve our objective of reducing the risk and burden of hypoglycaemia and ultimately improving glycaemic control in people with diabetes, we aim to gain a better understanding of hypoglycaemia through a series of integrated activities that are expected to include:

- non-clinical and clinical research into the mechanisms of counter-regulation and hypoglycaemia unawareness to identify targets for intervention;
- establishment of a large, consolidated data base of hypoglycaemia captured in clinical trials across glucose lowering drug development programmes from partner companies, and a pooled CGM database collected using various glucose monitoring devices;
- probing the databases to characterise clinically relevant hypoglycaemia and to determine the causes and consequences of such events;
- evaluating glucose measuring techniques to define standard detection guidelines for measuring hypoglycaemia events and the accuracy of the detection;
- developing best practice for the collection of clinical and laboratory data in clinical trials in order to assess hypoglycaemic events;
- shaping health economic outcomes research (HEOR) to determine the value of reducing hypoglycaemia risk;
- identifying existing patient-driven qualitative and quantitative research (self-reporting studies, surveys, etc.) and conducting a related meta-analysis of the data obtained;
- opening a dialogue with regulatory agencies to define clinically meaningful endpoints/methods to document rates of hypoglycaemia and the potential to reduce these with pharmacologic intervention.

Expected key deliverables

The proposed programme will lead to:

- the establishment of a unique clinical trial database developed specifically for this programme that will contain anonymised, standardised and harmonised data from patients with T1DM and/or T2DM on glucose lowering treatment regimens. This database will subsequently become available for other interested researchers to access;
- agreement amongst all stakeholders on the applicability of the definitions of clinically meaningful hypoglycaemia through examination of the combined clinical trial data set, clinical data and CGM;
- enhanced understanding and agreement of standard approaches for how best to design trials to assess hypoglycaemia and how to analyse the data;

- generation of information relating to existing and novel aspects of hypoglycaemia and hypoglycaemia risk leading to a better understanding of hypoglycaemia mechanisms, and novel targets for prevention and/or intervention;
- exploration of the relationship between clinical trial database findings and real-time glucose measurement datasets from continuous glucose monitoring;
- stronger evidence on the utility of non-laboratory glucose measurement and data analysis technologies;
- a 360° assessment of the burden of hypoglycaemia for patients and society that will enrich our understanding of hypoglycaemia, complement our understanding derived from clinical studies and add perspective to related clinical recommendations;
- generation of evidence-based data to support discussions with regulatory authorities on acceptable definitions of hypoglycaemia.

Expected impact

The establishment of clear, robust and consistent definitions of hypoglycaemia will lead to:

- the development of consistent approaches to the management of hypoglycaemia;
- improved design of diabetes trials for glucose lowering therapies;
- development of drugs and treatment paradigms with improved hypoglycaemia benefits;
- enhanced interpretation of clinical trial outcomes;
- clearer understanding of regulatory (licensing) requirements for existing and novel glucose lowering therapies.

Creating a standard guideline on how to measure hypoglycaemia episodes will allow for:

- choice of therapy that provides optimal glycaemic control within the context of individualised therapy;
- lowering the risk of hypoglycaemia through the use of newly developed devices, e.g. those with predictive alarms/guidelines;
- better comparison of blood glucose lowering drugs with respect to hypoglycaemic episodes and severities.

Agreement on a standardised approach for the collection of clinical and laboratory data in clinical trials will provide:

- a better understanding of factors and clinical consequences related to the development of hypoglycaemia;
- the basis for regulatory authorities to recommend standardised approaches of measurement to be included in clinical trials.

A better understanding of the causes and impacts of hypoglycaemia will provide:

- important guidance to patients, healthcare professionals and regulatory authorities involved in the management of patients requiring glucose lowering drugs to treat their diabetes;
- the development of therapeutic approaches that will help to:
    - reduce the risk of hypoglycaemia;
    - improve glycaemic control;
    - reduce the risk of short and long-term diabetes related complications.

This improvement in overall diabetes therapy will lead to better patient outcomes including physical, mental, social and economic benefits for the individual patient. These benefits will be extended to the patient family, friends and workplaces. At the local and national level, the will reduce the direct and indirect costs of

hypoglycaemia. Current US estimates suggest the direct cost for medical assistance per patient episode of hypoglycaemia to be EUR 1 000 [1], while in Germany and the UK, the yearly cost in terms of work productivity loss has been estimated to be around EUR 190 and EUR 500 per person respectively [2].

The outcome of the 360° assessment of the burden of hypoglycaemia for patients and society will complement and enrich the understanding of the importance of hypoglycaemia and the fear of hypoglycaemia as seen from a patient perspective. This perspective is key *vis-à-vis* the shared goal of the pharmaceutical industry and patient groups to alleviate the burden of disease through intervention on the symptoms and consequences of diabetes.

Potential synergies with existing consortia

Applicants should take into consideration, while preparing their short proposal, relevant national, European (both research projects as well as research infrastructure initiatives), and non-European initiatives. Synergies and complementarities should be considered in order to incorporate past achievements, available data and lessons learnt where possible, thus avoiding unnecessary overlap and duplication of efforts and funding. Applicants should consider any relevant diabetes related projects from IMI, FP7, H2020 and other relevant initiatives outside the EU.

The project will align with the International Hypoglycaemia Study Group (IHSG) and the TransCelerate/CDISC (Clinical Data Interchange Standards Consortium) Initiative, global groups of academic experts attempting to establish a new working definition of hypoglycaemia. The project will leverage their expertise and findings and validate their definitions in the pooled clinical trial database.

For knowledge sharing and to build on to learnings on how best to establish health authority interaction and optimal involvement of regulators as advisors, the project will establish a dialogue with the IMI2 RHAPSODY project where a regulatory work package is already in the process of establishing a platform for interaction with the regulatory agencies.

Industry consortium

The industry consortium is composed of the following EFPIA companies:

- Novo Nordisk A/S (lead)
- Sanofi
- Eli Lilly
- Abbott
- Dexcom
- Medtronic

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

- JDRF
- T1DExchange
- Helmsley Charitable Trust

Due to the nature of the participation industry partners and IMI2 Associated Partners, it is anticipated that some elements of the contributions will be non-EU/H2020 Associated Countries in-kind contributions.

The industry consortium will contribute their expansive clinical trial based hypoglycaemia data to establish a consolidated and pooled big data set. The data will most likely consist of more than 100 different clinical trials from 3 different companies containing a total of more than 80 000 patients. The industry partners will deliver the data anonymised and will agree upon what data points are in scope. Furthermore, standardised formats and naming conventions will be established to ensure that individual trial data can be combined. In addition,

real-time glucose monitoring data will be supplied from a different pool of patients undergoing intensive diabetes management which will be combined in a second database.

Furthermore, the industry partners will bring an in-depth knowledge in the fields of *in vitro* and *in vivo* non-clinical pharmacology, clinical data management, diabetes and glucose lowering therapy, drug development, regulatory affairs, health economics, patient associations and glucose monitoring devices.

Finally, a Patient Advisory Committee (PAC) comprising representatives from JDRF (T1D) and the International Diabetes Federation, IDF (T1D and T2D) will be established in order to ensure that patient-driven research and insights relevant for the project are identified and considered within and across the different work packages (WPs), particularly work package 6. In addition to being an active contributor to the key deliverables of the relevant work packages, the PAC will ensure communication internally and help disseminate external information and communicate about the project to the public. The PAC is expected to meet with WP leads four times a year, either in person or via teleconference. Both industry and academic partners are expected to contribute to PAC activities, and thus funds should be reserved for this purpose.

Indicative duration of the action

The indicative duration of the action is 48 months.

Future Project Expansion

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

The restricted call will be considered in order to further test the findings generated in this project. Further work will be based on the results of the clinical trial database analysis and it is envisioned that learnings from the project can be potentially applied to real world data to assess the validity of the original findings. Also, new clinical studies can be conducted wherein the standardised methodologies, guidelines, patient reported outcome instruments etc. that have been developed in this project can be implemented. It will be critical to ensure continuity from the original project by maintaining the established databases and applying the original findings and knowledge in the expansion period. However, the project expansion should open up to specific new partners, specifically those with access to real world data and specific patient populations of interest, and in particular, groups able to test non-clinical findings in clinical trials.

Indicative budget

The indicative EFPIA in-kind contribution is EUR 10 504 000.

The indicative IMI2 Associated Partners in-kind contribution is EUR 2 956 000.

The financial contribution from IMI2 is a maximum of EUR 13 460 000.

Applicant consortium

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

The applicant consortium is expected to address all the objectives and make key contributions to the defined deliverables in collaboration with the industry consortium which will join the selected applicant consortium in preparation of the full proposal for stage 2. This may require mobilising, as appropriate, groups with experience in medical diabetes research and clinical trials, including experience with research in hypoglycaemia detection. Access to clinical data from patients demonstrating hypoglycaemia unawareness will be highly valued. The consortia should also be able to demonstrate experience of the analysis and filtering

of glucose data, modelling of diabetes physiology including hypoglycaemia, and prediction of drug-glucose dynamics in humans. Academic groups that are able to conduct non-clinical research in the areas of molecular, cellular and physiological mechanisms of hypoglycaemia, recurrent hypoglycaemia and hyperglycaemic unawareness as well as addressing consequences of hypoglycaemia are also sought.

The clinical academic diabetes experts should provide:

- independent intellectual input into the clinical questions and queries being formulated by the oversight committee;
- execution of database queries and analysis of clinical data using data mining techniques for classification and clustering of events to characterise and predict clinically relevant hypoglycaemia and to determine correlations to causes and consequences;
- clinical academic input into the interpretation and subsequent presentation of data at international scientific meetings and in peer-reviewed publications.

An academic approach to translating and conveying data for regulatory purposes

A central part of the project will involve pooling of very large sets of clinical trial data and real-time glucose monitoring data in large databases. The structure of the data is expected to be provided in standardised, well accepted formats (such as SAS) that will need harmonisation. This may entail a significant workload. Accordingly, the applicants should have state-of-the-art experience and expertise in the establishment of databases, data harmonisation, database management and data security. In addition, proven experience in working with and analysing data from several combined trials is needed. Furthermore, it is essential that the academic consortium is capable of analysing and linking the results across the project in support of the overall hypotheses and the regulatory framework and expertise provided by the industry.

This may also require mobilising, as appropriate, access to clinical cohorts, datasets, old data generated from patients with hypoglycaemia unawareness and other special patient populations of interest such as pregnant women and paediatric groups.

The applicant consortium should have the expertise to drive the analysis of the research by patient organisations and examine the effectiveness of existing PROs as well as participate in the development of new hypoglycaemia relevant PRO instruments.

In addition to academic groups, relevant small and medium-sized enterprises (SMEs) are encouraged to participate in the applicant consortium.

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

Suggested architecture of the full proposal

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

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

Work package 1: Project management

The goal of this Work package (WP) is the overall project coordination, integration and dissemination including:

- financial management and monitoring of deliverables and milestones;
- legal and contractual management;
- ethics management;
- communication to the scientific community and the public;

Work package 2: Non-clinical studies addressing the molecular/cellular and pathophysiological mechanisms and consequences of hypoglycaemia

In order to address the mechanisms underlying hypoglycaemia, this work package is expected to address, among others, the following over-arching topics:

- counter-regulatory mechanisms that may be 'enhanced' to prevent hypoglycaemia, including the role of the brain, liver, pancreas, kidney, carotid bodies, circadian rhythms and epigenetics;
- causes of hypoglycaemia unawareness which may be reversed, including the role of the brain, autonomic nervous system, metabolic tissues, pancreas, genetic pre-disposition. Suitable animal models should be also explored.
- consequences of hypoglycaemia to be documented in animal models to support possible clinical outcomes such as cardiovascular disease (CVD), metabolic dysfunction such as dyslipidaemia, cognitive function, and sleep disorders.

Work package 3: Establish pooled clinical data for hypoglycaemia & various correlates

The goals of this work package are:

- converting anonymised data to a standard format;
- harmonisation of the anonymised and converted data into a common structure to be able to be pooled;
- database construction of pooled data and establishment of suitable database analysis tools;
- database management and administration of users, permissions and security;
- ensure legal issues including data sharing agreements;
- secure a plan for sustainability, ensuring continuation beyond the duration of the project.

Work package 4: Definition of hypoglycaemia and clinical analysis of hypoglycaemic events

- Address the lack of agreement on the definitions of hypoglycaemia and fill existing knowledge gaps in hypoglycaemia, by probing the datasets in order to:
    - inform a discussion surrounding the development of a consensus on the clinical categories of hypoglycaemia;
    - determine further predictors and consequences of hypoglycaemia and hypoglycaemia unawareness, such as, but not restricted to: age, duration of diabetes, type 1 or 2 diabetes, concomitant medications/disorders, treatment regimen, level of glycaemic control, timing and degree of hypoglycaemia, changes in body weight and mass, CVD risk, cognitive function and comorbidities including micro- and macro-vascular diabetes complications.

- Establish a multi-stakeholder, sub-group of clinical academics, patients and industry representatives whose objective will be to develop a recommended standardised approach for the collection of clinical and laboratory data.

Work package 5: Evaluate glucose measurement techniques & define standard guidelines

The goals of this work package are to:

- define the gaps that have not been addressed in the monitoring/detection of hypoglycaemia;
- map hypoglycaemia detection techniques and opportunities;
- perform a clinical study to evaluate sensitivity and specificity of hypoglycaemia detection methods, as well as patients' hypoglycaemia unawareness;
- define standard measurement guidelines for hypoglycaemia detection;
- evaluate optimised hypo-alarm detection methods based on big data analytics;
- evaluate the use and validation of *in-silico* modelling as a research tool and as an outcome measure for hypoglycemia.

Work package 6: Assessing the experienced-based impact and burden related to hypos: A meta-analysis of existing patient community-driven research

The goals of this work package are to carry out:

- a 360° assessment to identify and map relevant research conducted or commissioned by patient organisations with global and regional reach;
- a meta-analysis of the identified research;
- a gap assessment;
- if warranted based on consolidated conclusions from the project: design and execute a tailored-for-purpose patient population survey to bridge any identified 'high potential' knowledge gaps, including patient preferences and perspectives;
- dialogue with regulators and health authorities for improved acceptability of patients aspects in regulatory assessment and part of product information.

Work package 7: Determine economic consequences of hypos/value of hypo prevention and patient impact

The goals of this work package are to:

- analyse current patient reported outcome (PRO) instruments for assessing the burden of hypoglycaemia;
- reassess current patient questionnaires (Clarke, Gold) and the correlation with CGM data;
- develop new or refine existing PRO instruments to better understand the economic impact of hypoglycaemia.

Work package 8: Establish a process for engagement with regulatory authorities

The goals of this work package are to:

- take an academic approach to translating and conveying data for regulatory purposes;
- provide consensus amongst academic partners, regulatory authorities and industry on the definitions of clinically-meaningful hypoglycaemia based on clinical determinants and patient perspective;

- enable discussions with regulatory authorities about the types of data (including PROs) and clinical trials needed to support potential hypoglycaemic benefits in label;
- explore the increased understanding of hypoglycaemia in relation to benefit-risk assessments.

Glossary

CDISC	Clinical Data Interchange Standards Consortium
CGM	Continuous Glucose Monitoring
CVD	cardiovascular disease
EFPIA	European Federation of Pharmaceutical Industries and Associations
HEOR	Health Economic Outcomes Research
IDF	International Diabetes Federation
IHSG	International Hypoglycaemia Study Group
IMI	Innovative Medicines Innitiative
JDRF	Juvenile Diabetes Research Foundation
PAC	Patient Advisory Committee
PRO	Patient Reported Outcome
SAS	Statistical Analysis System
T1DM	type 1 diabetes mellitus
T2DM	type 2 diabetes mellitus
WP	Work package

References

[1] Shaefer C., Hinnen D., Sadler C.; Hypoglycemia and diabetes: increased need for awareness; Curr Med Res Opin. 2016 Apr 20:1-8.

[2] Brod M., Wolden M., Christensen T., Bushnell D.M.; A nine country study of the burden of non-severe nocturnal hypoglycaemic events on diabetes management and daily function. Diabetes Obes Metab. 2013 Jun; 15(6): 546-57. Doi: 10.1111/dom.12070.

Topic 2: How Big Data could support better diagnosis and treatment outcomes for Prostate Cancer

Part of the IMI2 Big Data for Better Outcomes Programme (BD4BO)

Introduction to the IMI2 Big Data for Better Outcomes Programme (BD4BO)

The IMI2 Big Data for Better Outcomes (BD4BO) programme **aims to catalyse and support the evolution towards value-based and more outcomes-focused sustainable and therefore better quality healthcare systems in Europe, exploiting the opportunities offered by the wealth of emerging data from many evolving data sources** by generating methodologies and data that will inform policy debates. The programme's objectives are to maximise the potential of large amounts of data from variable, quickly-developing digital and non-digital sources which will be referred to as 'big data' in the context of this initiative.

This programme will provide a platform and resources for defining and developing enablers of the outcomes transparency evolution, together with patients, payers, physicians, regulators, academic researchers, healthcare decision makers, etc. The key enablers are:

- definition of outcome metrics;
- protocols, processes and tools to access high quality data;
- methodologies and analytics to drive improvements.digital and other solutions that increase patient engagement.

Programme structure

The programme is composed of several topics which will address key enablers for the transition of healthcare systems towards more outcomes transparency, including an over-arching coordination structure (through a Coordination and Support Action (CSA) previously launched), several disease/therapeutic area (TA) topics focusing on a specific disease, population, therapeutic area or technology, and a potential distributed data network topic. Only one proposal under each topic will be selected.

In this Call, only the BD4BO prostate cancer topic is launched. The BD4BO action topics on Alzheimer's disease, haematologic malignancies, and cardiovascular disease, as well as the Coordination and Support Action, were launched under previous IMI2 Calls. Other topics may be launched in future Calls.

The Big Data for Better Outcomes programme at a glance

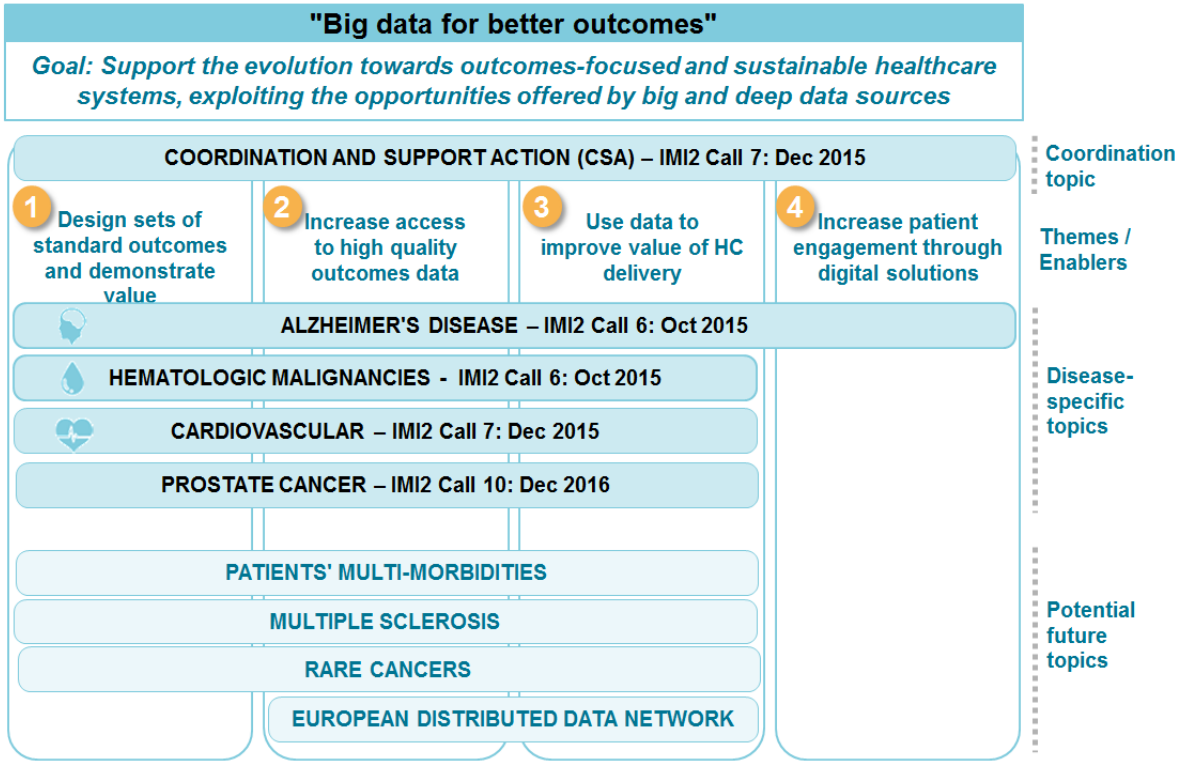

Figure 1: Programme structure, themes / enablers and CSA

The success of the overall programme will rely on a coordinated approach across projects to ensure strategic alignment and consistency and to define new business and health funding models (including incentive models) that will allow for healthcare systems transformation. In addition, integration of areas of expertise which are common to most projects (such as legal, ethics, data privacy, sustainability or collaboration with payers/HTAs) will yield higher quality results, consistency and increased efficiency by avoiding duplication of work.

The Coordination and Support Action (CSA) will therefore offer services to, and complement activities of, disease/therapeutic area related projects through:

- a central repository of knowledge/information;
- a common ethical and personal data protection review and advice;
- common standards for the collection, analysis and management of personal level data/knowledge;
- assistance on the implementation of common data models and in the aggregation of data from different sources.

The distribution of tasks with responsibilities across different project teams within the programme (subject to adjustments as projects evolve) is summarised in figure 2.

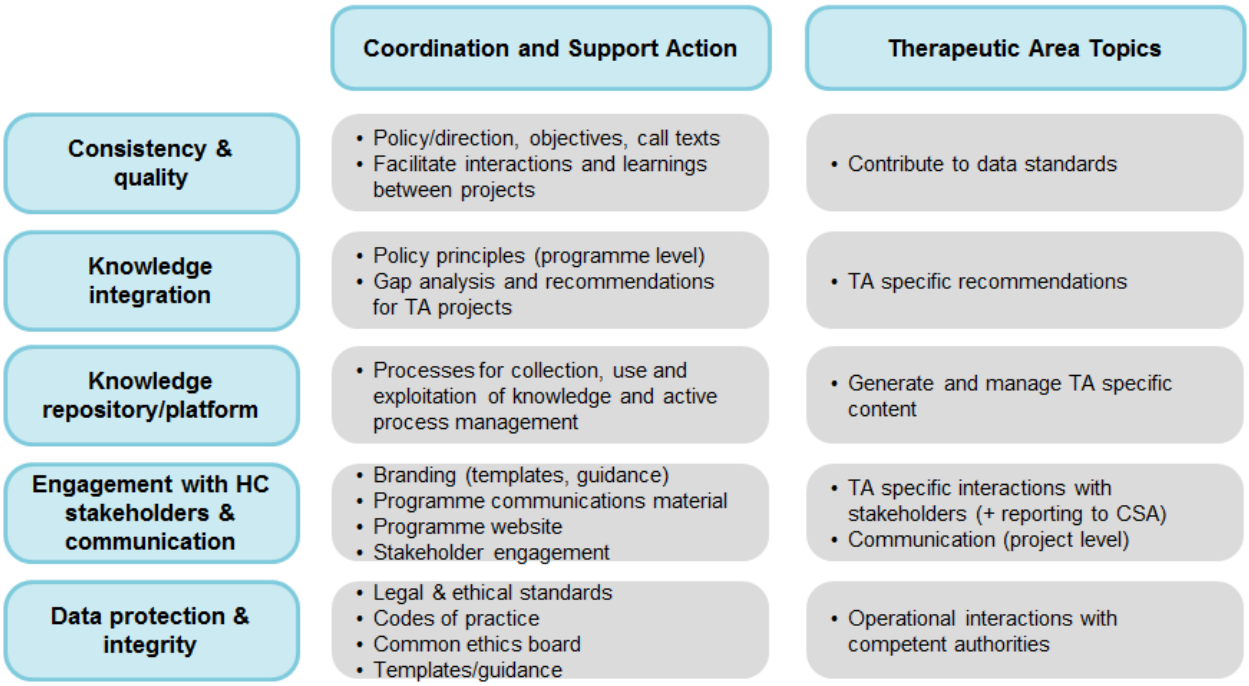

Figure 2: Allocation of tasks between Coordination & Support Action and therapeutic area focused projects

Collaboration agreements

To ensure the interactions between the projects under the BD4BO programme, the therapeutic area/disease (TA) projects are expected to actively contribute key results to the Coordination and Support Action (CSA), which will provide direct support to the TA projects, and collaborate with a potential European Distributed Data Network (DDN) project. Therefore all grants awarded for the TA projects will be complementary to the Grant Agreements under the CSA and potential DDN topic. The respective options of Article 2, Article 31.6 and Article 41.4 of the IMI2 Model Grant Agreement will be applied.

The TA consortia will conclude collaboration agreements with the CSA consortium and the forthcoming European DDN consortium. The collaboration agreements are expected to include details of the services provided by the CSA to the TA-specific projects, such as the provision of data collection standards and processes, an interim repository for knowledge storage and management, data privacy standards, compliance and ethics regulations, including templates and other operational support.

The TA-specific projects are expected to contribute to the CSA knowledge repository and integration of learnings, and also participate in joint advisory boards and coordination boards to align on strategic programme elements such as definition of health outcome measurements, data and knowledge collection and aggregation standards, common usage of IT infrastructures, communication of results, and operational issues as indicated in figure 2. All TA projects should ring-fence resources for these activities (approximately 5% on average, for example, for experts to participate in central programme boards, participate in the adoption, adaptation and/or definition of common data standards, and/or cash that will cover the cost of operationalising e.g. central ethical and data protection boards and maintenance of the common IT infrastructure).

Need and opportunity for public-private collaborative research under the BD4BO programme

The Big Data for Better Outcomes programme aims to provide high quality information to support decision makers with evidence on the enablers of value-based healthcare systems focusing on health outcomes. This healthcare system transformation would encompass payments, consider value, and support aligned incentives between primary and secondary care moving towards the common goal of better healthcare

delivery and high quality data availability. Therefore the engagement of industry with patient organisations, regulators, payers, providers and other public stakeholders throughout the BD4BO programme is essential to ensure findings from those projects deliver real impact in transforming healthcare systems.

Expected impact of the BD4BO programme

The expected impact of the programme would be a comprehensive plan for the development and implementation of key enablers to support the evolution towards value-based and more outcomes-focused and sustainable healthcare systems in Europe, exploiting the opportunities offered by big and deep data sources. The programme will also enable evolution and management of R&D portfolios and prioritisation of research methodologies in line with an outcomes focus.

Applicants should also refer to the 'expected impact' sections under each of the BD4BO topics.

How Big Data could support better diagnosis and treatment outcomes for Prostate Cancer

Topic details

Topic code	IMI2-2016-10-02
Action type	Research and Innovation Action (RIA)
Submission & evaluation process	2 Stages

Specific challenges to be addressed

Prostate cancer (PCa) is the second most common cancer in men[7]. In 2012, 399 964[8] men were newly diagnosed, and 92 000 died from prostate cancer [1]. PCa constitutes about 11% of all male cancers in Europe [2], and accounts for 9% of all cancer deaths among men within the European Union [3].

The only well-established risk factors for PCa are older age, ethnicity, and a family history of the disease [4]. There is less literature on factors associated with disease progression (some evidence on obesity and body fatness associated with late-stage diagnosis due to rapid development of tumour and/or technical difficulties for diagnosis) [5]. PCa mortality rates and trends are less affected by diagnostic practices but reflect differences in PCa treatment worldwide as well as underlying risk [4].

Most recent clinical research focuses on the late stages. In recent years, a plethora of new treatments have been shown to improve overall survival in metastatic castrate resistant prostate cancer (mCRPC). Prognostic factors linked with overall survival have been proposed, but there is no clear treatment path according to these factors. Particularly missing in this tumour type is the genetic information to inform treatment.

Some of the identified barriers to better outcomes are:

- Despite a large increase in new technologies, there is scarce data on whether real world outcomes of patients are changing, and on the differences between subpopulations (e.g. precision medicine).
- Lack of data about the impact of new imaging and diagnostic technologies and availability of multiple treatment options on clinical practice patterns[9].
- Lack of data to support clinical practice in the early stages of prostate cancer (i.e., before castrate resistance (poor data availability and/or transparency of clinical practice evidence)).
- Need for data and incentives within health systems which lead to improved outcomes (aim of BD4BO).

While changes in screening and detection programmes are enhancing our understanding of the incidence and prevalence of the disease (eg younger age at detection), these have not yet resulted in changing outcomes.

[7] WHO ARC data from: http://eco.iarc.fr/eucan/CancerOne.aspx?Cancer=29&Gender=1
[8] IARC/WHO: http://eco.iarc.fr/eucan/CancerOne.aspx?Cancer=29&Gender=1#block-table-f
[9] Office of Health Economics (OHE): https://www.ohe.org/news/new-report-published-improving-efficiency-and-resource-allocation-future-cancer-care

Need and opportunity for public-private collaborative research

The real-world data and evidence gap in prostate cancer cannot come from the pharmaceutical industry alone or from individual companies. With much of the prostate cancer research consortia focused on clinical trial inputs, tools, and operational efficiencies, relatively few efforts are focused on how PCa-related outcomes could be incorporated into the broader health and social care system. This type of effort additionally relies on IT, academic groups and subject matter experts. Patient, caregiver, and advocacy organisations will be crucial in understanding outcomes of relevance, and approaches. IMI allows pharmaceutical companies to collaborate with payer, regulatory, and other important stakeholder partners to understand the best path forward to improve health/social care and data systems for the treatment of PCa. Engagement between these partners in a pre-competitive space will have the added and crucial benefit of facilitating access to the relevant datasets that may improve our understanding of the disease course, including the International Consortium for Health Outcomes Measurement[10].

Scope

Address the scarcity of epidemiological, clinical, genomic/biomarker, economic, patient reported outcome, and humanistic data on the treatment path of prostate cancer including all stages of the disease. Leverage real-life data on patients from different European countries, using existing registries, trial data, and data from prostate cancer specialised centres as well as data from patient groups. Foster the collection and use of data to improve outcomes and health system efficiency, an aim of the entire BD4BO programme.

Primary objective:

The primary objective is to increase the body of evidence to improve prostate cancer outcomes by identifying and broadening the relevant outcome measures: epidemiological, clinical, economic, and patient reported outcomes.This includes screening/diagnosis and predictive factors that may have an impact on these measures (including complications/adverse effects) across all stages of disease through collection and analysis of available data.

Additional objectives:

Additional objectives are to:

- identify data sources and a data strategy to characterise PCa patients' pathways across multiple geographies;
- develop a pan-European, multi-country data sharing platform that empowers patients, clinicians and policy stakeholders to improve decision making for implementing new therapies;
- identify and share best practices in collecting real world clinical outcomes data, data curation and analysis to optimise diagnosis and therapeutic management of PCa patients;
- generate insights to support efforts to improve PCa patient access and the value of healthcare delivered;
- develop a network of recognised European prostate cancer stakeholders in positions to influence clinical practice, access, and policy decisions;
- develop a communication strategy to encourage participation of key stakeholders and share the results;
- work platforms and deliverables would be staggered in order to allow previously conducted projects to inform later decisions on forthcoming projects.

[10] ICHOM: http://www.ichom.org/medical-conditions/localized-prostate-cancer/

Expected key deliverables

Final deliverables will be determined by the full consortium in collaboration.

The main deliverables expected from this project are as follows.

1) Mapping of available data sources and key clinical, economic and quality of life/patient reported outcomes (QoL/PRO) measures.
2) Develop a data integration strategy:
    - leveraging expertise from previous IMI projects including EMIF, EHR4CR, and all current BD4BO projects including the CSA;
    - evaluation of the suitability of combining different data sources (incl. white paper / publication) and assessment of benefits of combining data sources;
    - evaluation of technical and legal feasibility of combining data sources.
3) Integration of multiple data sources into a multi-country data sharing platform and new electronic endpoint proposal (e.g. mapping of digital solutions / options across outcomes clinical and pharmaco-economic), potentially including:
    - demonstration (pilot) project based on results from evaluation of suitability;
    - peer-reviewed publications of validated innovative end-points, outcomes and technologies;
    - portable data capture protocols and modules for implementation in healthcare system electronic medical records;
    - data governance framework to address quality and privacy concerns of data integration (building on other existing IMI projects);
    - definition of data integration model to be potentially implemented in phase 2 of the project.
4) Assessment of prostate cancer epidemiology, disease course and progression and burden (e.g. prevalence, incidence, mortality, clinical, economic, and humanistic factors):
    - definition of relevant endpoints linked to PCa;
    - literature review of relevant topics in PCa with a focus on cognition, functional, behavioural, and diagnostic outcome measures across the different PCa stages;
    - alignment of key stakeholders (including patients) on relevance of those outcomes for different uses (e.g. reimbursement, assessments, etc.);
    - assessment of those outcomes in current data sources and expansion for additional data items where currently not available;
    - build on new knowledge developed during the project to guide and propose best practice outcomes.
5) Identification of patients' pathways and the sequences and modalities of treatments used by physicians, and associated health outcomes.
6) Make recommendations on personalised screening strategies and treatment plans based on knowledge learned from this project.
7) Recommendations on validated instruments of patient reported outcomes to be collected in future studies and registries as determined in number 4 above.
8) Identify what represents value for prostate cancer patients.
9) Collection of genomic data available in databases to better inform treatment choices and novel predictive and prognostic markers.
10) Collection of economic endpoints such as costs and resource utilisation and understand how the economic burden of the disease increases as PCa progresses.

11) Developing analytic methods and tools to describe the natural history of the disase, and inform epidemiological and health econonic models:
    - publications on model archetypes that characterise the patient journey across the spectrum of disease, using existing data sources to compare methodologies such as time to event, Markov modelling, linear regression and mixed-effect model repeated measure (MMRM);
    - peer-reviewed recommendation of disease modelling approaches, based on different methodologies.
12) To gain advice/alignment on all recommendations, frequent engagement and in-person symposia with representatives of health technology assessment (HTA) & regulatory agencies, as well as payers responsible for making access and reimbursement decisions will be considered.

Expected impact

The project will contribute to:

- identifying relevant outcomes (epidemiological, clinical, economic, patients reported outcomes) to assess the impact of prostate cancer on patients' lives (and their caretakers') and to optimise patients' diagnosis and management;
- identifying and building real-world data sets that are suitable for answering questions about the natural history, cost-effectiveness, and clinical utility of new and innovative diagnostic and treatment interventions across the disease;
- providing a road map of aligned outcomes and methods towards building data systems that will enable broader health and social care systems to efficiently enable initiation, maintenance, and evaluation of the right treatment for the right patient at the right time;
- engagement with HTA/national healthcare bodies, regulators, and patient advocacy groups, that will ensure future prospective data collection efforts;
- the anticipated generation of new diagnostics and treatments that will likely span the range of the disease relevant to access and reimbursement questions will be readily available.

The work of the consortium is critical to ensuring that the work proposed is realistic in scope, relevant to stakeholder needs, and complementary to ongoing IMI2 efforts in the clinical/diagnostic space.

Potential synergies with existing consortia

The consortium members will ensure integration of the work proposed with relevant initiatives within and outside of the EU to maximise resources and impact:

- **Big Data for Better Outcomes (BD4BO) Coordination and Support Action**: Serve as pilot project for big data initiative within IMI2;
- other **BD4BO projects** including Alzheimer's disease, haematological malignancies, and cardiovascular disease;
- **EHR4CR** initiative: developed a platform and open source tools for unlocking information contained in electronic health records (EHRs) for clinical research (http://www.imi.europa.eu/content/ehr4cr);
- **IMI-EMIF**: build upon databases (i.e. tranSMART), informatics, phenotyping and biomarker tools developed as part of IMI-EMIF and incorporate into the project;
- **RADAR** (Remote Assessment of Disease): incorporate technology platform and regulatory expertise on remote assessment;
- **ADAPT SMART – MAPPs** (Medicines Adaptive Pathways to Patients): coordination to leverage MAPPs enablers within IMI;
- **Get Real**: Consult with Get Real workstreams for input into analytical methods and data sources;

- **CAMD** (Coalition Against Major Diseases): Composite endpoint work may help inform domains of interest when considering measurement tools/outcomes;
- Observational Health Data Sciences and Informatics (OHDSI) / Observational Medical Outcomes Partnership (OMOP) and the common data model (CDM);
- Previous prostate cancer projects and other health registries and information systems such as :
    - **ERSPC** (http://www.erspc.org/)
    - **PROTECT** (http://www.nejm.org/doi/full/10.1056/NEJMoa1606220#t=article)
    - **ECIS** (http://www.encr.eu/index.php/activities/encr-jrc-project)
    - **IACR** and **EUROCIM** (http://eco.iarc.fr/)
    - **NORDCAN** (http://www-dep.iarc.fr/NORDCAN/English/frame.asp)
    - **EUROCARE** (http://www.eurocare.it/)
    - **RARECARE** (http://www.rarecare.eu/)

Industry consortium

The industry consortium is composed of the following EFPIA companies:

- Bayer (lead)
- Sanofi (co-lead)
- Janssen
- Astellas
- Varian
- Abbvie
- Orion
- SAS

The industry consortium will:

- facilitate collaborations and partnerships across geographies and specialties;
- provide relevant data sets (existing & future) on treatments and outcomes in PCa;
- bring expertise in the performance of clinical trials in prostate cancer with or without involvement of advanced therapies;
- bring expertise in the capture and analysis of outcomes research including real world data, biomolecular samples, etc.;
- bring expertise in statistics, in data mining, and in merging large data sets from various sources;
- bring expertise in project and result communications, and legal and regulatory requirements relevant to the project.

Indicative duration of the action

The indicative duration of the action is 60 months.

Recommendations on timing are welcome as part of submitted proposals.

Future project expansion

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

In the context of this topic, mapping of existing and required data sources and advances in other projects within the Big Data for Better Outcomes programme would help define the scope of the data platform and potential synergies with other projects for future development of the generated data and partnership structure.

Indicative budget

The indicative EFPIA in-kind contribution is EUR 6 000 000.

The financial contribution from IMI2 is a maximum of EUR 6 000 000.

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

Applicant consortium

Successful implementation will depend upon a consortium with the ability to engage with and manage multiple disciplines to deliver on the stated objectives of the proposal. The consortium will include expertise in regulatory, observational/cohort study execution, economic modelling, informatics, statistics, data management and integration, healthcare privacy/ethics, health outcomes, age-related research, clinical research, and electronic medical records. The consortium will include caregiver and patient advocacy organisations, and will engage health technology assessment bodies, national payer organisations, providers, and regulatory agencies in relevant work packages and consultations. The applicant consortium will have the resources to help manage project-related website and information-sharing infrastructures. Furthermore, access to real world datasets that have not yet been used in this context would be an asset. The ability to engage partners across multiple geographies is also expected.

To encompass all key dimensions and to include the insight of the relevant stakeholders, the applicant consortium should involve the following:

- HTA/payers
- academic networks
- cancer registries and information systems
- patient associations (several organisations would allow for a well-rounded independent group allowing for robust input)
- cancer reference centres
- genomic sequencing groups
- medical societies for information on guidelines and to disseminate results
- big data companies
- innovative SMEs.

Suggested architecture of the full proposal

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

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

The consortium is expected to have a strategy on the translation of the relevant project outputs into regulatory practices, clinical and healthcare practice. A plan for interactions with regulatory agencies/health technology assessment bodies with relevant milestones and resources allocated should be proposed to ensure that the proposed novel methodologies and potential prospective data collection meet qualification requirements (where applicable) and are reflective of regulatory/HTA requirements for drug evaluation.

In the spirit of the partnership, and to reflect that IMI2 Call topics are built upon 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 project leader, yet project coordination will come from the applicant consortium.

Work package 1: Project management and administration

Description:

- coordinate activities across all work packages to ensure deliverables are achieved according to plan;
- participate in coordination meetings with other projects within the Big Data for Better Outcomes programme;
- abstract the anticipated Applicant Consortium contributions (e.g. models, data meta-analyses, tools, technology, test systems);
- definition and implementation of consortium governance structure together with the WP leads.

Proposed objectives:

- project design and charters with clear accountabilities;
- provide coordination and support to project teams;
- project planning programme detailing bottom-up timeline calculations, resources and critical pathway across WPs;
- project governance structure;
- ensure key cross-functional partners are engaged;
- provide a consistent, project-wide view of progress, issues, and interdependencies;
- project level communication of key information throughout the project (e.g. timelines, updates, directives, etc.);
- detailed budget estimates versus expenses realised;
- meeting planning and participation scheduling;
- logistics coordination, agendas and meeting materials support;

- writing of minutes and reports, communication of conclusions and documentation archiving;
- address ethics issues.

Industry contribution:

Project leadership to support the coordination of the other WPs within the programme and provide expertise to ensure that WP leaders keep track of their respective objectives. Providing support on project design and daily operations including project tracking and reporting, meetings, and internal communication. To develop solutions when faced with stumbling blocks, maintain focus, momentum and motivation throughout the project's duration.

Expected Applicant Consortium contribution:

Project management expertise to run the day-to-day operational aspects as per proposed deliverables and project coordination.

The Applicant Consortium must have the capabilities and infrastructure to execute the project to fulfil the objectives, including, but not limited to, the following specific points:

- clinical expertise within prostate cancer (PCa) and links to recognised clinical guidance groups to define and endorse relevant outcomes for different uses (e.g. reimbursement, assessments, etc.);
- fully networked within the EU to potentially map and link data sources and know how; assess feasibility and build trust for collaborative partnerships;
- ability to provide appropriate governance, data quality, ownership and access rights, while maintaining data confidentiality and anonymity;
- build infrastructures for research opportunities for industry partners (patient level data access); clinicians and public policy (aggregated data through programs such as crossbow interfaces); future research partners (funding/grant mechanisms) to ensure the sustainability of the research platform;
- technical and technological capability in terms of clinical expertise and data analytics, epidemiology and modelling;
- research dissemination and communication.

Work package 2: Disease understanding and outcome definition

Proposed objectives:

- development of definitions for standard outcomes;
- assessment of prostate cancer epidemiology broadly (prevalence, incidence, trends, and risk factors), for the different disease stages, disease course, progression, socioeconomic burden, and the impact of disease screening;
- identification of the patients' journey from screening; including treatment decisions and sequences, and potential patient preferences, social, clinical and health system drivers behind the choices;
- define a core set of outcomes for prostate cancer that includes 'omics', physiological, and clinical endpoints, economic and patient reported outcome measures; these outcomes should be standardised according to the current literature (including guidelines and recommendations) and clinical practice for prostate cancer;
- critically assess the available quality of life and patient reported outcomes tools and their suitability for each stage of the disease; initiate the development and validation of new tools if needed;
- identify prognostic factors that can influence the disease course and/or treatment outcome;
- elaboration of a guidance document (e.g. treatment guidelines, screening guidelines, etc.);
- work with the available databases and other work packages to propose recommendations and outcomes;

- publications.

Activities:

- literature review of relevant existing treatment guidelines, patient reported and diagnostic outcome measures across the different disease stages, including screening in collaboration with key opinion leaders (KOLs), patients, providers, registry experts, and other stakeholders;
- development and validation of new tools for outcomes measurement if needed;
- establish value to patients beyond clinical setting when defining the set of core outcomes (e.g. PRO, QoL);
- collaboration with KOLs, patients, providers, registry experts and other stakeholders during the definition of the set of core outcomes;
- collaboration with payers, regulatory agencies, HTA agencies, and other stakeholders on the relevance of the core standard outcome set for different uses (e.g. reimbursement, value assessment, etc.).

Industry contribution:

- clinical, medical and drug safety expertise;
- expertise in HEOR, epidemiology, and translational science;
- medical writing and medical communication expertise;
- work package co-chairs.

Expected Applicant consortium contribution:

- expertise on determining relevant outcomes in collaboration with multiple stakeholders and conducting literature reviews;
- expertise in developing and validating new patient reported outcome measure if needed including conducting qualitative patient/clinician interviews and psychometric analysis of the new instrument;
- data management and statistical programming expertise if an academic consortium contributes data in the scope of the project;
- expertise in: medical research, academic environment, regulatory agencies, HTAs, payers, clinical research organisations, patient organisations and advocacy, and cooperative international groups.

Work package 3: Data access and sources

The data required for a complete variety of analyses will come from many different sources and no standardisation of data from particular sources is expected. Each source from each site will likely be in a different data model and likely use different terminology for similar concepts. The existing data export capability of source systems will likely be inadequate or incomplete. We anticipate the following tasks and challenges in accessing and importing source data into the data aggregation platform.

- Identify data sources and a data strategy across multiple geographies.
- Identify best practices in linking data sources.
- Enumerate available data sources. These will include (minimally) electronic health records, patient encounters, problem lists, medication lists and histories, cancer therapy data, molecular and other lab results, pathology reports.
- Exhaustively list data desired for analyses.
- Locate desired data in each data source.
- Create multiple strategies for extracting these data from these sources. In the simplest cases the data will be already available for export as discrete data through existing application program interfaces (APIs). In

other cases, we may be able to leverage the EHR4CR tools to extract data needed, or we may need to design (and get permissions to execute) queries against a data source or specify and acquire a health level seven (HL7) feed. In the most difficult cases the needed data will be trapped in free text and require some combination of natural language processing and human mediated extraction.

- Plan, design, execute those strategies as resources allow.
- For each data extraction we will need to programme a corresponding data transformation to turn the data into the message format required by the data aggregation platform.
- For each data transformation and each datum within each transformation, specify and implement a terminology mapping in order to apply a proper standard terminology code to each concept before sending the message.
- Note: depending on the implementation decisions made for the aggregation platform (central vs. federated vs. combination) each collection of site level sources will need further software developed to sample and send the data at the appropriate time intervals and with the correct level of security and privacy. Close interaction with the CSA should be sought to ensure that learnings from other BD4BO projects can be taken into account.

Data sources (detailed specifications):

In order to source this data, data sharing agreements will be sought with:

- small oncology practices and primary care providers;
- large and distributed group practices;
- large regional medical centres;
- academic medical centres;
- National health services;
- central laboratories;
- cancer and other health registries and information systems;
- databases created for different research projects;
- pharmacies;
- social media;
- data companies.

We anticipate the need to export data from or directly capture data in the following kinds of systems:

- electronic health records (EHR);
- Clinical pathology/laboratory;
- anatomic pathology;
- admission/discharge/transfer;
- billing;
- pharmacy;
- nursing;
- registry software;
- patient reported outcome;

- registry data entry forms (preferably web-based) – these would need to be completed by the participants at the sites; ideally such a system would be integrated with the EHRs and related systems at the sites, but early on this will be mostly by hand entry;
- economic data such as resource utilisation, work productivity, quality of life data.

Industry contribution:

- expertise in HEOR, epidemiology, clinical, safety and PROs;
- literature search, review and assessment;
- database information and assessment;
- biostatistics/programming;
- data management;
- potentially provide clinical trial and other data.

Expected Applicant consortium contribution:

- expertise in HEOR, epidemiology, clinical, safety and PROs;
- literature search, review and assessment;
- database information and assessment;
- biostatistics/programming;
- data management;
- provide access to databases;
- medical: clinical expertise in the key diseases areas, and also in literature search, review and assessment;
- data management: data access and data cleaning expertise;
- biostatistics/programming: data analysis and programming expertise;
- Patient associations: data on patient perspectives and advocacy expertise.

Activities:

- **Development of value proposition for data providers:** Given historic challenges in accessing and integrating real world data sources in Europe, the development of value proposition presentation materials will be necessary for conveying benefits to data providers of joining the project and addressing any concerns over data privacy and security. The team will leverage internal discussions and conversations with data providers who are already part of other IMI initiatives to craft suitable value stories for different data provider types to encourage participation in the project.
- **Recruitment of data providers:** The team will initiate conversations with potential data providers (not already consulted in value proposition development phase) to solicit potential interest and confirm any procedural requirements, budgetary needs, and additional resources required to incorporate data. This will be an ongoing effort throughout the initiative, as recruitment of data partners will be gradual.

Work package 4: Data platform

Description:

The intent of the data platform is to provide an elegant, accessible model so that researchers across the EU can readily design and execute any reasonable analysis over the data set. The goal is the creation of large, harmonised data sets that form a repository of PCa data that can be used to generate evidence for overall patients and/or subset of population of interest.

This platform will enable a wide variety of data re-use scenarios. The fundamental requirements are that it should be able to make available for any reasonable analysis, all data about patients across the EU who undergo treatment for prostate cancer. This means facilitating the capture and aggregation of information about patients' characteristics, medical history, detailed cancer diagnosis, treatment history specifics, and near and long term outcomes such as survival, performance status, and adverse events. Specifically, the platform will need to:

- improve public access to the descriptive epidemiology of prostate cancer including time trends, variation between countries/regions, and inter-individual characteristics;
- understand the implication and impact of screening practice (how it can affect the incidence and mortality of prostate cancer;
- understand how patients are treated in different stages of the disease, treatment sequencing, geographical differences in treatment options, and the levels of treatment adherence;
- improve knowledge about established and emerging risk factors, protective factors and prognostic factors including comorbidities, biomarkers, defined outcomes of interest and results from genomic analysis (and proteomic analysis);
- establish systems to allow identification of patients at earlier stages of PCa to better understand and predict disease progression;
- research and regulation for individual patient care and for health system measurement;
- provide an agile and scaleable platform to address evolving clinical and research challenges;
- aggregate data from multiple sources, in a variety of formats and standardize on a common data model and set of ontologies (eg. OMOP v5);
- capture sufficient clinical detail to support complex research and clinical management analyses;
- enable advanced analysis and data sharing while also protecting patient privacy and confidentiality consistent with EU and country regulations;
- minimise the effort required by participants;
- support multiple data query tools and languages including natural language processing, and support batch, ad hoc and in memory analytics;
- support both centralised and federated data relationships;
- allow for the development and testing of innovative analytic methods, analytics and software;
- establish data provenance and audit trails;
- provide appropriate data security and governance.

Activities:

- Data aggregation. The aggregation tier could be a centralised database running on servers which are managed and accessed on the cloud. It could also be a virtual aggregation in which servers at different contributing sites are presented in common views. It could be a combination of these two general approaches.
    - data mapping;
    - data curation;
    - building data exports;
    - data dictionary and terminology.
- Data security, access and governance. The platform will have appropriate security and audit capabilities to ensure monitoring, tracking, and logging what is happening in the environment. Close interaction with the CSA should be sought to ensure that learnings from other BD4BO projects can be taken into account.

Industry contribution:

Knowledge on existing data sources including population-based electronic healthcare databases, cancer registries, prostate cancer specific registries, clinical trial data sets.

Expected Applicant consortium contribution:

- medical/scientific community: data access and ownership, clinical endpoints definition, health care delivery;
- healthcare administration bodies: logistics aspects of diagnostics and therapeutic interventions, availability and distribution of technologies and expertise within healthcare systems, social impact of diseases and treatments;
- informatics: information optimisation and hardware expertise; data management, hosting platform, access portal, and security;
- identification of potentially relevant cohorts will be achieved by the consortium, which will detail the availability of biobanked plasma/serum and other suitable samples with proper patient consents, together with disease outcomes as defined by WP2 and other measurements relevant to the designated analyses;
- cohorts may also be developed and managed by the applicants prospectively;
- cohort access: identify or establish patient cohorts with suitable patient consent, biological samples and clinical information availability;
- medical: clinical management in the key diseases areas;
- care innovation: collaborate with participating EFPIA members to explore alternative approaches to managing patients as defined by data from WP2 and WP3;
- biostatistics/programming: data access and programming expertise;
- government: data ownership controlling access;
- other: data collection techniques, hardware and software development and optimisation.

Work package 5: Data analytics

Description:

Define a pan-European framework to value and evaluate health outcomes achieved with therapies through natural disease history data.

Once the platform is running and significant data sets have been imported, the consortium partners will perform example analyses to demonstrate the capabilities of the platform and show its relevance.

Initial thoughts on the kinds of demonstration analytics we should consider are listed in bullets below:

- data visualisations and explorations showing the geographic and demographic distribution of prostate cancer throughout the European Union;
- machine learning to discover patterns relating to prostate cancer grade, stage and molecular markers, and treatment to 5 year survival and adverse events;
- advanced analytics to develop predictive models of patient outcomes, disease progression and therapy selection;
- analysis demonstrating the epidemiology of prostate cancer including incidence, prevalence, risk factors, natural history of disease, disease progression, and the socioeconomic burden such as QOL;
- analysis demonstrating the economic burden of prostate cancer, including the impact of resource utilisation and work productivity to payers and patients;
- build on existing technologies for conducting advanced analytics including predicting health outcomes and modelling disease progression using traditional and new sources of data;

- routine laboratory values and patient characteristics to build scores or normograms for the prediction of outcomes (including potential biomarker and imaging developments (new technologies);
- pilot patient evaluation and treatment strategies based on these new predictive analytical tools;
- provide recommendations or guidance documents on the appropriateness of different approaches based on feasibility examinations/pilot studies explored during the project.

Activities:

Data laboratory with configurable individual and collaborative workspaces; enable cross-site, spontaneous online collaboration. Find collaborators; agree to terms of collaboration, share data, share methods, share results.

- Query language support, multiple standards, e.g SQL, SPARQL;
- Data reporting, querying, visualization, exploration and analysis web based tools including standard statistical analysis tools like SAS, SPSS and R.

Governance of research requests:

A joint research governance committee (JRGC), comprising representatives from partner organisations will convene at regular intervals to review research project concepts, study protocols, and study findings. Individual project requests will be submitted as project concepts by project teams. Project teams will be composed of individuals from organisations interested in a particular research topic. Functional representation will be sufficient to meet research project needs (for example, primary investigator(s), statisticians, data analysts, subject matter experts). After approval of the concept by the JRGC, the project team will prepare a study protocol for review by the JRGC. Study results will also be presented to the JRGC upon study completion.

Industry contribution:

- informatics;
- hardware expertise;
- information optimisation expertise;
- programming;
- biostatistics;
- imaging expertise;
- data handling/visualisation expertise;
- data analysis;
- clinical and drug safety expertise;
- quality of life, patient reported outcomes and other HEOR expertise;
- study design and epidemiologic data analysis expertise;
- patient advocacy expertise;
- medical writing;
- e-health experts (e.g. remote monitoring, imaging, etc.);
- collaboration with additional health systems to test and refine stratification strategies.

Expected Applicant consortium contribution:

- Medical: clinical expertise and scientific input;

- informatics: choice of data model;
- biostatistics/programming: data analysis and programming expertise;
- HTA/regulatory: drug approval and reimbursement procedure input, comparative analyses of relevance, etc.;
- study design: design and implement studies that can achieve the key goal of this project and thereby enable improved treatment strategies..

Work package 6: HTA – regulator – payer integration

Description:

- understanding the current regulatory and payer landscape in management of prostate cancer;
- understanding the reimbursement challenges of new and evolving therapies used to treat different stages of prostate cancer;
- understanding the evidence needs and data gaps among current treatments from a payer/HTA perspective;
- what are the evidence requirements for achieving optimal price and reimbursement for new emerging therapies and for regulatory/HTA (re)assessments;
- understanding the current regulatory/HTA guidance on PCa study design/outcomes measure and limitations with existing designs/outcome measures;
- regulatory / HTA position on relevant key PCa outcomes measures and (in partnership with WP 2);
- position on the role of diagnostics / biomarkers in patient outcomes, diagnostic accuracy and cost of resource utilisation in future regulatory / HTA agency interactions;
- incorporate the impact of diagnostics/biomarkers on patient outcomes, diagnostic accuracy, cost of resource utilization;
- position on the value of economic models in HTA and reimbursement submissions and the use of real world evidence (RWE) data for HTA assessments.

Proposed deliverables:

- face-to-face meetings with relevant stakeholders to achieve understanding of mutual opportunities, challenges and needs, define common goals and roles and responsibilities to maximise data utilisation;
- provide advice and support to other WPs for HTA, regulators, payers, and patients advocacy groups to use findings from those and write papers / publications relevant for those stakeholders;
- regulatory / HTA expert panel to help understand the current reimbursement landscape and the evidence requirements for reimbursement and access. The expert panel will also inform and evaluate WP plans and output;
- face-to-face meeting with relevant stakeholders;
- qualitative interviews with HTA/payer/regulatory bodies to understand and evaluate the payer landscape in management of prostate cancer;
- white paper/publications.

Industry contribution:

Provide expertise in developing proposals and recommendations to gain HTA & regulatory acceptance, including writing of briefing books as well as presentations of positions and supporting arguments on behalf of the consortium as follows:

- regulatory, reimbursement and HTA expertise; establishing partnerships with relevant stakeholders based on common goals;

- editorial support;
- medical expertise.

Expected Applicant consortium contribution:

- medical/scientific community: establish link between clinical outcomes and value creation (for individuals and society); insights on future developments in diagnostics and therapeutics;.
- regulatory, reimbursement, HTA bodies and patient organisations: healthcare delivery needs, gaps and opportunities; insight into policy evolution and potential changes;
- patients' advocacy and representative groups: provide point of view of patients in terms of relevant outcomes and current challenges within healthcare delivery.

Work package 7: Dissemination and communication

Proposed deliverables:

- overall communication strategy for the project including a communication plan by stakeholder type;
- external publications on outputs of project through white papers, conferences;
- develop and manage communication via web portal;
- repository of key documents;
- quality assessment of documents.

Activities:

- compiling and disseminating communication material to all relevant partners;
- message development and guidance to all work-packages;
- production of high-quality public relations materials;
- communicate with other relevant IMI projects, including other projects within the Big Data for Better Outcomes programme.

Industry contribution:

- medical communication;
- media interactions;
- medical writing;
- contact with healthcare provider (HCP) professional organisations and their communication groups, i.e. European Society for Medical Oncology (ESMO);
- contact with patient organisations.

Expected Applicant consortium contribution:

- pharma communication and/or media expertise;
- HCP professional organisations ;
- clinical expertise in the key diseases areas;
- guideline commissions;
- expertise on payers / healthcare provider financing;
- market research organisation;

- public relations organisation;
- communication contacts with relevant public health services, governmental bodies, health authorities, and patient organisations.

Work package 8: Legal, ethics and governance

Develop an ethical and legal framework to provide guidance on addressing patient confidentiality concerns and data ownership concerns to other WPs.

Proposed deliverables:

- guidance on highest attainable standards of data protection and adherence to data protection, including but not limited to all legal aspects such as patient consent, patient confidentiality, and data ownership according to applicable legislation;
- input into evaluations of different WPs including legal and ethical guidance on issues as needed;
- outcomes of the legal work package from BD4BO (WP4) on informed consent forms (ICF) will be reviewed and incorporated into this project as needed;
- oversight of white papers and publications.

Actions:

- advise WPs on ethical and legal implications of proposed recommendations;
- ensure awareness and responsiveness to European and national legislation that impacts data usage (e.g. privacy laws, data portability laws);
- coordinate with other relevant IMI projects, including projects within the Big Data for Better Outcomes programme.

Industry contribution:

Expertise in:

- legal;
- compliance;
- communication.

Expected Applicant consortium contribution:

Expertise in:

- legal;
- ethical;
- compliance;
- academia;
- patient advocacy;
- technical writing support;
- project co-chair.

Expertise in applicable laws and ethical principles of human subjects' research and data sharing, technical writing support.

Glossary

APIs	application program interfaces
BD4BO	Big Data for Better Outcomes
CAMD	Coalition Against Major Diseases
CSA	Coordination and Support Action (within the Big Data for Better Outcomes programme)
DDN	European Distributed Data Network
EFPIA	European Federation of Pharmaceutical Industries and Associations
EHR	Electronic Health Records
EHR4CR	Electronic Health Records Systems for Clinical Research
EMIF	European Medical Information Framework
ESMO	European Society for Medical Oncology
HEOR	Health Economics Outcomes Research
HC	Healthcare
HCP	Health Care Provider
HL7	Health Level seven
HTA	Health Technology Assessment
ICF	informed consent forms
IMI	Innovative Medicines Initiative
JRGC	joint research governance committee
KOL	key opinion leaders
mCRPC	metastatic castrate resistant prostate cancer
MMRM	mixed-effect model repeated measure
OMOP	Observational Medical Outcomes Partnership
OHDSI	Observational Health Data Sciences and Informatics
PCa	Prostate cancer
PROs	Patient-reported Outcomes
QoL	quality of life
RWE	real world evidence
TA	therapeutic area
WP	Work package

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Topic 3: Improving the care of patients suffering from acute or chronic pain

Topic details

Topic code	IMI2-2016-10-03
Action type	Research and Innovation Action (RIA)
Submission & evaluation process	2 Stages

There is a very high need for improving healthcare for the management of pain, which is the scope of this topic. Acute and persistent pain of different origins represents a common medical, social, and economic burden, and its pharmacotherapy is still an unresolved issue. In order to achieve an optimised management of pain patients and to support the process of decision making in clinical practice, objective assessments of treatment success are needed. Successful new approaches for patient stratification could reduce the still high number of non-responders. Developing new analgesics is challenging because promising preclinical data are often not reproduced in the clinic, and often without knowing the reason. Improved pharmaco-dynamic biomarkers could define whether an intended target is adequately engaged, greatly reducing the risk in the clinical development of a new drug. Finally, for many pain indications, there are no adequate preclinical models available, precluding preclinical investigations and leaving affected patients with little hope of relief. The goal of this topic is to make advances in three pain areas in a complementary manner. These three subtopics, each of which addresses a specific scientific challenge, together offer significant opportunities for cross-fertilisation:

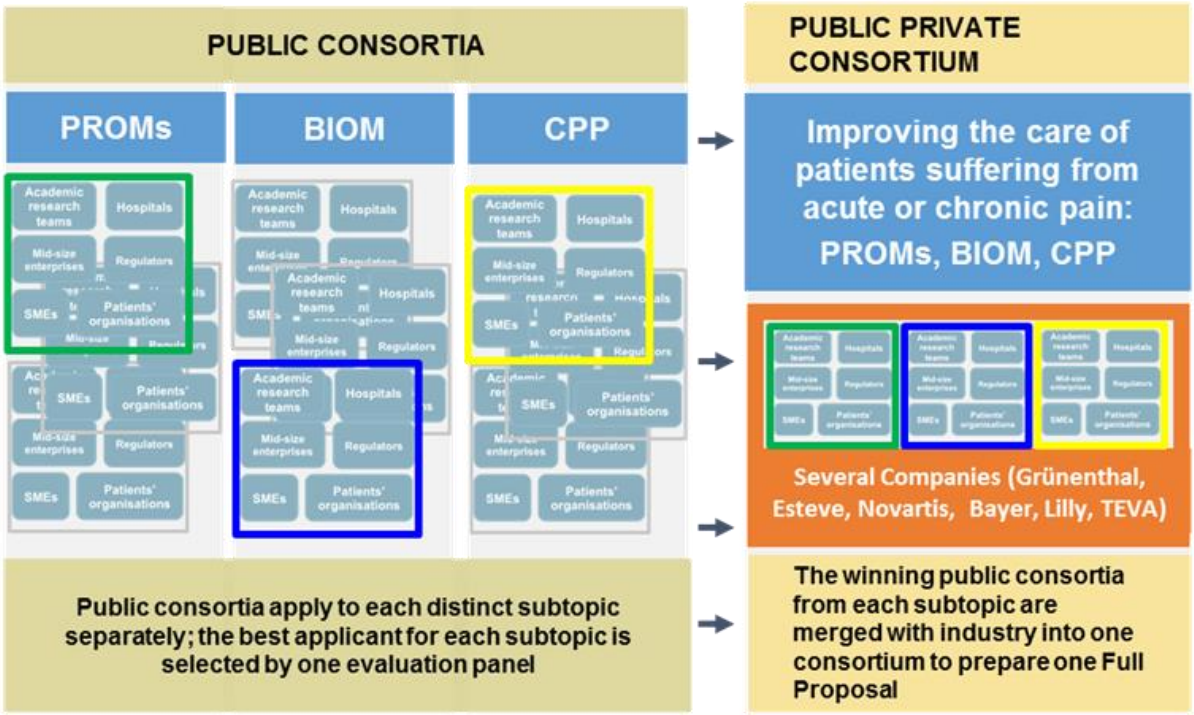
Subtopic 3A: using patient reported outcome measures to improve the management of acute and chronic pain (PROMs);

Subtopic 3B: improving the translatability of pharmacodynamic biomarkers in pain pathways of healthy subjects and preclinical species (BIOM);

Subtopic 3C: improving translation in chronic pelvic pain (CPP).

Stage 1 short proposals from applicants should address only one of these subtopics. Applicants can submit a proposal to any of the subtopics and are not obliged to apply for all.

If applicants wish to submit for more than one subtopic, separate short proposals should be submitted.



Pain topics and the Call process: Allow sub-consortia for the three subtopics at stage 1 and merge the winning sub-consortia at stage 2 in a single consortium with the industry consortium

Whilst contributions to each subtopic will require mobilisation of specialist expertise, it is a key objective of this topic to create a research platform for pain that will significantly contribute to reducing fragmentation and generating the highest impact on the whole area. Thus, to maximise cross-learnings and full data sharing while ensuring economy of scale, it is envisaged that a single full proposal should be submitted at stage 2. This full proposal will include activities covering all three subtopics, as well as overarching joint activities such us overall governance, communication and dissemination, and data and knowledge management.

Thus at Stage 2, the full proposal will be submitted by the consortium created by the merger of the winning applicant consortia of all subtopics (3A+3B+3C) with the industry consortium.

All participants working under this topic (i.e. subtopics 3A, 3B and 3C) will be part of the same grant agreement.

An overall project coordinator (which may be one of the leading applicant members of the winning consortium of one subtopic, or another suitable applicant consortium member) and overall project lead (from the Industry consortium) will be nominated by the consortium at the start of the full proposal preparation.

In the event of no short proposal being over the threshold for one/two subtopic/s, the second stage of the Call will still be initiated by the merger of the remaining two/one consortia and the industry consortium, but the net IMI2 funding and the EFPIA in-kind contributions will be adapted appropriately.

Specific challenges to be addressed

Subtopic 3A: Using patient reported outcome measures to improve the management of acute and chronic pain (PROMs)

Individual pain is a disease state which is driven by many objective but also subjective factors and thus can only be described properly by the patient. As the nature and quality of this reporting is very variable, it is now recognised that there is a need to standardise it by the introduction of accepted patient reported outcome

measures (PROMs). However, the systematic documentation and routine evaluation of PROMs in treatments of both acute pain (e.g. pain caused by traumas such as surgery, disease or terminal illness) and chronic pain (pain lasting more than 12 weeks such as neuropathic pain, chronic pelvic pain) is still not standard clinical practice. This is regrettable because the introduction and use of standardised validated PROMs would not only greatly support the ability of health care professionals (HCPs) to follow the experienced success of the treatment in individual patients, but would also help in assuring objectivity and transparency of treatment qualities between different institutes, regions and European countries, and thereby encourage the introduction of improvements where needed. Such improvements are also necessary because pain treatments incur net societal costs far in excess of those caused by treatments of heart disease, diabetes, cancer or Alzheimer´s in both the USA and Europe. In particular, there is a need for identifying factors and therapies which provenly minimise the risk that acute post-surgical pain develops into enormously burdensome chronic post-surgical pain (CPSP).

Despite the initiatives of a few groups in Europe and the USA during the past decade, there is currently no consensus on which PROMs are best able to assess the impact of individual therapies on pain and other related domains (e.g. cognition, physical function or quality of life (QoL)). As a consequence, objective assessments of the therapeutic efficacies of different treatment options based on real-world data generated from PROMs are still not possible. Much relevant data is stored in the health registries of various European states, but as this has not been collected in a standardized manner, its analysis is hindered by many practical hurdles.

The challenge is therefore to identify PROMs which are both validly indicative of treatment success, and which are acceptable to HCPs in daily practice. Their validation will require retrospective analyses of PROMs used in clinical trials conducted during the course of drug development, and prospective analysis of PROMs selected for use in trials which have not yet been completed. In order to make the collected information available to HCPs, it should be stored in an appropriate data bank, and analysed by accepted statistical techniques. The vision is that the success rate of treatments chosen by HCPs will be increased, thereby significantly reducing the suffering of patients and the burden on health services.

Subtopic 3B: Improving the translatability of pharmacodynamic biomarkers in pain pathways of healthy subjects and preclinical species (BIOM)

Establishing the regular use of PROMs will improve measures of the individual subjective experience of pain. There is also a great need for improved measures of the objective effects of pain. Novel drugs which are efficacious analgesics in preclinical models often prove to have low or no clinical efficacy. In many Phase 2 clinical studies, it is not even known whether the anticipated mechanism of action was modulated by the drug under investigation. Enabling robust translatable measures, which prove unequivocally a drug has bound to and engaged the target of interest at high enough levels to have a biologically meaningful effect, would allow Phase 2 efficacy studies to be initiated with the confirmation that the hypothesis can be tested. The availability of these validated pharmacodynamic biomarkers would greatly improve the success of drug development by allowing early selection of drugs with promising characteristics, reducing the attrition rate of new therapies in the clinic.

There are many drug targets within many tissue compartments which are relevant to pain. This diversity in target and target compartments, in combination with difficulties in defining target exposure to modulating drugs, has significantly hampered the development of robust pharmacokinetic/pharmacodynamic (PK/PD) models for novel analgesics. Neuronal electrical activity is altered by pain, and this alteration should be reversed by analgesics. Electrophysiological and imaging techniques are available to assess nociceptor activation, peripheral nerve excitability, and ultimately the registration of pain centrally, but they are not well standardized and seldom used in early clinical studies or preclinical studies. These techniques either measure neuronal activity directly, or use proxies generated at various sites within the pain pathway. For example, neurography, threshold tracking, and assessment of spinal reflexes allow assessments of peripheral nerve function; electroencephalogram (EEG) or functional magnetic resonance imaging (fMRI) allow assessment of central functions; and event related potentials (ERPs) /oscillations allow combined readouts. Importantly, these objective pharmacodynamic biomarkers all have the potential for back-translation from the clinic to preclinical species, providing a vital bridge in the clinical and preclinical development of analgesics.

The specific challenge of the applicant consortium is to pharmacologically validate threshold tracking, pain ERPs, EEG and fMRI biomarker techniques using at least three different standard of care dugs that target different compartments in the pain pathway. In addition, the applicant consortium is encouraged to develop novel methodologies and/or analysis techniques that may be more sensitive, reliable and informative in defining PK/PD models within these different compartments.

Subtopic 3C: Improving translation in chronic pelvic pain (CPP)

Chronic pelvic pain (CPP) is an example of a highly prevalent pain indication – or rather, complex of indications – which is recognised as a neglected field in pain research. Causes and mechanisms of CPP are still poorly understood. CPP is non-menstrual pelvic pain in the lowest abdominal quadrant which lasts longer than 6 months and has an intensity which causes functional disability requiring clinical or surgical treatment. Current therapies offer only poor relief, with little prospect of improvement without new and game-changing information.

This subtopic focusses on two forms of CPP with particularly high unmet medical needs. The first, endometriosis, is the primary cause of CPP in women of reproductive age; it affects over 25% of all gynecologic patients, and is the cause of 5–10% of all laparoscopies and 20% of all hysterectomies. The second is bladder pain syndrome (BPS), formerly described as interstitial cystitis. Although it has a low prevalence (0.06%), BPS patients have quality-of-life scores lower than those treated for end-stage renal disease, and many of them suffer from depression, anxiety, sexual dysfunction, and loss of social interactions.

Endometriosis is a painful estrogen-dependent inflammatory disease characterised by growth of benign endometrial tissue tumours (lesions) outside the uterine cavity. Its main symptoms are chronic or frequent pelvic pain, dyspareunia, dyschezia, dysuria and sub- or infertility, symptoms which severely impair patients' quality of life and lead to various debilitating comorbidities. These are also relatively unspecific, so that the mean time from initial symptoms to diagnosis is 7-10 years, an unsatisfactory situation related to the lack of any diagnostic biomarker which might permit stratification of patients.The identification of such a biomarker is a major challenge of this subtopic.

Retrograde menstruation may be a cause of endometriosis, and many believe that the associated pain is related to the lesions, although this is controversial. However, various inflammation markers are upregulated in the lesions. Neither this upregulation, nor the mechanism of retrograde menstruation, is reflected in any established animal model. In particular, it is certain that currently used rodent models lack validity as rodents do not menstruate. As regrettably little information is available about the clinically relevant pathways which lead to pelvic inflammation and chronic pelvic pain in endometriosis, it is of key importance to make efforts to understand these better. A second major challenge of this subtopic is to develop valid preclinical models with a higher translational value, allowing far better chances of identifying improved clinical therapies.

BPS can affect both women and men at any age, with women being more at risk. Diagnosis is based on history, urine frequency/volume chart, post-void residual volume, physical examination, urinalysis, culture, cytology, smoking history, symptom questionnaire and pain evaluation. Available animal models of BPS reflect the pain and voiding dysfunction characteristic of the human disease pathology. However, potential biomarkers such as inflammatory mediators, proteoglycans, urinary hexosamines, proliferative factors, nitric oxide, and urothelial pro-inflammatory gene analysis, as well as histological findings, differ between the animal models and the clinical situation. As in the case of endometriosis, there is evidently a need to identify clinically relevant BPS biochemical biomarkers, to develop more valid animal models, and to use these to develop improved drug therapies of BPS.

Need and opportunity for public-private collaborative research

The magnitude, variety and complexity of the challenges implicit in the three subtopics, as well as in the whole area of the topic globally are such that they can only be addressed by a major public-private partnership involving a variety of stakeholders equipped with complementary areas of expertise and working together with a multi-disciplinary integrated approach. Indeed, the combination of proprietary data inputs and R&D expertise from industry, together with contributions from the validated capabilities of small and medium-sized

enterprises (SMEs), and novel approaches from academic groups, promise a platform from which significant improvements can be anticipated: in the care of patients, in the discovery of novel therapies and in the commercial productivity of drug discovery. Last but not least, collaboration with patients and patient organisations in the context of PROMs and CPP research activities is needed.

In the case of the PROMs subtopic 3A, previous initiatives have led to the generation of registries of PROMs relevant to pain assessment. Results from well-controlled clinical studies are on file at the pharmaceutical companies which performed them. These dispersed information sources need to be centralized and integrated in collaboration with other stakeholders, and supplemented with further proprietary data collected during observational trials. This would generate valuable supplementary real-world information, the analysis of which is expected to provide insights which will assist in the diagnosis of individual patients and assessing the success of their clinical treatments, and ultimately, convince HCPs of the value of employing PROMs routinely in daily practice. Development and validation of the novel assay technologies envisaged for the BIOM subtopic 3B is beyond the focus of the pharmaceutical industry. Success will require contributions from academic groups conceptualizing and validating technologies and methodologies, and from specialist SMEs who are able to design and construct the requisite electronic assay devices. Likewise, in the CPP subtopic 3C, specialist SMEs and academic groups are needed to join the industry efforts in order to understand better the causes of, and possible therapies for, endometriosis and BPS by contributing both preclinical and clinical data.

Scope

The ultimate goal of the topic is to improve the quality of life of patients who suffer for various reasons from acute or chronic pain. To achieve this goal the three subtopics have been defined each with its own objectives.

Subtopic 3A PROMs:

The scope of the PROMs subtopic will be to establish operational benchmarks in the management of post-operative and other acute pain conditions, in the prevention of its chronification, and in the management of chronic pain conditions such as neuropathic pain and chronic pelvic pain (CPP). In particular, these will allow identification of risk factors for the transition of acute into chronic neuropathic post-surgical pain, and thus enable novel therapeutic mitigations to be developed. The results are expected to provide motivation for all stakeholders involved in pain management (e.g. HCPs, patients, scientific societies, and policy makers) that the use of PROMs to monitor post-operative and other pain conditions in daily clinical practice, together with their documentation into a readily accessible database, is of benefit for assuring the success of treatments and aimed at preventing pain chronification.

Subtopic 3B BIOM:

The scope of the BIOM subtopic is to generate valid clinical pharmacodynamic biomarkers of peripheral, spinal and central neuronal activities, and to develop detailed PK/PD models for drugs which target these compartments in healthy subjects. The PD read-outs should include threshold tracking, quantitative pharmaco-EEG, laser-evoked event-related potentials (ERPs), pharmaco- or evoked-pain fMRI, and will be compared to pain ratings assessed by visual analogue scales.

The clinical biomarkers will be back-translated into rodents to investigate the effect of comparable pharmacological exposures. As with the clinical studies, preclinical PK/PD models will be generated and the results compared to more classical pain model outcomes to gain understanding of potential PD efficacy relationships.

Subtopic 3C CPP:

Despite the high incidence of chronic pelvic pain, understanding of the pathological conditions leading to it is sparse, and diagnostic tools such as biomarkers are unspecific or do not exist at all. Consequently the scope of the subtopic CPP is to improve this unsatisfactory situation by thorough analysis of patient phenotypes.

This should identify specific clinical and molecular markers which would permit a patient stratification which increases the chances for selecting effective therapies. Back-translation of clinical biomarkers into preclinical models is sought, as well as the subsequent refinement of these models to more adequately reflect clinical disease phenotypes. Such refined models will generate new opportunities to evaluate the clinical potential of novel therapeutics.

Scope of the full proposal merging subtopic 3A+3B+3C:

It is further anticipated that the merger of all three subprojects into an integrated full project, with assured exchange of data gathered during its execution between all members of the full consortium, and leveraging of learnings among the three areas of the subprojects, will generate significant synergies by cross-fertilisation and integration between the very wide range of activities within the consortium – from genetic analyses to data management. For example, the PROMs and CPP teams (3A + 3C) should exchange their learnings on measures to characterise the pain phenotype and predict treatment success, QoL, comorbidities, markers for stratification and diagnosis, and risk factors for chronification to enable innovative insights into CPP. Further possibilities for positive interactions exist between the three subtopics, which will be specified in detail and addressed by the full consortium while preparing the full proposal.

In addition, it will be of high value to develop a common approach for data and knowledge management.

Further areas for joint activities will have to be identified and addressed by the full consortium while preparing the full proposal.

Expected key deliverables

The key deliverables for each subtopic are as follows.

Subtopic 3A PROMs:

- systematic literature research on the use of PROMs in clinical trials with acute and chronic pain patients;
- systematic research on guidelines of post-operative and other acute pain conditions, and of chronic pain conditions, to provide a thorough overview of recommended treatments;
- identification of appropriate PROMs from the literature research, and implementation of their application and documentation in daily practice;
- development of a decision framework based on PROMs to achieve optimised and individualised pain management for patients;
- establishment of a registry to document and analyse PROMs suitable for following the success of treatments of post-operative pain and for identifying risk factors for chronification of acute pain in order to develop therapeutic mitigations;
- establishment of a prospective registry to document and analyse PROMs suitable for following chronification of acute pain;
- correlation of baseline characteristics and PROMs for specific chronic pain conditions (e.g. painful diabetic neuropathy (PDN), post-herpetic neuralgia (PHN), pelvic pain, dysmenorrhea, dyspareunia);
- establishment of standardized cognitive and functional assessments of chronic pain patients to permit correlation of pain with cognition and function;
- implementation of a technology platform to collect, transmit, store, analyse and visualise PROM data and measures prioritized by the expert consortium.

Subtopic 3B BIOM:

- validation of at least five pharmacodynamic biomarkers that must include laser-evoked ERPs, pharmaco-EEG, acute pain fMRI, pharmaco-fMRI and threshold tracking in peripheral nerves in both preclinical

species and healthy subjects. Pharmacological validation of above biomarkers using at least three standard-of-care (SOC) drugs targeting different compartments in the pain pathways, e.g. central, spinal and peripheral pharmacological modes of action;

- develop PK/PD models for these biomarkers in preclinical species and healthy subjects to generate a clear understanding of the translatability of these models in future clinical trials;
- in-depth investigations to define which of the preclinical biomarkers can predict, and which cannot predict, clinical target engagement;
- standardisation of biomarker methodologies;
- test-retest reliability using intra-class correlations for all biomarkers developed and ideally a test retest of the pharmacological effect size and variability;
- analysis of site-to-site reproducibility of biomarker results;
- compare effect sizes between techniques and standard of care (SOC) pharmacology for central, spinal, peripheral mechanisms of drug action;
- development of novel methodologies and advanced analysis techniques to identify specific target engagement in different compartments of pain pathways.

Subtopic 3C CPP:

- identification of human biomarkers of endometriosis and BPS to enable diagnoses and/or patient stratification. Areas of interest include blood transcriptomics (including miRNA), urinary proteomics/metabolomics for BPS, and biopsy analyses for endometriosis. Stratification criteria such as comorbidities, PROMs for treatment response and quality of Life (QoL) and quantitative sensory testing (QST), should be considered;
- back-translation of the novel human biomarkers in existing and emerging models of endometriosis and BPS in preclinical species. Analysis of potential biomarkers derived from matrices such as urine, blood and tissue;
- refinement of available or establishment of novel models of endometriosis and BPS in preclinical species to improve their translatability into the clinic, ideally employing a multi-center approach.

Expected key deliverables of the full proposal merging subtopic 3A+3B+3C:

Furthermore, overall deliverables of the topic are expected, which will be addressed by the full consortium while preparing the full proposal. The overall deliverables of the topic include:

- a joint approach to data and knowledge management to ensure the same standards are used for the three subprojects and that data are fully interoperable to allow data integration and meta-analysis, enabling leveraging of learnings and cross-fertilisation;.
- a joint approach for communication and dissemination of data and results, as well as for engagement with external stakeholders and collaborators, including ethical considerations;
- an articulated and comprehensive strategy for sustainability.

In addition, possible scientific benefits across the subtopics and further joint key deliverables might be identified and addressed by the full consortium.

Expected impact

The overall key impact of the execution of this topic, via its three components as indicated in the subtopics, will be to improve and standardise different patient-centric treatments for the management of acute and

chronic pain, ostensibly the most burdensome disease in terms of patient suffering and healthcare costs. In particular, it is anticipated that new tools and methods will pave the way for the identification of improved treatments which are able to reduce both the disease intensity of acute and chronic pain and the risk of chronification of post-surgical and other acute pain conditions. This would assure a better quality of life for pain patients. Another impact will be that by deepening the disease understanding, stratification and enrichment markers will be identified and refined, helping to enable precision medicine.

In addition, it is expected that better understanding of the successful translation from preclinical into clinical studies and of back-translation from the clinic into improved preclinical models will reduce attrition rates in drug discovery, and enhance the feasibility and speed of the development of novel drugs.

One impact on academic research will be to improve the statistical quality of their analyses of treatment outcomes because access will be made available by the industry consortium to data from multi-centric studies involving many hundreds of patients. A further impact will be that they will gain access to diseased human tissues which will greatly enhance the ability to draw valid translational conclusions from preclinical models and improve the chances of identifying biomarkers predictive of therapeutic success.

Finally, it is expected that cross-fertilisation across the teams of specialist experts will generate new innovative insights for the whole pain area.

SMEs could benefit because identification of predictive PROMs would automatically generate the need for the implementation of a secure European data-bank. SMEs could also benefit from the validation of physical and pharmacodynamic biomarkers as these would require novel standardised and validated assays which would have to be made available.

Potential synergies with existing consortia

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

The project generated from this topic in particular should, among others, build strongly on achievements and knowledge from the IMI project 'Europain – Understanding and controlling pain'[11] that finished in September 2015.

In addition, further synergies should be considered with the IMI project **StemBANCC** (http://stembancc.org/), at the European level with Horizon 2020 (e.g. **DOLORisk** (https://www.ndcn.ox.ac.uk/research/neural-injury-group/research-projects/dolorisk), PHC-01-2014 – 'Understanding health, ageing and disease: determinants, risk factors and pathways') and FP7 initiatives (e.g. **GLORIA** (http://gloria.helsinki.fi/?page_id=168), **ncRNAPai** (www.ncrna-pain.eu), **PAINCAGE** (http://www.paincage.eu/), the **Neuropain project** (http://upf.edu/neuropain/), **PROPANE STUDY** (http://www.propanestudy.eu/en/), **PAIN-OMICS** (http://www.painomics.eu/) and **EPIONE** (http://project-epione.eu/), and at national or regional levels (e.g. the SFB ('Sonderforschungsbereich') 1158 which was established at Heidelberg University (Germany) with the topic: 'From nociception to chronic pain: Structure-function properties of neural pathways and their reorganisation').

It is also conceivable that beneficial synergies for the PROMs subtopic would be generated by collaboration with the IMI2 RADAR (Remote Assessment of Disease and Relapse) programme[12]. This has developed resources and components specifically to improve patient outcomes through remote assessments such as PROMs, with a particular emphasis on mobile applications and sensors, linked to an open-platform database.

[11] www.imi.europa.eu/content/europain
[12] http://www.radar-cns.org/

Industry consortium

The industry consortium is composed of the following EFPIA companies:

- Grünenthal (lead subtopic 3A PROM)
- Eli Lilly (lead subtopic 3B BIOM)
- Bayer (lead subtopic 3C CPP)
- Novartis
- Esteve
- TEVA

All members of the industry consortium anticipate the need to provide project management expertise to optimize the consortium's efforts. Furthermore, their specialists for clinical and preclinical pain research, molecular biology, and behavioural pharmacology will actively participate in all working packages.

Subtopic 3A PROMs:

The industry consortium will contribute a comprehensive literature review of reports on PROMs for acute pain patients, and assessments of their abilities to differentiate treatment success. Prospective observational data collected after surgery and at the follow-up using validated questionnaires (EQ-5D, PGA, EOC) and sleep quality will be made available. PROMs will be also made available from controlled clinical trials with patients undergoing major surgeries of the upper limb in which anaesthesia will be provided by normal anaesthetic administration or by wound infiltration of local anaesthetics.Results from validated PROMs (e.g. NRS, NPSI, QST) will be followed for up to 6 months after surgery, and will allow identification of PROMS which best predict individual post-operative pain outcomes and the need for additional analgesics. Pharmacogenetic samples will also be made available.

Further data will be made available from prospective multi-national, multi-centre, prospective, randomized, double-blind, parallel-group, placebo-controlled clinical studies of chronic neuropathic pain conditions (e.g. PHN, PDN) and other chronic pain conditions (pelvic pain, dysmenorrhea, dyspareunia). Data at baseline for all patients and follow-up data of placebo patients up to 52 weeks using validated PROMs for pain, QoL and comorbidities will be available. Results from a selection of validated PROMs (e.g. NRS, BPI, ISI, HADS, NPSI) and pain status assessments (e.g. BPI, DN4) will be correlated for individual patients to identify which most reliably predict treatment success.

Subtopic 3B BIOM:

The main industry contribution to the biomarkers consortium will be the setup and pharmacological validation of all chosen biomarkers into rodents. The same drugs chosen for the clinical studies will be used in these rodent models including full pharmacokinetic sample analyses in both plasma and central compartments. In addition, these same drugs will be tested in a battery of pain assays at relevant exposures to bridge to the more classical preclinical measures.

The industry consortium will provide all sample analyses for the clinical and preclinical experiments. In addition, any historically available pharmacokinetic and pharmacodynamic measures collected for chosen drugs will be made available to the consortium to aid in dose setting and final biomarker section. The industry consortium will provide clinical trial design, management, statistical and PK/PD modelling expertise to complement those from the applicant consortium.

Subtopic 3C CPP:

For the CPP subtopic, the industry consortium intends to contribute with both reference compounds and animal models of endometriosis and BPS with evoked and non-evoked read-outs. It will also analyse tissue samples from endometriosis patients as well as endometriosis and BPS animal models of these diseases.

The analysis of such tissue on the molecular level will be performed with the goal to identify disease and model relevant pathways. These animal models will be modified and improved with the aim to provide meaningful translatable endpoints. These contributions will allow thorough investigations of the translatability from preclinical to clinical studies and of the events responsible for disease chronification.

Indicative duration of the action

The indicative duration of the action is 39 months.

The successful achievement of the expected deliverables of this project might be the basis of a follow up action building from the assets and results of this initiative and to be launched as part of a future Call for proposals. Applicants are encouraged to explore these aspects while building a sustainability strategy.

Indicative budget

The indicative EFPIA in-kind contribution is EUR 11 230 000.

The financial contribution from IMI2 for each subtopic is:

Subtopic 3A PROMs:

The financial contribution from IMI2 is a maximum of EUR 4 250 000.

Subtopic 3B BIOM:

The financial contribution from IMI2 is a maximum of EUR 4 140 000.

Subtopic 3C CPP:

The financial contribution from IMI2 is a maximum of EUR 2 840 000.

For all subtopics:

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

Applicant consortium

The first ranked applicant consortium of each subtopic will be selected on the basis of the submitted short proposals.

The applicant consortium is expected to address all the research objectives of a particular subtopic and make key contributions to the defined deliverables in synergy with the proposed industry consortium contributions.

Applicants should summarise their abilities to make assured contributions to these requirements within the framework of the project duration and the maximum IMI2 contribution as specified for each subtopic. Inclusion of research intensive and service SMEs is strongly encouraged. Relevant inclusion of patients and patient organisations in the consortia applying to subtopic 3A (PROMs) and 3C (CPP) is encouraged as well.

The successful applicant consortia for each subtopic will be expected to work together and with the industry consortium to assure a high level of integration of the subtopics in preparation of the full proposal for stage 2.

The size of the applicant consortia should reflect expertise needed to achieve the proposed objectives within the indicated budget while ensuring the manageability of the overall topic consortium, and efficient and effective team work. Therefore, the number of members of the applicant consortium needs to be thoroughly justified in the proposal.

This may require mobilising, as appropriate, the following expertise and resources for each subtopic:

Subtopic 3A PROMs:

An existing network of hospital centres to set up an aligned approach in the use and documentation of PROMs in different surgeries; a functional technology platform enabling research studies using PROMs, and meta-analysis of the results; sufficient IT expertise and infrastructure required to collect, transmit, store, analyse, and visualise data; smart-phone technology or other biosensors that may be particularly well suited for measuring functional changes in pain patients; data and knowledge management, building of databases; project management.

Subtopic 3B BIOM:

Experience in the development and validation of clinical experimental pain models and neurophysiological measurements using fMRI, laser-evoked pain, EEG, and measures of peripheral nerve excitability; strong experience in analytical and data management; expertise in clinical pharmacology, including a proven track record in delivering proof-of-concept clinical studies in healthy subjects; competence in pharmacokinetic/ pharmacodynamic modelling in healthy subjects and preclinical models; translational research expertise and data and knowledge management, building of databases; project management.

Subtopic 3C CPP:

Strong clinical expertise in target indication and capability/interest in developing corresponding preclinical models; strong preclinical expertise in models addressing the target indication strictly combined with strong expertise in assessment methodologies for allodynia and hyperalgesia, alternative behavioral endpoints, histology, and molecular biology; strong expertise in proteomics and/or metabolomics; translational research expertise and data and knowledge management, building of databases; project management**.**

Suggested architecture of the full proposal

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

The final architecture of the full proposal will be defined by the participants in observance of IMI2 rules and in contemplation of achieving the project objectives.

This topic consists of three subtopics, each with several inter-connected work packages (WP) which, in combination, will deliver the desired research results.

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.

In the full proposal, the subtopic-specific governance structures will be maintained and guaranteed for each sub-topic by a partnership between one leading member of the respective applicant consortium together with

one leading member designated by the industry consortium. These roles will be supported by appropriate managerial resources, which should be foreseen in the Stage 1 short proposals.

Governance of the overall project will be assured by a partnership between a project coordinator from the applicants on one side and a project lead from the industry consortium on the other, with assistance from a grant manager. The coordinator and grant manager will be agreed upon by the full consortium created by the merger of the winning subtopic consortia at the start of the preparation of the full proposal. This may require slight adjustment of the work-package 1 of all subprojects to accommodate the new structure.

Particular attention will be given to implement the scientific exchange of the specialist experts across the three subtopics ensuring the integration of learnings, synergies and cross-fertilisation and thereby maximizing the outcome of this project.

The industry consortium may adopt a leading role as facilitator as soon as the full topic consortium is formed, to enable efficient negotiations of the project content and the required agreements. This will ensure the maximum of synergy within the topic consortium, for example with respect to data management or genetic analyses.

In order to further enhance synergies within the overall topic, it is foreseen that data gathered in the project generated from this topic will be shared between all members of the consortium, which will require the use of standard data formats to ensure compatibility, and enable meta-analysis.

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

Sustainability

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

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

Subtopic 3A PROMs:

Work package 1: Project Management, sustainability, communication and dissemination

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

The goals of this work package are:

1.1 grant administration;

1.2 communication within the consortium and with external collaborators;

1.3 dissemination of scientific results and research data as described in the general conditions of the Call, and communication with patient organisations;

1.4 development of a sustainability plan facilitating continuation of the project beyond its currently anticipated duration.

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

Expected applicant consortium contribution: grant administration, communication and dissemination of scientific results, and development of a sustainability plan.

Work package 2: Acute pain

The goals of this work package are:

2.1 systematic research on PROMs which have been used to assess the treatment of acute pain patients;

2.2 identification and alignment with expert groups on one PROM per pain model to be used in daily practice and documented in a shared database;

2.3 systematic research on guidelines in acute pain;

2.4 implementation of PROMs as identified in 2.2 in different hospitals after surgery types which have to be aligned by the clinical experts. A validated data collection and storage system will be employed to collect, transmit, store, analyse, and visualise the data and measures prioritised by the expert consortium.

EFPIA consortium contribution: A systematic review on PROMs in post-operative pain has been conducted which includes studies up to Q3/2015. Prospective observational data will be collected from post-operative pain patients over 72 hours and at their 28-day follow-up using validated questionnaires (EQ-5D, PGA, EOC) and sleep quality, and assistance provided with the interpretation of the meta-analysis performed by the applicants.

Expected applicant consortium contribution: update of the systematic review on PROMs in post-operative pain studies; systematic research on guidelines in acute pain; assembly of an academic consortium to identify PROMs which reliably inform about the success of post-operative pain treatments, data capture and management; initiation of a large multi-center, prospective observational trial to collect data on CPSP through web-based or other electronic means at defined time points before and after surgery, with at least a 6-12 month follow-up; and to identify risk factors for chronification of post-operative pain (see also WP3).

Work package 3: Chronification of acute pain

The goals of this work package are:

3.1 systematic research on literature about chronification of acute pain, and on PROMs which have already been used to assess chronic neuropathic pain patients in clinical trials;

3.2 initiation of a large multi-center, prospective observational trial to collect data on CPSP by web-based or other electronic means for at least 6-12 months following surgery. Data will be collected from surgical patients at their 6 and 12 month follow-ups using validated questionnaires (BPI, DN4) to assess the incidence and characteristics of moderate to severe chronic post-surgical pain (CPSP). Physiological and activity-based parameters, if available, will be remotely and continuously measured using non-obstructing on-body sensors or smartphones with intent to identify more sensitive core metrics for remote patient assessment through use of new technologies and platforms. This will include preparing and operating the platform or use of existing platforms to ensure that data are collected, transmitted, stored, analysed and visualised. The suitable measures for use in clinical practice will be identified by the expert panel;

3.3 comparison of PROMs in a clinical trial with patients undergoing major surgery of the upper limb with classical anaesthesia with those from another clinical trial in which analgesia will be provided by wound infiltration with local anesthetics, with the aim of identifying which PROMs are predictive of pain outcomes and the need of individual patients for additional analgesics after surgery. Different PROMs (e.g. NRS, NPSI, PGIC, EQ5D) will be followed for up to 6 months; these have to be collected, transmitted, stored and analysed;

3.4 PROMs will be pooled from clinical trials in post-surgical pain and follow-ups after different times, and also with that from the observational study, with the aim of following CPSP;

3.5 the impact of the type of surgery and of other risk factors on the incidence of CPSP will be analysed together with its neuropathic characteristics using validated PROMs to identify factors which lead to chronification.

EFPIA consortium contribution: PROM data from two multi-centre trials on post-surgery pain collected by web-based or other electronic means for at least 6 months following surgery; baseline data and that after surgery will also be provided. As in the case of the acute pain data, assistance will be provided with the interpretation of the meta-analysis performed by the applicants.

Expected applicant consortium contribution: Systematic review of available literature about chronification of acute pain conditions. Initiation of a large multi-centre, prospective observational trial to collect data on CPSP by web-based or other electronic means for at least 6-12 months following surgery (see also WP2). Prospective observational data will be collected from surgical patients at their 6 and 12 month follow-ups using validated questionnaires (BPI, DN4) to assess the incidence and characteristics of moderate to severe chronic post-surgical pain (CPSP). The impact of the type of surgery and of other risk factors on the incidence of CPSP will be analysed together with its neuropathic characteristics using validated tools to identify factors which lead to chronification. Pooling of clinical trial data from prospective observational trial with data from clinical trials in post-surgical pain conducted by the industry consortium. Perform meta-analysis of data provided by the industry consortium in post-surgical pain and identify subgroups sensitive to chronification which leads to either chronic nociceptive, neuropathic or mixed pain conditions.

Work package 4: Chronic Pain

The goals of this work package are:

4.1 systematic research on PROMs which have already been used to assess chronic neuropathic and chronic pelvic pain patients in clinical trials, and on other recommendations found in white papers or other publications;

4.2 correlation of PROMs in chronic neuropathic pain conditions (for example PHN, PDN) with baseline characteristics of patients (age, sex, DN4, NPSI), and in other chronic pain conditions (e.g. pelvic pain, dysmenorrhea, dyspareunia). Data at baseline for all patients and placebo treatment group follow-up data up to 52 weeks will be collected using different PROMs, for example NRS, VAS, patient global assessment ratings, EHP-30, BPI, EQ5D, SF36, HADS and ISI in chronic neuropathic pain conditions. The data have to be collected, transmitted, stored in an appropriate database and analysed. They then have to be visualised and suitable measures for use in clinical practice will be identified and communicated by the expert panel.

EFPIA consortium contribution: data from multi-national, multi-centre, prospective, randomized, double-blind, parallel-group, placebo-controlled studies in neuropathic pain and chronic pain conditions (pelvic pain, dysmenorrhea, dyspareunia). Data at baseline and up to 52 week follow-ups will be collected using validated PROMs for pain, QoL and comorbidities. As before, assistance will be provided with the interpretation of the meta-analysis performed by the applicants.

Expected applicant consortium contribution: pooling of prospective clinical trial data conducted by the EFPIA consortium from different indications; conduct systematic research on PROMs which have already been used to assess chronic neuropathic and chronic pelvic pain (including dysmenorrhea and dyspareunia) of patients in clinical trials, and on recommendations in white papers or other publications; conduct meta-analysis of data provided by the EFPIA consortium in neuropathic pain and chronic pelvic pain conditions (including dysmenorrhea and dyspareunia); contribute data from clinical trials of different chronic pain conditions/ indications conducted by academic organisations and SMEs.

Subtopic 3B BIOM:

Work package 1: Project Management, sustainability, communication and dissemination

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

The goals of this work package are:

1.1 grant administration;

1.2 communication within the consortium and with external collaborators;

1.3 dissemination of scientific results and research data as described in the general conditions of the Call, and communication with patient organisations;

1.4 development of a sustainability plan facilitating continuation of the project beyond its currently anticipated duration.

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

Expected applicant consortium contribution: grant administration, communication and dissemination of scientific results, and development of a sustainability plan.

Work package 2: Consensus on study designs

The goals of this work package are:

2.1 define primary and exploratory endpoints for each pharmacodynamic biomarker;

2.2 define drugs, doses and biomarker sampling times to satisfy the need to target at least the three pain-relevant peripheral, spinal and central compartments;

2.3 inaugurate academic and industry working groups to review clinical literature on the effects of different SOC pharmacology on the chosen biomarkers in healthy subjects;

2.4 review biomarker selection and specific protocol designs, and justify decisions in a published review;

2.5 review the novel exploratory analysis endpoints to be used in WP3 (e.g. spectral analysis, machine learning, dynamic causal modeling techniques).

EFPIA consortium contribution: active participation in working groups to review and refine clinical protocols; contribution of PK and or PD data on selected drugs to help with choice of dose and PK sampling times; provision of an inventory of relevant clinical and preclinical methods, data and instruments that could be applied in the clinical/preclinical studies.

Expected applicant consortium contribution: propose and review options for final clinical study design, including choice of biomarkers, primary endpoints, test drugs, doses and PK sampling times, statistical and analysis plans; together with EFPIA consortium, write a review article to justify all defined protocols.

Work package 3: Data engineering and statistics for analysis of data sets

The goals of this work package are:

3.1 provide statistical expertise for study set-up and multi-modal data acquisition; provide the data management infrastructure needed for e.g. cross-modal analysis of ERP/EEG signals and blood oxygen dependent (BOLD) responses, threshold tracking, PK data;

3.2 define experimental statistical designs including full power calculations from literature data;

3.3 standardize, harmonise and document all data pre-processing steps required to generate all outcome variables if multi-site studies are required;

3.4 define and provide PK/PD statistical expertise and modelling;

3.5 cross-modal analysis of relative effect sizes between the read-outs from the novel techniques and from classical pharmacology methods.

EFPIA consortium contribution: contribute to and review the statistical and PK/PD modelling plans for clinical and preclinical outcome variables.

Expected applicant consortium contribution: define statistical analysis pipelines for all clinical and preclinical outcome variables; provide the infrastructures required to store, analyse and protect all collected clinical and preclinical data; ensure IT infrastructures would allow for long-term storage and open access to data for future dissemination and re-analysis, and allow its future dissemination; complete and publish final analyses of both clinical and preclinical PD/PK modeling, pharmacological effect size calculations and reliability of all biomarkers tested.

Work package 4: Clinical study implementation and operations

The goals of this work package are to:

4.1 study set-up, execution and close-out of the multi-centre clinical investigation to identify the most sensitive and robust neurophysiological parameters to support dose finding and to investigate PK/PD relationships for drug targets in different pain-relevant compartments;

4.2 study and risk management, plus informed consent and other regulatory requirements;

4.3 develop synopsis and protocol for clinical investigation;

4.4 develop, standardise and deploy human EEG, laser-evoked ERPs, pain-evoked fMRI, threshold tracking and other biomarker paradigms in the context of experimental medicine;

4.5 provide training on paradigms at all centres in multi-centre studies;

4.6 provide recruitment and in-study procedures for an appropriate number of healthy subjects per iteration;

4.7 collect PK samples and organise their analysis;

EFPIA consortium contribution: analysis of PK samples taken during clinical studies;

Expected applicant consortium contribution: complete responsibility for completing the set-up, execution and close-out of the clinical study.

Work package 5: Preclinical biomarker back-translation, including PK

The goals of this work package are:

5.1 implement chosen biomarkers into rodent models and/or into *in vitro* assays e.g. threshold tracking *in vivo* or in isolated nerve preparations;

5.2 detailed preclinical PK evaluation of drugs used in WP4, including drug exposures in the plasma, brain and nerve compartments;

5.3 using results from WP4 and WP5, evaluate drugs in preclinical biomarker models;

5.4 develop PK/PD models, and relate these to clinical effect-size evaluation;

5.5 test battery of SOC pharmacology to identify drugs for any potential second clinical validation studies;

5.6 confirm that drug exposures drive changes in PD biomarkers, and are relevant to preclinical models of efficacy.

EFPIA consortium contribution: responsible for the set-up, implementation and pharmacological validation of all chosen biomarkers and drugs into rodent models, including PK sample collection and analysis;

contributions to the development and analysis of PK/PD models for all biomarkers studied; examine whether drug exposures, proven to be clinically effective with the validated PD biomarkers back-translate into more classical preclinical rodent models of efficacy.

Expected applicant consortium contribution: using the EFPIA preclinical data, generate PK/PD models for preclinical experiments; identify and implement analysis routines to confirm which preclinical biomarkers are most predictive of clinical PD responses for drugs targeting different compartments in pain pathways.

Subtopic 3C CPP:

Work package 1: Project Management, sustainability, communication and dissemination

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

The goals of this work package are:

1.1 grant administration;

1.2 communication within the consortium and with external collaborators;

1.3 dissemination of scientific results and research data as described in the general conditions of the Call, and communication with patient organisations;

1.4 development of a sustainability plan facilitating continuation of the project beyond its currently anticipated duration.

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

Expected applicant consortium contribution: grant administration, communication and dissemination of scientific results, and development of a sustainability plan.

Work package 2: Clinical Part

Analyse BPS and endometriosis patient populations for comorbidities, treatment responses and phenotype.

The goals of this work package are to:

2.1 phenotype for e.g. pain characteristics, comorbidities and hormonal status;

2.2 characterize functional properties specific for CPP rather than other pain conditions;

2.3 analyse treatment responses of different phenotypes in real world situations;

2.4 analyse tissue, peritoneal fluid, blood and urine samples from patients and controls.

EFPIA consortium contribution: provide and analyse biopsies from endometriosis patients.

Expected applicant consortium contribution: generate data from clinical endometriosis and BPS studies.

Work package 3: Preclinical back-translation

Analysis of animal models corresponding to WP2. More specifically, the goals of this work package are to:

3.1 characterize models regarding translational value in context of human biomarkers;

3.2 link clinical data to animal models, and analyse respective biomarker strategies (e.g. proteomics, micro-RNA);

3.3 Analyse functional aspects of pain *in vitro* with e.g. DRG preparations, or *in vivo* with evoked and non-evoked behavioural read-outs, and correlate with biomarkers to prepare for translation into clinical settings;

3.4 characterize preclinical models for their translational value regarding predictive validity, relevant mode of action, and pharmacological character.

EFPIA consortium contribution: rodent animal models and non-human primate tissue for endometriosis; rodent models of BPS, evoked and non-evoked behavioural read-outs; translational value studies.

Expected applicant consortium contribution: models in preclinical species; proteomics, micro-RNA studies, metabolomics with tissues including but not limited to peripheral and central nerve systems.

Work package 4: Preclinical Refinement of BPS models

Based on results from WP2 and WP3, optimize models for biomarkers that were shown to back-translate from patients. More specifically, the goals of this work package are to:

4.1 optimize models for factors which influence their validity;

4.2 provide behavioural and other functional read-outs including non-evoked responses and analysis of reference compounds;

4.3 chronification of the selected preclinical BPS model;

4.4 test reproducibility of refined preclinical models, ideally in a multi-centre manner with the aim to show robust reproducibility of the models in more than one laboratory.

EFPIA contribution: provision of reference compounds; rodent models of BPS, evoked and non-evoked behavioural read-outs, pharmacology, chronification.

Expected applicant consortium contribution: preclinical models of BPS; proteomic, miRNA and metabolomic analyses of tissue and urine samples.

Glossary

BIOM	Subtopic of this Call: 'Improving the translatability of pharmacodynamic biomarkers in pain pathways'
BPI	Brief pain inventory
BPS	Bladder pain syndrome
CPP	Chronic pelvic pain; Subtopic of this Call: 'Improving translation in chronic pelvic pain'
CPSP	Chronic post-surgical pain
DN4	Douleur Neuropathique 4
EEG	Electroencephalogram
EOC	Ease of care
EQ-5D	Questionnaire to measure quality of life - EuroQol Group EQ-5D
ERP	Event-related potentials
fMRI	Functional magnetic resonance imaging
HADS	Hospital anxiety and depression scale
HCP	Health care professionals
ISI	Comorbid anxiety, depression, sleep disorders

NPSI	Neuropathic pain symptom inventory
NRS	Numeric rating scale
PD	Pharmacodynamic
PDN	Painful diabetic neuropathy
PGA	Patient global assessment
PHN	Post-herpetic neuralgia
PK	Pharmacokinetic
PROM	Patient-reported outcome measure
PROMs	Subtopic of this Call: ‘Using patient reported outcome measures to improve the management of acute and chronic pain’
QoL	Quality of life
QST	Quantitative sensation testing
SF36	Short form health survey measure QoL
SMEs	Small and medium-sized enterprises
SOC	Standard-of-care
VAS	Visual analogue scale
WP	Work package

Topic 4: Creation of a pan-European paediatric clinical trials network

Topic details

Topic code	IMI2-2016-10-04
Action type	Research and Innovation Action (RIA)
Submission & evaluation process	2 Stages

Specific challenges to be addressed

Improvements in child health depend in part on access to new and improved medicines. Based on previous assessment, only 30% of marketed drugs in Europe and worldwide include a paediatric authorisation and less than 50% of authorised medicines commonly used in children had been properly tested in this population, and the impact of specific supportive legislation put in place in 2007 may require a longer interval to change these percentages [1] [2]. This rate drops to 10% in the vulnerable patient population in neonatal intensive care units [3]. The current consensus is that children should be protected from inadequate anecdotal data about dosage and use of medical therapies. This protection comes from participation in completed, well-designed clinical trials that generate data necessary for regulatory approval of new drugs and new information on efficacy, dosing, and safety in the label of already approved drugs; or for comparisons between medical therapies in current practice.

Due to the implementation of the European Paediatric Regulation in 2007, both the number of clinical studies for new drug approval or to produce additional information for drug labels in children, and the number of children involved in such studies, has increased steadily in the EU. It is estimated that there are currently (2015) approximately 750 ongoing paediatric investigation plans (PIPs), and 760 paediatric trials requiring approximately 210 000 enrolled children to complete the necessary trials [4]. At the same time, the paediatric research infrastructure needed to conduct such studies is not developing at the same pace to meet this growing need. Given the paucity of patients available for study in many paediatric indications and the need for multiple capable sites to satisfy enrolment in trials, the clinical trial infrastructure across the EU is not sufficiently organised, and lacks adequate funds and scale to consistently and efficiently deliver both industry-sponsored and academic non-industry sponsored clinical trials leading to new drug approval, complete labelling of existing drugs, valid comparisons between existing marketed therapies, or observational studies informing the natural history of disease indications. Currently, we mainly see local or single-indication networks that very often struggle to get sufficient studies and adequate funding to develop the knowhow and capacities needed to interact with partner networks, or to fulfil quality standards to attract industry sponsored studies. In most EU countries no such networks exist at all.

This environment leads to increased competition between studies for existing available resources (investigators, sites, patients), and delays in completion of studies and the availability of innovative medicines to children. In the EU, approximately 40% of PIPs are either delayed with justification or not completed without justification [4] [5] [6]. This deficiency in clinical research capability also negatively impacts the capacity to complete academic-sponsored research in areas of unmet medical need. In addition to improved infrastructure for efficient study execution, collaborative efforts to maximise the coordination of paediatric networks across the EU, utilise innovative study designs, and engage regulators in planning drug development programs are all needed to guarantee that Europe can augment its current capability as a critical region for developing medicines for children.

Need and opportunity for public-private collaborative research

While the industry has access to new innovative medicines with potential effectiveness to fill unmet medical needs in the paediatric population, and the expertise to design and monitor clinical development programmes that meet regulatory standards for drug approval and labelling, the industry lacks access to patients and does not have their own sites to run clinical studies. Usually, paediatric trials require multiple clinical sites each supplying only a few patients, and often these are large publicly supported sites with expertise and access to children with chronic and even rare diseases. Thus, the success of many paediatric clinical trials depends on a public-private partnership between multiple stakeholders including private sponsors (pharmaceutical companies, contract research organisations/CROs) and publicly funded organisations including paediatric networks, medical centres, learned societies, patient advocacy and advisory groups, and government research organisations. In contrast to what exists for clinical trials in adults, there is no developed infrastructure of private research organisations that can reliably supply adequate numbers of subjects for paediatric studies.

Rather than perpetuating the current wasteful, cumbersome paradigm of creating a new network of sites for each new paediatric trial only to see that network dissolve at the conclusion of the trial, this initiative seeks to create a collaborative, sustainable, pan-EU paediatric clinical trial network. But this architecture requires the involvement of all possible stakeholders across all European countries. Under the auspices of IMI2, this project will provide the non-competitive space for all to work together with resources and funding to create this sufficiently large-scale, organised, operational clinical trial infrastructure capable of complete enrolment and timely execution of multiple trials from all sponsors. It will also efficiently deploy clinical research personnel and resources to maximise its ability to be financially self-sufficient and sustainable beyond the years of initial EFPIA company and EU support.

Academia, industry, patient/parent organisations, disease-specific and national networks, contract research organisations, small and medium-sized enterprises, and regulators were all represented at a recent consultative workshop on this subject sponsored by IMI. All agreed that the current paediatric clinical trial infrastructure in the EU is fragmented and not sufficiently large, resourced, organised, and efficient. A broad multidisciplinary public-private consortium is required to meet the challenges described and be transformative for collectively addressing children's needs for better medicines. With IMI being an established public-private partnership, this unprecedented collaborative effort provides a ready and transparent mechanism for assembling the key stakeholders to develop an integrative, open, sustainable, pan-European paediatric clinical trials network. This will be transformative and put Europe in a competitive place for delivering high quality paediatric clinical trials.

Scope

The overall vision of this proposal is to create a large collaborative paediatric network that will facilitate the development and availability of new drugs and other therapies (e.g vaccines, devices, drug/device combinations), and the expansion of knowledge about drugs currently in practice for the entire paediatric population. This will be accomplished by not only advising on how best to do the necessary research, but by actually building sufficient infrastructure and best practices to support planning, running, and completion of all types of clinical studies (phase I-IV) by all kinds of sponsors (industry and non-industry) that can be used for regulatory review and approval, and for answering important scientific questions for already available drugs.

To achieve this vision the objectives of the proposal are to:

- create a network with a lean central coordinating organisation, arranged around 'national hub coordinating centres' (e.g. qualified paediatric institutions) cooperating with multiple sites within each member state. This architecture will be expanded over time to include both additional sites/countries and additional studies focused on new indications based on medical need;
- install scientific advice and trial readiness groups to consult with all sponsors on the dose rationale, scientific soundness and feasibility of their proposals and to help drive innovation in paediatric clinical trials. Innovations may include implementation of modelling and simulation and other tools to foster extrapolation, as well as new biomarkers, patient-reported outcomes (PROs), study designs and/ or

endpoints jointly developed by companies, academia, patients, and regulators while developing new studies and /or guidelines;

- test the viability of the network by measuring performance metrics during the execution and completion of a number of different clinical studies (phase I-IV) from different sponsors (industry, non-industry) and different therapeutic areas, across all age groups. The objective of this topic is not to conduct a clinical trial for purposes of compound testing per se, but solely to test the viability of the network;
- develop and implement a sustainable business model for the network as a major focus from the outset of the project;
- prepare the network to become a member of the European Network for Paediatric Research at the European Medicines Agency (Enpr-EMA), after positive proof of viability and submission of a self-assessment report that satisfies Enpr-EMA recognition criteria.

Expected key deliverables

The key deliverables of this project are as follows:

- **Establish the structure and governance of the network**
  - A lean central coordinating organisation to steer the network and to oversee coordination of network activities, including coordination of scientific advisory and feasibility groups.
  - A central point of contact for all sponsors (industry, non-industry).
  - Procedure for a single point of entry into the network for any clinical study, which allows:
    - rapid scientific evaluation and related feedback;
    - assessment of feasibility and;
    - initiation of studies;
    - contracting and invoicing of such services.
  - 'National hub coordinating centres' in each participating member state. Centres may come from large Member States with already existing infrastructure and/or available paediatric networks. Initially, at least 2-3 centres must also come from countries without any such existing infrastructure.
  - Multiple clinical sites within each participating member state, including at least one 'model site' per member state (which may double as the national hub coordinating centre). When fully functional, model sites should be able to provide well-trained clinical research nurses, data entry personnel, research pharmacy support, country-wide regulatory intelligence, program management and administrative support, and a physician trial coordinator.
  - Effective, network-wide quality management system to monitor and evaluate network performance.
  - Processes that ensure data protection and privacy within and outside the network. This may include, but not be limited to, all processes around scientific review, data collection, data processing, data coding, and transfer of data from and to the sponsor or between research sites as part of ongoing quality and performance evaluations.
  - Effective stakeholder management processes, including but not limited to interactions with: Enpr-EMA and related paediatric networks; patient/parent advocacy and advisory organisations; pan-EU research infrastructures; and non-European paediatric networks (e.g. C-Path Paediatric Clinical Trials Consortium that is aiming to create a complementary network).
- **Set up and maintain groups of scientific experts to trigger innovation** (develop and implement innovative methods, including dose selection, biomarkers, endpoints and/or study designs) that support the dose rationale and increase the feasibility and scientific merit of paediatric clinical trials. These groups might consist of experts in designing and conducting clinical trials from academia and industry in various functional and therapeutic areas, and may collaborate with the regulatory bodies like EMA and its

paediatric development committee (PDCO) and similar working groups already established under the umbrella of Enpr-EMA.

- **Implement standing disease or condition-focused network clinical advisory groups** who consult with all sponsors on scientific and clinical questions for specific paediatric drug development programmes and protocols within the field of their expertise. This may include evaluation of the rationale for a clinical development plan, the requirements for data generation/integration, and whether a study proposal can be implemented and successfully conducted by the network.

  Evaluation could be based on study design, scientific soundness of the proposal, availability of patients, patient/parent advisory group assessment, trial readiness of sites, and satisfactory ethical criteria; all combined to give a robust feasibility assessment.

  Groups shall consist of non-industry clinical trial experts and wherever possible shall include representatives of patient/parent organisations.

- **Develop and implement standardised processes, procedures, and performance metrics** necessary for efficient initiation and execution of studies and maintenance of high-level performance across the network, as follows:
  - harmonised administrative and site-initiation procedures including site confidentiality agreements, site master contracts and budget templates throughout the network;
  - consistent, standardised study procedures for all sites, including standardised electronic data capture (EDC) processes and uniform data collection standards;
  - uniform, and if possible, centralised ethics committee approval procedures including all sites within each participating country based on new and already existing guidelines and regulations, including the implementation of EU Clinical Trials Regulation;
  - uniform site accreditation and performance standards utilised throughout the network;
  - information technology (IT) and data management solutions that foster stringent standardised data collection and delivery of analytical datasets that can be shared among investigators and meet specifications for regulatory submission;
  - standard definitions for coding of data and shared definitions of terminology and process to allow interoperability;
  - data coordinating centre to create tools for monitoring overall network performance and performance at each participating site;
  - concept and curriculum for mandatory annual network-wide good clinical practices (GCP) training for all site staff acceptable to all study sponsors (industry and non-industry);
  - uniform drug development-based curriculum for network-wide training of paediatric clinical trialists.

- **Test the readiness of the network** by conducting three to four industry-sponsored ‘proof of viability studies’ selected by the industry consortium, and at least one non-industry sponsored study (phase I – IV) within the indicated duration of the IMI2 project. Only studies with a study start (First Patient First Visit) after the project has been awarded to the winning applicant consortium will qualify as proof of viability studies. To allow testing against the highest possible standards, these should be clinical studies pivotal for the registration/paediatric labelling of the studied compound.
  - Variables to assess network readiness may include:
    - feasibility and acceptability of European Union, Member State and /or Institution wide standard contracts;
    - acceptability of a common informed consent/assent process and informed consent forms (ICF) to ethic committees, sponsors and sites;
    - validity of feasibility assessment;
    - readiness of data coordination centres (electronic case report form / eCRF, data transfer, data handling);

- readiness of sites (IT capability, training of site staff etc.);
- proper compliance with all regulations for handling intellectual property (IP);
- enrolment of subjects and completion of study procedures to time and target at each site.

- **Build and expand the clinical trials infrastructure** of the network at national hub sites and affiliated sites in multiple EU Member States over the course of the IMI2 project, as follows:
  - Create a process to open the network to industry sponsors beyond the initial EFPIA consortium members, and to all types of public, non-industry sponsors;
  - Develop a strategy to expand the network throughout Europe during the life of the IMI2 project.
- **Develop a business model and funding mechanism** that will provide sustainability of the network after the period of IMI2 funding. Possible business models may include public-private partnership models or other non-profit organisation operational models.

  Funding sources may include but are not limited to: fee-for-service (study planning and execution); subscriptions from research funders; dues from participating sites; grants from government research institutions and foundations; in-kind contributions from national governments, universities and/or health care systems; philanthropy.
- **Build a process to open the network for submission of studies from all kinds of sponsors** to increase the throughput of studies during the six year timeframe of the IMI2 project, and further refine network operational capability and test the applicability of the business model.

Under this topic, the applicant consortia may research and develop pre-existing product candidates owned by one of the beneficiaries participating in the proposal, to validate the clinical trial network. By performing such activities, clinical results that are generated from the pre-existing product candidates (or compounds) tested will be owned by the generating beneficiary(ies). These results may be improvements (or directly related) to the pre-existing product candidate.

When solely owned by the generating beneficiary, the IMI2 rules allow the consortium to establish that the ownership of such results can be transferred to the owner of the pre-existing product candidate. Considering the value of the asset and the objective of the action, the applicant consortium should be fully comfortable to establish in the consortium agreement that the ownership of clinical results generated from the pre-existing product candidate(s) tested – when and only where not jointly owned according to Article 26.2 of the IMI2 Model Grant Agreement – will be transferred to the initial owner of the pre-existing product candidate(s) at no additional cost, when requested so by the pre-existing product candidate owner.

When jointly owned by the generating beneficiaries according to Article 26.2 of the IMI2 Model Grant Agreement, the decision on the terms of transferring their ownership shares to a single owner with access rights for the other participants can only take place after the results have been generated.

Expected impact

Children are twice as likely to experience disability-adjusted life years (DALYs) than other age groups, and thus saving lives and improving the health of children has longer-term benefits than health care for other age groups, and will help set the stage for healthy aging. Many of the disease categories called out for emphasis in the Horizon 2020 Work Programme 2016-2017 are present in the paediatric population [7]. These include diseases of the immune system (SC1-PM-01), rare diseases (SC1-PM-03; SC1-PM-08), and certain chronic diseases (SC1-PM-09). In all of these areas, the existence of an organised, pan-EU paediatric network with broad access to rare and chronic disease patients, and the ability to mobilise and complete natural history studies, organise registries, and intervene with early studies of new therapies or comparisons of existing therapies in collaborative trials would be highly advantageous. This initiative also fits precisely into SCI-PM-04-2016: Networking and optimising the use of population and patient cohorts at the EU level. Children are recognized as one of the cohorts with common scientific interests that need to be “exploited” using integrative methods and access that can be provided through a pan-EU collaborative network.

This initiative is clearly focused on the IMI2 goal of increasing the success rate in clinical trials, by completing paediatric clinical trials agreed to in PIPs. It is expected that the investment in the infrastructure and scaling up to a pan-EU paediatric clinical trial network will: attract a steady critical mass of paediatric clinical trials from diverse sponsors; attract national investment from health ministries in Member States; become a recognised resource for research into the advancement of paediatric clinical trial science and practice; and be sustainable and continue to benefit respective participating organisations and institutions well beyond the initial six year period of this IMI2 action. This action provides the opportunity for European clinical research personnel, clinical research sites, and clinical research organisations to collaborate across national borders making Europe a more competitive place for the conduct of paediatric clinical trials. By aligning European paediatric clinical trial network procedures and processes with other concurrent network-building initiatives going on in the US and Canada, a functionally global paediatric clinical trial network may eventually be realised. This is clearly aligned with the concepts expressed in SC1-HCO-14-2016: EU-US interoperability roadmap. This project will have an impact on a number of areas:

- access for paediatric patients to new experimental therapies in well-designed clinical trials aimed at facilitating the approval of new medicines for children;
- the efficiency of executing trials with reduced timelines and reduced cost for all sponsors;
- enhancing the role of clinicians and patient/parent advocacy groups in planning and designing studies, and reducing the number of paediatric trials that cannot be completed due to unfeasible study design and inability to recruit and retain subjects;
- broadening the access of academic medical centres and clinical faculty across Europe to new experimental therapies for multiple clinical indications, and increasing the opportunity to conduct trials designed to:
    - generate new information on commonly used but inadequately labelled drugs,
    - establish the dose regimen for different age groups,
    - measure the comparative efficacy of marketed drugs currently used in practice,
    - define the natural history of poorly understood conditions and the long-term drug safety of newly approved drugs,
    - study potential new biomarkers, surrogate markers of efficacy, and innovative study designs for rare diseases;
- regulatory policy around feasibility, innovative study design, meaningful endpoints, and risk-benefit assessment by providing a network that can act as an honest broker based on its robust experience and expertise.

Potential synergies with existing consortia

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

Multiple synergies with other existing EU and non-EU consortia are available and offer the opportunity to investigate and adapt already developed products and procedures, and collaborate with existing networks, and other relevant European paediatric medical organisations. These may include but are not limited to:

- inclusion of the masters-level curriculum in paediatric clinical drug development produced by **GriP** (**Global Research in Paediatrics Network of Excellence,** http://www.grip-network.org/index.php/cms/en/home) as a part of training for national hub site network champions, and adoption of guidelines for the development of paediatric clinical trial protocols developed by GriP featuring common data elements and interoperability;

- collaboration with consortia already established and ready in the context of **FP7-funded studies** of off-patent medicines currently commonly used off-label in the paediatric population;
- the IMI2 paediatric clinical trials network will build on the experience and success of Enpr-EMA category 1 existing national paediatric networks (http://enprema.ema.europa.eu/enprema/showall.php?found_records_page=1). They may become affiliated with the pan-EU paediatric network by leveraging their organisation as the national hub coordinating centre for their country, and including their sites in trials accepted by the pan-EU paediatric clinical trials network. Collaboration with existing successful disease-specific paediatric networks such as **PENTA-ID** (HIV /AIDS and infectious diseases)**, PRINTO** (rheumatology)**, ITCC** (oncology)**, ECFS-CTN** (cystic fibrosis) may allow expansion of the number of sites across Europe that are available to participate in disease-specific studies, and leverage the experience and expertise inherent in these disease specialty networks for study planning, data analysis, and publication.
  Other standard-setting organisations are also relevant and offer opportunities for synergy. **The Alliance for Clinical Research Excellence and Safety (ACRES)** (http://www.acresglobal.net/) is a non-profit organisation made up of a diverse group of stakeholders with a focus on a 'Site Accredited Standards Initiative (SASI)'. Uniform global standards for clinical research sites and independent third-party accreditation do not exist at this time. ACRES is developing such a set of standards, and the IMI2 paediatric clinical trials network will work with this consortium to develop paediatric site specific standards, and utilise them for evaluation of network sites. **Transcelerate** (www.transceleratebiopharmainc.com/) is currently developing a paediatric common protocol template that could be adopted for network studies;
- international collaboration and alignment in the area of paediatric clinical trials is expected with the **Critical Path Pediatric Trials Consortium (PTC).** This will foster the goal of developing a global paediatric clinical trials network (https://c-path.org/programs/ptc/);
- leveraging synergies and learnings from existing consortia and European Research Infrastructures (Ris) will also facilitate the crucial aspect of developing transnational collaboration and standards for paediatric clinical trials. **The European Clinical Research Infrastructure Network (ECRIN)** (http://www.ecrin.org/) is one such Research Infrastructure. ECRIN's focus has been on investigator-driven clinical trials mostly in adults, but they are now turning more of their attention to paediatric trials. Sustainability of the IMI paediatric network beyond the funding period of IMI2 is a key goal, and a sustainable successor organisation to an IMI-2 funded European Paediatric Clinical Trials Network will be a key deliverable of this initiative that may well continue to require both public and private support embedded in a broad group of stakeholders. That broad stakeholder support will require specific government support at the European level (including countries that are members of the European Union and other European countries). The best model for the development and maintenance of a sustainable way of working is provided by current Research Infrastructures (RI), stimulated by the **European Strategic Forum for Research Infrastructure (ESFRI),** and funded by the European Commission through successive Framework Programmes, including **Horizon 2020**. The experience of one such RI**, ECRIN,** is that the development of the governance and legal entity for a sustainable RI that supports the management of multi-national clinical trials takes 3 – 5 years. Thus, the development of a successor organisation to an IMI2-funded paediatric network needs to start in parallel with the initial setup of this network and can learn from ECRIN's experience. To some extent this work has started. **The European Paediatric Clinical Trials Research Infrastructure-(EPCTRI)**
  (http://www.ema.europa.eu/docs/en_GB/document_library/Presentation/2016/06/WC500209404.pdf) is included in the 2016 Road Map for European Research Infrastructure as an RI that is complementary to **ECRIN. EPCTRI** and **ECRIN** have already worked on grant applications. The work of **EPCTRI** will bridge between activity that contributes to **ECRIN,** and the activities planned as part of this IMI2 initiative.

Industry consortium

The industry consortium is composed of the following EFPIA companies:

- Janssen (lead)
- Bayer (lead)
- Novartis

- Pfizer
- Lilly
- GlaxoSmithKline
- Roche
- Servier
- Sanofi/Genzyme
- UCB

As in-kind contributions, industry consortium members will bring the following assets/skills and expertise to the project:

1) program management to oversee budgets, timelines, and administration of all uniform processes and procedures including confidentiality agreements (CDAs), master contracts, budget templates, and institutional review board/ethics committee (IRB/EC) processes;
2) clinical trial design including adaptive design and the use of modelling/simulation, and extrapolation technologies for determination of dose selection, sample size, and other parameters;
3) clinicians, clinical pharmacologists, or clinical scientists from each company to act as a company network champions and facilitate company communication and participation with the network;
4) clinicians for communication, on-site visits, and other interactions with academic medical centres, investigators, and advisory boards;
5) information technology/ data management expertise to co-lead the central network data coordinating centre, co-maintain the central organisation website, and co-lead the installation of needed performance monitoring tools and procedures at all participating sites;
6) regulatory expertise in interacting with EMA/PDCO, and other regulatory health authorities;
7) clinical operations including feasibility assessment, informed consent forms (ICFs) and assents, recruitment and retention of subjects, clinical trial monitoring, and assessment of trial performance metrics;
8) business planning and development; contractual agreements;
9) financial planning and implementation;
10) legal counselling;
11) industry-sponsored clinical trials to test the viability of the network.
The industry-sponsored studies will focus on areas of unmet medical need, including but not limited to: infectious disease (e.g. respiratory syncytial virus, influenza, hepatitis C); chronic auto-immune diseases (e.g. juvenile idiopathic arthritis, psoriasis, Crohn's and ulcerative colitis, lupus); serious paediatric epilepsy and neonatal epilepsy; metabolic disease; paediatric oncology (leukaemia, solid tumours); autism; spinal muscular atrophy; retinopathy of prematurity; and inherited diseases such as haemophilia and lysosomal storage diseases. The final selection of industry-sponsored studies will be made once the network is established based on the then current portfolio development. To ensure the validation of the network, the selected studies will target a variety of indications. Studies will be sponsored and 100% funded by the respective company including the cost of full-time equivalents (FTEs) and other expenses to run the studies, including but not limited to CRO costs, laboratory costs, and investigator and institutional grants based on respective site contracts. For sites belonging to the network and for other network related services, payments will be based on respective agreements with network related sites and/or network scientific advisory groups.

Indicative duration of the action

The indicative duration of the action is 72 months.

Future project expansion

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

In the context of this topic, it is envisioned that such an extension may include:

- expansion of the network into any EU countries not yet incorporated into the network;
- continued scaling up of the capacity for multiple simultaneous clinical trials at each national hub plus sites in each member state;
- continued efforts to achieve international collaboration and alignment in the area of paediatric clinical trials in order to create a functional global paediatric network;
- expansion of types of clinical trials run through the networks including:
  - multi-arm, multi-company master trials of multiple drugs for uncommon or rare diseases,
  - collaborative trials with disease-specialty networks,
  - observational 'registry' trials for long-term safety assessments,
  - studies of off-patent drugs commonly used off-label in the paediatric population;
- integration of the learnings from the network's scientific advisory groups into regulatory guidance and daily practice regarding endpoints, biomarkers, and the impact of organ maturation, growth and development on drug disposition, pharmacodynamics, efficacy and safety of medicines;
- leverage the learnings of the IMI project EHR4CR (Electronic Health Records for Clinical Research)[13] and work with *i*~HD[14], the non-profit organisation that now houses the system and data of EHR4CR, to use anonymised electronic health record data from all network member sites to assess feasibility of clinical trials based on inclusion/exclusion criteria;
- expansion of the scope of the network to include development of new vaccines, paediatric medical devices and companion diagnostics.

Indicative budget

The indicative EFPIA in-kind contribution is EUR 67 000 000.

The financial contribution from IMI2 is a maximum of EUR 67 000 000.

The indicative EFPIA in-kind contribution will include EUR 12 000 000 in-kind resources for the network and three to four industry-sponsored clinical studies (phase I – III) to be conducted by the network to test its viability. These studies will be sponsored and 100% funded by the respective company including the cost of FTEs and other expenses to run the studies. Due to the global nature of paediatric clinical trials and the global nature of the participating industry partners, part of the EFPIA contribution may be provided from non-EU/H2020 Associated Countries.

[13] http://www.ehr4cr.eu/
[14] http://www.i-hd.eu/

The IMI2 JU contribution will solely be used to fund the creation of a sustainable network infrastructure plus the funding of at least one non-industry sponsored proof of viability study.

Applicant consortium

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

- experience and know-how in conducting paediatric clinical trials including clinical operations and clinical program management; or have extensive experience in conducting adult clinical trials with the wish to expand into paediatrics;
- expertise in the science of paediatric drug development, including all aspects of clinical pharmacology, modelling and simulation, extrapolation, regulatory science, statistical methods, epidemiology and use of clinical databases, study design (including adaptive designs and collaborative/master clinical trials), and ethical considerations;
- access to a large paediatric population covering the entire spectrum of diseases and conditions across all age groups;
- physicians and other health care providers covering a wide array of clinical paediatric subspecialties;
- patient/parent organisations able to actively contribute to the development and standardisation of study procedures and processes (e.g. creation of study documents, patient/parent information), and assessments of feasibility, clinically meaningful endpoints, and risk-benefit assessment;
- experience in working with the use of standardised procedures and processes in all clinical trials, uniform training of all research personnel, assistance in the design of clinical trials, inclusion of the patient/parent perspective in clinical trials, and the sharing information related to clinical trials;
- information technology/data management;
- expertise in legal and clinical compliance/ICH GCP (International Council for Harmonisation – Good Clinical Practice) aspects;
- strong project management and communication expertise;
- office administration and website management.

Organisations fulfilling the criteria listed above will be expected to be large children's hospitals and medical centres, existing regional or national paediatric networks, transnational, pan-EU disease-specialty networks, and possibly small and medium-sized entities with specialised expertise in aspects of paediatric drug development. Additionally, patient advocacy organisations and youth advisory groups are essential to include the patient perspective.

Efforts should be made to include organisations in as many European countries as possible from the outset as part of the applicant consortium. National hub sites and/or affiliated sites to be added to the network over the course of the project may be recruited from both members of the original applicant consortium or from organisations independent of the consortium.

Due to the expected close relationship and interdependencies between the network and Enpr-EMA, and the potential impact that the network focus on development of innovative study designs and new endpoints may have on paediatric drug development, it is anticipated that the EMA will participate in some aspects of the creation of the network. The EMA would be willing to join the selected applicant consortium with the highest ranked short proposal (stage 1) and the industry consortium to develop a full proposal (stage 2). The EMA will carry its own cost.

The EMA contribution is listed under the relevant work packages and needs to be taken into account by the applicant consortia.

Suggested architecture of the full proposal

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

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

Especially with regards to expected output from work packages 2, 4 and 7 below, the consortium is expected to have a strategy on the translation of the relevant project outputs into regulatory practices, and clinical and healthcare practice. A plan for interactions with regulatory agencies/health technology assessment bodies, with relevant milestones and resources allocated, should be proposed to ensure this.

A plan for aspects related to sustainability, facilitating continuation of the network beyond the duration of the project should also be proposed (see also work package below).

In its short proposal, the applicant consortium is also expected to come up with a preliminary suggestion for the non-industry sponsored study(ies) for the testing of the network including the process for selection and proposed reserved budget (see also work package 2). At stage 2, the full consortium will consider and agree upon the number of non-industry sponsored studies and their budget**.**

Work package 1: Project management and oversight of IMI project

The overall objective for work package 1 is to establish a framework for collaboration and ensure minimisation of duplicate work and maximisation of sharing across the various work packages, as well as to ensure the strategic alignment of efforts. Specific deliverables include:

a) project design and charters with clear accountabilities;

b) set-up of joint governance structure;

c) provide coordination and support to work package teams;

d) define work expectations of different work streams, deliverables, dates and activities and review progress regarding adherence to budget, timelines and quality;

e) ensure that key cross-functional partners are engaged;

f) define project interdependencies, stakeholders and risks;

g) ensure meetings and interactions between work packages, sub-groups, and consortium governance bodies to coordinate and follow-up on work effort.

Industry contribution:

- project management support with project design and day-to-day operation;
- legal expertise, clinical operations, data management, and clinical expertise to support regular review of deliverables regarding quality and operational ability;

- industry co-leads to contribute to consortium governance structure and meetings.

Expected applicant consortium contribution:

- ensuring the implementation of the coordinating tasks and running the day-to-day operation, such as project tracking and reporting, meetings, internal communication, budget management, etc.

Work package 2: Organisation and governance of the pan-European paediatric clinical trials network

The goals of this work package are to:

a) establish the structure and governance of the network;

b) build a lean central coordinating organisation to steer the network;

c) establish a single point of contact for entering the network for all kind of sponsors;

d) develop a transparent process and criteria for selection of studies to be performed by the network. A process needs to be installed that ensures proper selection and allocation of all kinds of studies (industry and non-industry studies) to the network:

    - this process is to be applied to all new studies brought to the attention of the network after successful conduct of all planned proof of viability studies (three to four from industry and at least one non-industry study);
    - in the initial period, a separate process will be needed to allow allocation and selection of at least one non-industry sponsored study (including budgeting) to test the network;
    - the project will also need to ensure that network's own scientific advisory groups (to be implemented under work package 4 are adequately involved in this process.

e) build network-wide processes for contracting and invoicing of respective activities (studies, scientific advice etc.);

f) build governance processes ensuring close management of budgetary, quality and data protection/privacy related processes and activities, including coordination of scientific advisory and feasibility groups;

g) build quality management processes to ensure all network activities are in compliance with common research standards and (inter-) national regulations for the conduct of clinical trials;

h) build external stakeholder management process to:

    - establish liaison with governments of participating countries, and with identified national hub sites and other participating sites;
    - leverage synergies with other IMI2 projects, existing research consortia, existing national and disease specialty networks, and patient advocacy groups;
    - collaborate with other emerging paediatric clinical trial networks (in North America and beyond) to assure international interoperability.

Industry contribution:

Industry will support generation and implementation of governance, organisational and quality management processes by providing expertise related to:

- project Management;
- controlling and budget planning;
- legal and data privacy / data protection regulations;
- clinical operations management (incl. GCP Compliance);
- clinical expertise, with a focus on clinical/medical governance processes.

Expected applicant consortium contribution:

- project management (including budget planning);
- quality management;
- legal, contract development and data privacy/data protection regulations;
- clinical operations management;
- clinical expertise, with a focus on clinical/medical governance processes;
- business development.

EMA contribution:

- EMA through Enpr-EMA may facilitate interaction with relevant non-consortium stakeholders by organising multi-stakeholder meetings, exploring synergies and avoiding duplication of work, thereby helping to ensure the most efficient use of public funding.

Work package 3: Business plan development, expansion of the network and sustainability of the network funding sources post-IMI2 support

The goals of this work package are:

a) development of a business model to ensure sustainability and sufficient funding of the network after the end of the IMI project;

b) development of a fee structure for participating sites, networks, and other organisations that are part of the network, and for sponsors submitting studies to the network for consideration and execution;

c) development of a procedure to recruit and integrate new sites into the network, and to allow new, additional industry and non-industry sponsors to use the network;

d) engagement with national entities (ministries of health, national government research organisations) to support the clinical trial infrastructure that has been developed for the network in their country;

e) investigation of other sources of continued funding.

Industry contribution:

- business development, with focus on public private partnership models;
- project Management;
- regulatory to support interaction with national entities;
- legal.

Expected applicant consortium contribution:

- business development;
- business planning, funding models for public-private partnership/non-profit organisations;
- financial operations, grant applications in participating EU countries;
- project management;
- legal;
- clinical research leaders in each country to facilitate discussions with national entities, foundations, learned medical societies, etc. about sustained support of the network within the country.

Work package 4: Scientific advice, feasibility and innovation

The goals of this work package are to:

a) implement expert panels evaluating the rationale for a clinical development plan, the requirements for data generation/integration, and whether a certain study proposal can be implemented and successfully conducted by the network (feasibility groups);

b) set-up and maintain groups of scientific experts to trigger innovation (develop and implement innovative methods, including dose selection, biomarkers, endpoints and/or study designs);

c) implement standing disease or condition-focused network clinical advisory groups (made up of non-industry medical experts) who consult with all sponsors on scientific and clinical questions for specific paediatric drug development programs and protocols within the field of their expertise;

d) set-up process to allow patients/parent representatives to give input to new innovative study designs and to participate in evaluation of feasibility, design, meaningful endpoints, and risk-benefit of given paediatric study protocols;

e) creation of the charter, definitions of operations, and selection of members of the different scientific bodies.

Industry contribution:

- clinical/medical expertise in different therapeutic areas and experience in study design;
- expertise in clinical pharmacology, modelling and simulation, and extrapolation of efficacy to maximise efficient completion of paediatric trials;
- data sciences/statistics;
- clinical operations;
- feasibility assessment, including leveraging large datasets and the electronic health record.

Expected applicant consortium contribution:

- medical/ clinical experts in respective therapeutic area;
- clinical study design, clinical pharmacology;
- data sciences / statistics;
- clinical operations;
- feasibility assessment;
- patient recruitment;
- patient/parent organisations to feedback patient/parent expectations.

EMA contribution:

- introduction to the relevant Enpr-EMA working groups to help support 4b, to help ensure that the new innovative methods developed are considered for incorporation into regulatory guidelines and to help identify work already ongoing so as to avoid duplication of effort. This should not be seen to replace regular EMA Scientific Advice procedures;
- signpost the consortium to the EMA Patients and Consumers Working Party and the Healthcare Professionals Working Party and, through them, the larger network of eligible organisations for consultation on 4d and to EMA Scientific Advice procedures, Innovation Task Force briefing meetings, or other opportunities for interacting with regulatory authorities, as appropriate, to ensure that regulatory requirements are taken into account.

Work package 5: Data coordinating centre and data quality standards

The goals of this work package are to:

a) establish procedures and systems/tools to monitor performance metrics in all network trials at the sites, national hubs, and in the central network organisation;

b) promote shared definitions of terminology enabling uniform process for collection and storage of clinical data;

c) contribute to common eCRF definitions (e.g. common paediatric data dictionary);

d) contribute to common program/process to allow electronic storage and archiving of study related documentation.

Industry contribution:

- data sciences/statistics;
- data management, data coding & data dictionaries;
- medical standards;
- IT/clinical data management systems.

Expected applicant consortium contribution:

- medical/clinical experts in respective therapeutic area;
- data sciences/statistics;
- data management;
- IT/clinical data management systems;
- Coding of clinical data.

Work package 6: Network research personnel education and training

The goals of this work package are:

a) adoption of an eTraining platform for GCP training for all personnel;

b) define and implement a training curricula on paediatric drug development, for all network clinical leaders (synergies with GriP and other IMI projects);

c) development and implementation of age appropriate information on clinical trials and the importance of new drug development for children and their families (taking synergies with existing information into account).

Industry contribution:

- clinical and clinical operations;
- generation of e-Training platforms and curricula;
- clinical compliance / ICH GCP expertise;
- IT;
- legal.

Expected applicant consortium contribution:

- clinical and clinical operations;
- generation of e-training platforms and curricula;
- clinical compliance/ICH GCP expertise;
- IT;
- expertise in generation of patient-centric, age-appropriate information material;
- patient/parent organisations and youth advisory groups to feedback patient/parent expectations and help develop and vet study information.

EMA contribution:

- advisory and active contribution to WP 6b and 6c to ensure that regulatory requirements are taken into account.

Work package 7: Planning and execution of clinical trials

The goals of this work package are to:

a) develop and implement uniform standards and processes for clinical project management (subject to country variations), including processes for study planning and budgeting, contracting, clinical monitoring, data management, regulatory interactions, CRO interactions;

b) develop network-wide standardised study procedures and documents, including but not limited to confidentiality agreements (CDAs), master contracts, budget templates;

c) network-wide unique procedures/templates for ethics committee (ICFs, assents) liaisons, and regulatory reporting and procedures (at least uniform and centralised at member state level), in accordance with EU clinical trial regulations;

d) define and utilise all available tools for a robust assessment for trial readiness and feasibility at each site;

e) develop an operational implementation plan to execute the study of a new drug, including execution of three to four industry and at least one non-industry study to be conducted to test the viability of the network;

f) organise a procedure for applying performance metrics to measure site and network performance in the execution of clinical trials, and institute measures to improve efficiency, including but not limited to requirements for site accreditation, performance metrics, and quality control;

g) after finalisation of the 'proof of viability studies', evaluate the performance of the network based on performance metrics created under f) above and feedback results to network governance, the full consortium management board and IMI.

Industry contribution:

- clinical operations;
- contracting expertise;
- feasibility assessment;
- clinical project management;
- regulatory;
- clinical compliance;
- legal;
- three to four industry sponsored studies to test the viability of the network.

Expected applicant consortium contribution:

- clinical operations;
- feasibility assessment;
- clinical project management;
- regulatory expertise with focus on clinical trial applications/Investigational Medicinal Product Dossier (CTA/IMPD) application process;
- clinical compliance, ICH GCP expertise;
- legal.

EMA contribution:

- advisory and active contribution to WP 7c to ensure that regulatory requirements are taken into account;
- introduction to the relevant Enpr-EMA working groups to help ensure appropriateness of the informed consent forms.

Glossary

ACRES	Alliance for Clinical Research and Safety
CDA	Confidentiality agreement
C-Path	Critical Path Institute
CRO	Clinical research organisation
CTA	Clinical trial application
DALYs	Disability-adjusted life years
EC	Ethic committees
ECFS-CTN	Cystic Fibrosis Clinical Trials Network
eCRF	electronic case report form
ECRIN	European Clinical Research Infrastructure Network
EDC	Electronic data capture
EFPIA	European Federation of Pharmaceutical Industries and Associations
EHR4CR	Electronic Health Records for Clinical Research
EMA	European Medicines Agency
Enpr-EMA	European Network for Paediatric Research at the European Medicines Agency
EPCTRI	European Paediatric Clinical Trials Research Infrastructure
ESFRI	European Strategic Forum for Research Infrastructure
EU	European Union
EU-CTR	European Union Clinical Trials Regulation
EUR	Euro
FP7	7th Framework Programme (European Commission)
FTEs	Full time equivalent
GCP	Good clinical practice
GriP	Global Research in Paediatrics
H2020	Horizon 2020
ICF	Informed consent form
ICH	International Council for Harmonisation
IMI JU	Innovative Medicines Initiative Joint Undertaking
IMPD	Investigational Medical Product Dossier
IP	Intellectual property
IRB	Institutional Review Board

IT	Information technology
ITCC	Innovative Therapies for Children with Cancer
PDCO	Paediatric Committee of the European Medicines Agency
PENTA-ID	Paediatric HIV/AIDS and Infectious Diseases Network
PRINTO	Paediatric Rheumatology International Trials Organisation
PROs	Patient reported outcomes
SC1-HCO-14-2016	European Commission Social Challenges Health; EU-US interoperability roadmap

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Topic 5: Biomanufacturing 2020: Development of innovative high throughput analytical tools and methods to characterize cell culture fluid during development and commercial cell culture processes

Topic details

Topic code	IMI2-2016-10-05
Action type	Research and Innovation Action (RIA)
Submission & evaluation process	2 Stages

Specific challenges to be addressed

Although the industrial animal cell technology has become a well-established platform for biopharmaceutical production, substantial issues remain, calling for increased research and innovation. The absence of predictive tools and the poor understanding of how bioprocesses impact cell and protein quality increase production risks and costs. There is a need for the development of innovative analytical technology, leading to faster, leaner, more controllable, cost-effective and more industrious production. This should lead to more effective products manufactured by predictive, economic and competitive processes and thus to more cost savings that benefit both industry and healthcare systems, whilst ensuring safety.

Animal cell technology has evolved from a fringe technology into a mainstream application, now accounting for more than 60% of all new drugs being brought to market. This technology focuses on the active use and application of cell-based technologies in the development and production of biopharmaceuticals. Fundamental questions in cellular and systems biology, physiology and bioprocess science relevant to animal cells remain unresolved. A better control and higher prediction of cellular behaviour in the manufacturing of biopharmaceuticals can only be secured by increased basic and applied research.

The cell culture process for the production of biopharmaceuticals has a big impact on quality and safety of the final product; this is well established for almost all quality attributes of biological molecules. Such attributes can relate to the molecule and its heterogeneity or to other process impurities.

- Molecule heterogeneity originates from different proteolytic processing, post-translational modifications resulting in multiple glycoforms, diverse phosphorylation, additions, isomerisation, amino acid changes, oxidation, deamidation, acetylation, pyro-glutamate formation.
- Process related impurities are host cell proteins, lipids and DNA; process reagents or process components that are challenging to remove such as antifoam, shear stress polymers (poloxamer), or media additives.

A well understood process will have gone through a thorough and detailed evaluation of the cell culture parameters on the cell culture and harvest quality attributes. Today's use of high-throughput, scale-down cell cultures allows the use of large experiments to evaluate the cell culture process. Linking this with high-throughput analytics to measure cell culture and harvest parameters, and quality attributes, increase the efficiency of such experiments and provide a good basis for process understanding and the establishment of quality by design (QBD). In addition, the development of new methods to measure the attributes that are not yet well characterised with routine methods will help improve the robustness of the purification process and overall the quality of the biopharmaceuticals. Finally, analytical methods may also be used to provide direct control (process analytical technology, i.e. PAT) of the cell culture and/or harvest operations based on automated feedback controls.

Need and opportunity for public-private collaborative research

Development of novel analytics to measure cell culture parameters and product quality attributes will lead to increased efficiency of the animal cell production platform, and provide a basis for process understanding that will lead towards a more economical production of biopharmaceuticals. Special expertise is required for these developments and requires great flexibility as well as in-depth knowledge of chemistry/technology and equipment design, automation and engineering. As these developments are not the core business of the biomanufacturing companies, there has been little significant innovation in this field. Consequently, most methods currently used for monitoring and controlling the cell culture process are the same as 20 years ago and not well adapted to the challenges given the increase in complexity of cell culture processes, the variability of the raw materials and the move to disposable technology. Most innovation in this area comes from academia and smaller companies. However they struggle with the translation and validation of their new technologies due to limited availability of opportunities for testing in real conditions and lack of financial resources.

A joint venture of SMEs, academia and the pharmaceutical industry raises the chances to develop these new urgently required tools, in particular if researchers and industry collaborate by combining their knowledge and tools.

Scope

The overall objective is to develop/determine the best high-throughput or novel analytical and/or feedback control methods/tests to be used for the parameters that need to be measured during manufacturing of biopharmaceuticals, in particular the cell culture. The cell culture process, with all its individual and critical steps for the production of a biopharmaceutical, has an essential impact on the quality of the final product. Monitoring and subsequent adjustments (process analytical technology (PAT)) of cell culture processes ensure the manufacturing of biopharmaceuticals with a consistent quality that meets specifications according to regulatory requirements every single time. Analytical tools and methods that could lead to this are the scope of this project.

A modern production process is based on a systematic and comprehensive evaluation of the cell culture parameters (e.g. media components, feeding regiment, seeding density, pH, temperature, aeration level) and harvest outputs (viable cell concentration and density, metabolites, titer and molecule attributes). High-throughput scale-down cell culture and –omics sciences (genomics, proteomics, metabolomics…) allows the use of large experiments (design of experiments, DOE) to evaluate the impact of those parameters and to develop fast and simple analytical control methods that can be used in a PAT-guided system.

High-throughput methods

Several aspects need to be considered to establish high-throughput methods/analytics. The testing volumes should be small, leading to miniaturisation and automatic sample preparation to enable fast (at-line, online) testing, eliminating time-consuming testing in laboratories away from the bioreactors.

Novel methods

The research would lead towards novel technologies for online non-invasive testing, such as spectrophotometric methods and technologies to test cell culture conditions. Parameters to be measured are cell density, viability, sugars, amino acids, metabolites, trace elements, vitamins, lipids, titer, molecule attributes and contaminants. For harvest, parameters like particle size, redox, enzymatic assays and turbidity could be tested on-line in addition to the molecule attributes.

Feedback control

Once the analytical method has been developed, parameters that have an impact on the attribute can be adjusted to bring the attribute to the desired level. The automated controls, algorithm or data analysis needed to perform such modelling and feedback control would be beneficial for a better control of manufacturing operations.

Finally, all these efforts result in an increasing amount of biochemical data that calls for the development of knowledge and data management tools essential to maximally explore these datasets and to push strategies for future concepts.

Expected key deliverables

The expected deliverables from the project are the development and qualification of the following high-throughput and/or novel methods:

1) methods for high-throughput testing, novel analytical methods or feedback control and related elements that measure key attributes of cell culture processes (preferably technologies that are mature enough to be applied without the need of a dedicated scientist in the field of this application, and technologies that are good manufacturing practices (GMP) and designed to facilitate their validation);
2) novel miniaturized microfluidic-based technologies that allow real-time, automated, high-throughput product quality target product profile (QTPP) monitoring and control of cell culture processes;
3) online/at-line or in-line tools for parameter measurement;
4) new technologies for cell culture development and the selection of these technologies so that they can be applied in GMP manufacturing to allow for PAT control for full scale;
5) best suited instruments and/or tools to perform the analytical methods;
6) tools to measure critical process parameters;
7) better process understanding;
8) high-performance single-use sensors for the disposable bioreactors;
9) data management tools: tools for the integration of data and data management enabling the efficient use of the raw measurement data that will be generated by the new technologies and new applications of existing technologies;
10) knowledge database and the appropriate statistical tools to make useful knowledge of the data generated and to make use of this data to gain more in-depth knowledge of the cell culture process, metabolic pathways and quality of product to be expected.

Expected impact

Through this project, innovative analytical tools developed by academic partners and SMEs can get **translated**, **validated** and **implemented** at larger companies for commercial purposes, making the partners stronger in a highly competitive environment. An added impact could be the creation of spin-offs specialized in these analytical tools.

The innovative analytical tools guarantee a more effective control and execution of the production phase and will lead to the qualitative and consistent manufacturing of biopharmaceutical therapies, increase supply chain reliability and reduce drug shortages, securing the delivery of these therapies to patients who need them. This means also production of biopharmaceuticals in a more predictable and more cost-effective way, potentially leading to lower overall costs of biopharmaceuticals.

An important share of the analytical tools developed as part of the project will be immediately ‘fit for use’ in the manufacture of advanced therapies medicinal products (ATMPs: cell therapies, gene therapies, organoids, genetically modified cell therapies…), others would probably need small adaptations but could be quite useful as well.

With the ‘Biomanufacturing 2020’ vision, European industry will be taken to the next higher level of competitiveness where biopharmaceuticals can be produced in a more efficient and cost effective way, substantially increasing the significance of the European biopharmaceutical industry.

Potential synergies with existing consortia

Despite the fact that biomanufacturing is one of the major steps in the development process of innovative biopharmaceuticals, none of the currently funded IMI projects address bio-production specifically. Yet investigative research on general features of biomanufacturing can dramatically contribute to achieving a safer, faster and more cost-effective process for the production of a wide range of biopharmaceuticals, vaccines and advanced therapies. Furthermore, it can complement currently existing IMI projects by accelerating their implementation and production of new medicines. Indeed, the success of biopharmaceuticals in the last years has led to a permanent increase of this group of drugs, only dampened by their higher complexity and production costs. Thus, efficient and safe bio-production is a key factor to further facilitate the implementation and use of biopharmaceuticals.

Industry consortium

The industry consortium is composed of the following EFPIA companies:

- Sanofi (lead)
- Bayer
- GSK
- Pfizer
- Rentschler Biotech
- Synthon
- UCB

The expertise brought by the industry consortium to the project includes: high throughput, biopharmaceuticals, cell line development, robotics analytical testing, quality by design, sample preparation, sample technology, data handling tools, modelling, feedback control.

Indicative duration of the action

The indicative duration of the action is 48 months.

Indicative budget

The indicative EFPIA in-kind contribution is EUR 4 700 000.

The financial contribution from IMI2 is a maximum of EUR 4 700 000.

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

Applicant consortium

The applicant consortium will be selected on the basis of submitted short proposals. The applicant consortium is expected to address all the objectives and make key contributions to the defined deliverables in synergy with the industry consortium which will join the selected applicant consortium in preparation of the full proposal for stage 2.

The applicant consortium is expected to develop or adopt innovative, on- or at line methods, methodologies, instruments, tools and technologies of high throughput and small quantities. The applicant consortium should include academic and especially SME partners demonstrating expertise to/in :

- develop innovative, automated highly-sensitive measurement tools and high-throughput measurement methods for proteins, lipids, growth factors, amino acid, vitamins, nucleotides, CO_2, O_2, lactate, glutamate, ammonium, Lactate Dehydrogenase (LDH);
- develop high-throughput tools to measure product quality attributes like purity, binding/activity, aggregation, glycosylation, phosphorylation, de-amidation, oxidation, MW, isomers;
- develop innovative micro-scale fed-batch cultures;
- develop rapid spectrophotometric methods for cell culture monitoring (Raman, NIR, Fourier transform infrared spectroscopy (FTIR), nuclear magnetic resonance (NMR)) for in-line CHO cell culture monitoring;
- high-throughput screening (HTS) assays;
- 'omics' method development (proteomics, metabolomics, glycomics…);
- develop process analytical technology for biopharmaceutical products;
- management, interpretation and modelling of complex data sets;
- development and manufacturing of online probes and of devices for aseptic at-line sampling and rapid sample preparation.

Suggested architecture of the full proposal

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

The final architecture of the full proposal will be defined together with the industry consortium in observance of IMI2 rules and in consideration of the project objectives.

In the spirit of the partnership, and to reflect that IMI2 Call topics are built upon 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.

Glossary

ATMP	Advanced therapies medicinal products
DOE	Design of experiments
FTIR	Fourier transform infrared spectroscopy
GMP	Good manufacturing practices
HTS	High-throughput screening
LDH	Lactate Dehydrogenase
NIR	NIR = Near-infrared spectroscopy

NMR	Nuclear magnetic resonance
PAT	Process analytical technology
QBD	quality by design
QTPP	Quality target product profile
WP	Work package

Topic 6: Unlocking the solute carrier gene-family for effective new therapies (unlock SLCs)

Topic details

Topic code	IMI2-2016-10-06
Action type	Research and Innovation Action (RIA)
Submission & evaluation process	2 Stages

Specific challenges to be addressed

The healthy functioning of living cells requires strict control over the import and export of ions, metabolites and nutrients across membranes. Highly regulated transport proteins fulfil this role, and it has been estimated that ~10% of the human genome is linked to membrane transport. The solute carrier (SLC) family is the largest class of such proteins (~400 members), and SLCs play vital roles across practically all cell types in all tissues. For example, the SLC2 glucose transporters regulate 'fuel' uptake into tissues such as skeletal muscle and adipose tissue in response to the varying demands of the body. SLCs are also of great importance in controlling tissue distribution of drugs. For instance, the varying therapeutic index of statin drugs is believed to be governed by their differential uptake into liver versus skeletal muscle, mediated by solute carrier organic anion transporter (SLCO) transporters.

The importance of SLCs in disease can be illustrated by human genetic data which suggest that roughly 50% of SLCs are associated with a human disease-related phenotype compared to a rate of only ~20% for the broader human genome. Some notable recent examples include associations of single nucleotide polymorphisms (SNPs) in SLC30A8 and SLC16A11 with type-2 diabetes and SLC9A9 with autism. Dysregulation of SLCs appears to be a common feature in many tumour types.

SLCs appear to be generally small-molecule druggable and have given rise to a few important drug classes, such as the selective serotonin re-uptake inhibitors (SSRIs) for depression, and the SGLT2 inhibitors for diabetes. However, only ~2-3% of current drug targets are SLCs, whereas the similarly-sized Class A G-protein coupled receptor (GPCR) family make up about 25%. Furthermore, a recent publication analysis suggests SLCs are highly understudied, with >200 SLCs having less than 15 publications where the target is mentioned. These data suggest SLCs are heavily underexploited as drug targets [1].

The most heavily studied SLCs appear to be those highly expressed in easily isolated, important cell types such as SLC2A1 (GLUT1) and SLC4A1 (bicarbonate exchanger) both in erythrocytes, and the monoamine transporters which can be studied in synaptosomes. A significant barrier to the study of SLCs is gaining access to relevant reagents and cell systems in which they are expressed – which is also consistent with their nature as complex multi-spanning integral membrane proteins (IMPs).

This proposal aims to unlock the therapeutic potential within the SLC gene family by overcoming many of the technical barriers that have hindered their study and prevented their exploitation as drug targets by generating research tools and by making them freely available to the scientific community.

Specific technical barriers that if overcome would help unlock the therapeutic potential of the SLCs include:

- knowledge of the endogenous substrates for each SLC;
- access to cell systems and/or reagents which express the whole of the SLC family;
- access to purified SLC proteins and/or cell free systems in which SLCs are expressed – such as proteoliposomes – to allow for more detailed study of the proteins;

- high-quality antibody reagents for SLCs, e.g. to allow the study of tissue and cellular locations, and trafficking of SLCs;
- methods to study the SLC interactome in order to identify obligate binding partners necessary for SLCs to be functional (which appears to be a common phenomenon);
- application of interactome data to the study of regulatory processes for SLCs;
- novel methods of screening for modulators of SLCs – particularly those which allow the study of transport across intracellular membranes.

The SLCs have recently gained significant attention in the scientific literature, with a commentary article recently published making the case for a more systematic study of SLCs [1] and a further article making the case for SLCs as an emerging drug target class [2].

Need and opportunity for public-private collaborative research

Advances in a range of scientific disciplines and methods hold great promise to rapidly accelerate the field, particularly if applied in concert. These include:

- advances in techniques for the production, isolation and characterization of integral membrane proteins largely driven by the structural biology field;
- techniques for re-incorporation of purified proteins into membranes in cell-free vesicle systems;
- metabolomic techniques may be applied for the more rigorous characterization of endogenous SLC substrates;
- advances in methods for studying protein interactomes may allow the identification of obligate binding partners for SLCs and help uncover regulatory mechanisms;
- new physical methods and techniques for the detection of membrane transport, for example based on membrane potential and/or cell impedance, may facilitate more reliable and cost-effective high-throughput techniques of screening against SLCs;
- gene-editing capabilities hold the promise of accelerating SLC research through the generation of knock-in and knock-out cell lines for the whole family.

However, the scale of work required to unlock the SLCs is beyond the reach of any single company or institution with near-term horizons. No single company or institution would have the scale of resources or the breadth of scientific expertise to take on this challenge. The benefits of a consortium approach involving public-private partnership would be substantial in providing a large acceleration to the science of SLCs.

The combination of state-of-the-art inputs and expertise from industry, together with the agility and validated capabilities of SMEs and the novel approaches and insights of academic researchers will ensure that new tools and methodologies will be developed, validated and implemented by the research community much more rapidly than if single companies or institutions acted alone. It is expected that the science and technology developed in this collaborative research project will lead to advances in basic academic research through increased capabilities to delineate the fundamental roles that SLCs play in health and disease. Thus, the discovery of new SLC drug targets will be accelerated.

Further, the results from this project will lead to the development of scientific tools and methods that will increase speed and efficiency in applied research, e.g. accelerated prosecution of drug discovery programs targeting SLCs and increased scope of SLC targets that can be effectively prosecuted. It is anticipated that these advances will benefit large pharmaceutical companies and SMEs alike through providing new opportunities for drug discovery projects and/or services in support of drug discovery.

Overall, we believe this public-private partnership will lead to an acceleration in the discovery of effective, new medicines for patients suffering from a range of diseases, to the benefit of society at large.

Bringing together a consortium of leading pharmaceutical companies, academic groups and SMEs through the IMI scheme to make a system-wide attack on the family will lead to the step-change in knowledge and capabilities required to unlock the potential of the SLCs.

Scope

The scope of this project is to 'unlock' as much of the SLC family as possible to enable drug discovery efforts to be conducted 'at will' across the whole family of ~400 proteins. In order to achieve this goal we believe it will not be necessary to study all SLC proteins to the same depth. In order to simplify workflows, the project will be divided into two parts and the scope is different for these two halves of the proposed work plan.

- The scope of the first half of the project is broad and ambitious (aiming for >80% coverage of the gene family) in the areas of transporter deorphanization (identification of endogenous substrates for transporters), generation of cell lines expressing SLC family members, and in the development of new screening methodologies. These are areas where more radical innovation from the public contributors will be required to achieve the goals of the project (work packages 1-2).
- The scope of the second half project is more focused (on roughly 20% of the gene family) in areas where the proteins will be studied in more detailed and resource-intensive fashion e.g. in the study of the transporter interactome (work packages 3-6). It is anticipated that knowledge, reagents and methods gained from this subset of the SLCs will provide an accelerator for other researchers (outside of this proposal) to study additional SLCs.

Expected key deliverables

Overall we aim to deliver new research tools, techniques, reagents, and knowledge to the biomedical research community such that on completion of the five-year project, the pace of research in the field of SLCs will markedly increase, thus leading to accelerated discovery of new drug targets and drugs which target SLCs. Specific key deliverables are listed below.

Gene Family Wide Deliverables:

- generation of cell systems which express – in functionally competent form – a large majority (>80%) of the ~400 SLCs;
- generation of a methodology to 'deorphanise' (identify endogenous substrates for) the large majority (>80%) of the ~400 SLCs, and application to rigorously assign endogenous substrates for the vast majority of SLCs (e.g. using metabolomics methods);
- development of novel, broadly applicable screening methodologies for SLCs:
  - for example, use of purified recombinant proteins in cell-free vesicle systems;
  - aim for screening methods to be available that would be applicable for >80% of the gene-family;
  - aim to develop specific assays that cover >50% of the protein family;
  - aim to develop novel assay methodologies for SLCs located in intracellular compartments (currently a particular challenge).

Deliverables for a Focused Set of ~72 SLC Targets:

- generation of purified SLC protein and/or cell-free systems containing e.g. proteoliposomes systems, that will facilitate the detailed study of SLCs;
- generation of high-quality biochemical reagents and techniques for studying the focused set of roughly 60 SLC family members:
  - highly selective SLC antibodies, e.g. to study SLC localization at tissue and/or subcellular levels;
  - techniques to define the interactome of SLC members to build knowledge of obligate binding partners and regulatory mechanisms;
- generation of high-throughput screening assays for studying a focused set of SLCs;

- either directly through this project or through collaboration with the ULTRA-DD project[15] we may also elect to:
  1) leverage the protein reagents developed in the project to invest in X-ray crystallography of SLC proteins in order to:
     - increase the number and diversity of SLC protein structures in the public domain;
     - accelerate advances in structure function knowledge of SLC transport mechanisms;
     - drive capabilities in structure-based drug design at SLCs;
  2) leverage the SLC assays developed in the project to generate chemical tools that inhibit or modulate the function of SLCs.

Expected impact

This IMI project is expected to deliver new open-access research tools, techniques, reagents, and knowledge to the biomedical research community that will rapidly accelerate the pace of research in the field of SLCs. These advances are expected to impact both basic research and drug discovery alike.

Given the large size and untapped potential of the SLCs as potential drug targets, it seems certain that there are many new drug targets remaining to be uncovered within the family. Since SLCs are expressed in practically all cell types across all tissues, their therapeutic potential spans many disease areas, including oncology, immunology, neurosciences, metabolism and cardiovascular diseases.

Thus, it can be anticipated that this project will benefit patients and society through the accelerated discovery of new drugs targeting SLCs, which will provide effective therapies for a broad range of diseases.

Potential synergies with existing consortia

IMI Project Unrestricted Leveraging of Targets for Research Advancement and Drug Discovery (ULTRA-DD)

The ULTRA-DD project has a focus on integral membrane proteins (of which SLCs are a subset) including structural biology efforts and chemical probe generation. It is hoped that, if determined necessary, collaboration with this project for activities such as protein crystal structure determination and chemical probe generation may be possible where this is mutually beneficial for both projects. Such an interaction depends on the results produced by the consortium, the capabilities of the eventual project partners and would only be undertaken after discussion and agreement by consortium partners.

However, while a possible interaction may be foreseen in work packages 5 and 6, the possibility to conduct protein crystallisation and chemical probe generation directly within this SLC IMI project has been included.

Additional IMI projects which may have synergies with this SLC project

a) **European Lead Factory (ELF)** focuses on identifying novel leads from industry-scale chemical libraries to pioneer drug targets[16].

   The eventual project resulting from this topic will be developing high-quality protein reagents and biochemical assays. A partnership between this initiative and ELF would marry world-class screening capabilities with structure-enabled hit to lead science – thus providing synergy and efficiency in the generation of chemical probes.

[15] http://www.ultra-dd.org/
[16] http://www.imi.europa.eu/content/european-lead-factory

b) **Integrating bioinformatics and chemoinformatic approaches for the development of expert systems allowing the *in silico* prediction of toxicities (eTOX)**[17].

By deorphanising SLCs and by identifying potential drug-drug or drug-metabolite interactions mediated by SLCs, the results from this project could help inform the prediction of drug safety and side effects. Similarly, insights emerging from eTOX could help deorphanise SLCs.

c) **Oral biopharmaceutical tools (ORBITO)**[18] aims to enhance our understanding of how orally administered drugs are taken up from the gastrointestinal tract into the body and to apply this knowledge to predict the performance of drugs in patients.

By providing insight into the movement of small molecules (drugs and metabolites) into and out of cells, this project could provide insight into the uptake of drugs from the gastrointestinal tract and their subsequent distribution throughout the body.

The Structural Genomics Consortium

The SGC[19] focuses on a large number of protein families and has developed techniques to promote rapid structure determination, and also has an epigenetics chemical probe program. The SGC has a comprehensive approach on integral membrane proteins and experience with transporters. Therefore, there may be potential areas of interaction between this IMI project and the SGC, and thus coordination with SGC may be important to avoid duplication of effort and, if necessary, to establish a technology-exchange partnership. The SGC is also an important contributor to IMI's ULTRA-DD project.

Industry consortium

The industry consortium is composed of the following EFPIA companies:

- Pfizer (lead)
- Novartis
- Boehringer-Ingelheim
- Vifor Pharmaceuticals
- Sanofi
- Bayer

The EFPIA contributions will largely be in the form of *in vitro* biology resources, expertise and reagents in support of work packages 1, and 4-7.

EFPIA contributions will not be limited to these areas, however. For example, data and data-mining techniques may prove useful for work package 2. Support for protein crystallography and chemical tool generation may also be provided should these activities be undertaken as part of work packages 5 and 6.

Indicative duration of the action

The indicative duration of the action is 60 months.

[17] http://www.imi.europa.eu/content/etox
[18] http://www.imi.europa.eu/content/orbito
[19] http://www.thesgc.org

Future project expansion

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

This project has been planned in a way that it may interface with the currently running ULTRA-DD project for areas of structural biology and chemical tool generation. As a result, there are potential scenarios where it may be beneficial to expand the resulting SLC project into these areas of science e.g. if relevant results generated in ULTRA-DD can be capitalised in the SLC project to advance the state of the art.

Indicative budget

The indicative EFPIA in-kind contribution is EUR 12 000 000.

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

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

Applicant consortium

The applicant consortium will be selected on the basis of submitted short proposals. The applicant consortium is expected to address all the research objectives and make key contributions to the defined deliverables in synergy with the industry consortium which will join the selected applicant consortium in preparation of the full proposal for stage 2.

The applicant consortium (including where possible relevant SMEs) is expected to demonstrate expertise, leadership and a proven track record in the following areas:

- human genetic screens involving state-of-the-art human cell culture technologies for high-throughput assessment of individual and combination loss- and gain-of-function variants (e.g. human haploid cell culture, CRISPR or other genome-editing technologies, lentiviral or other suitable transduction systems for gene expression), preferably with prior experience with the SLC family;
- next-generation sequencing for high-throughput RNA and/or DNA sequencing, chromatin immunoprecipitation sequencing (ChIP-sequencing) technologies;
- applying mass spectrometry to understand systems-wide cellular changes in proteins and metabolites in response to environmental or other chemical perturbations, including:
    - methods applicable to the enrichment and evaluation of membrane proteins at scale;
    - methods suitable for the detection of protein-protein interactions (e.g. AP-MS, BirA-mediated BioID);
    - methods to detect, identify and quantify metabolites and other small molecules and to assess changes in these molecules (e.g. targeted metabolomics, LC/GC-MS, library of metabolites);
    - bioinformatics capabilities necessary to analyse systems-level data, also at the metabolite level;
- studies of physiologically and therapeutically relevant proteins;
- expression of human full-length membrane proteins or membrane protein domains in multiple systems (e.g. bacteria, eukaryotic cells), including expression vector design and expression strategies;
- production and characterization of recombinant protein binding tools [e.g. antibodies, Fab fragments, designed ankyrin repeat proteins (DARPins), nanobodies];
- *in vitro* and in-cell target engagement assays;
- quality control metrics established and used in practice;

- expression, characterization and structure determination of integral membrane proteins in an integrated project at large scale, adopting a family-coverage approach to systematically map the knowledge space (e.g. single-particle cryo-electron microscopy, X-ray crystallography);
- production and characterization of high-quality chemical probes in relevant biophysical, biochemical, and cellular/phenotypic assays.

The applicant consortium (including where possible relevant SMEs) is also expected to demonstrate excellence and a track record in the following areas:

- having an established network of recognized thought leaders in all relevant sectors, with a track record of success, as evidenced by collaborative publications:
    - a global network that spans chemistry, biological assays, human biology, and clinical research,
    - proven track record of achieving high-value/high-impact outcomes catalysing research in pioneer target areas of drug discovery,
    - history of collaboration with clinical researchers to achieve relevant results,
    - ethics approval to efficiently engage in such collaborations,
    - history of renewed research programmes,
    - ability and history of leveraging additional funds with a variety of organisations,
    - history of making research output widely available (open access),
    - sustainable mechanism in place to efficiently disseminate chemical and biological research materials (e.g. chemical probes, protein constructs, antibodies) and protocols,
    - mechanism in place to efficiently disseminate chemical and biological research materials (e.g. chemical probes, protein constructs, antibodies);
- successfully collaborating in a network with industry:
    - demonstrated impact on launching or adding value to internal drug discovery projects in the pharmaceutical sector,
    - demonstrated success in collaborations among networks of academics and SMEs – as evidenced through shared projects and co-authored publications,
    - demonstrated success in governing and managing large projects, including finance, intellectual property etc.,
    - demonstrated ability to consistently set and achieve milestones on time and within budget,
    - experience in managing varying interests of multiple stakeholders.

The applicant consortium may also require mobilising, as appropriate, public databases: such as Protein Atlas, Bioparadigms SLC Tables, IUPHAR Guide to Pharmacology.

Suggested architecture of the full proposal

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

The final architecture of the full proposal will be defined by the participants in compliance with the IMI2 rules and with a view to achieving 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 below architecture for the full proposal is a suggestion; different innovative project designs are welcome, if properly justified.

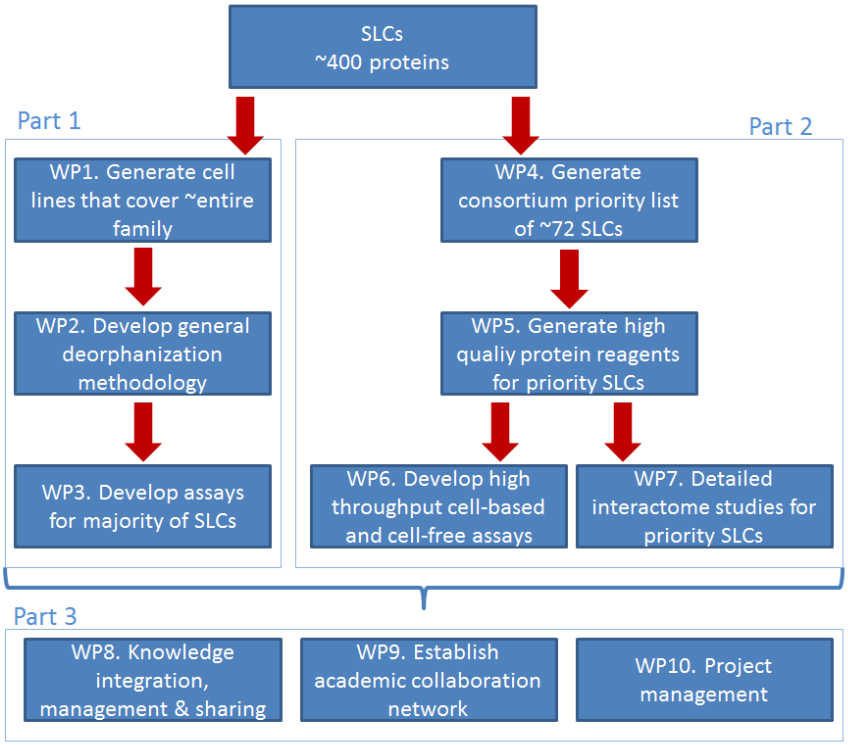

Fig 1. Overall project architecture

Part 1 – SLC gene family wide phase

(Part 1 to run concurrently with Part 2)

Work package 1: Generation of cell lines to allow system-wide study of the entire SLC gene family

Deliverable: Validated cell systems that express functionally competent SLC proteins that cover the whole family and are applicable to transporter deorphanization campaigns.

Industry contribution:

- cDNA clones;
- endogenous and/or engineered cell lines for expression and/or knockdown;
- small molecule ligands to facilitate validation of protein transport;
- validated sh/siRNAs (or CRISPR reagents) for generation of knockdown cell lines for antibody validation.

Expected applicant consortium contribution:

- design of experiments;

- cDNA clones;
- supply of cells from mouse KO and transgenics of SLC proteins;
- additional endogenous and/or engineered cell lines/types for expression and/or knockdown;
- validated sh/siRNAs (or CRISPR reagents) for generation of knockdown cell lines for antibody validation.

Work package 2: Development of transporter 'deorphanization' methodology(ies) with an aim to apply system-wide to the whole SLC family

Deliverable: New technique(s) able to determine substrates (endogenous and potentially also exogenous) for currently orphan transporters. Through application of these techniques to cell lines delivered from work package 1, assign endogenous (and potentially also exogenous) substrate(s) for >80% of all human SLC.

Industry contribution:

- small molecule ligands to facilitate validation of protein transport;
- metabolomics assistance.

Expected applicant consortium contribution:

- design of experiments;
- mass spectrometry expertise – targeted and untargeted metabolomics;
- other biophysical methods that may be applicable to the problem.

Work package 3: Development of quantitative transport assays for >50% of the SLC family

Deliverable 3: Use cell line and deorphanization knowledge developed in work packages 1-2 to deliver quantitative transport assays covering at least 50% of the SLC family.

Industry contribution:

- assay development capabilities;
- high-throughput screening methodologies, technologies.

Expected applicant consortium contribution:

- design of experiments;
- mass spectrometry expertise – targeted and untargeted metabolomics;
- other biophysical methods that may be applicable to the problem.

Part 2 – Detailed study of prioritized SLCs

(Part 2 to run concurrently with Part 1)

Work package 4: Selection of the 'SLC priority list' of targets. Each EFPIA consortium member is able to select 12 SLCs.

Deliverable: Consortium-approved **SLC priority list** to study in detail in work packages 5-7.

Industry contribution:

- each member to propose a list of priority SLC targets;
- targets may be selected for their interest as drug targets, their role in drug distribution and pharmacokinetics, or their role in toxicology;
- members may use public domain or in-house knowledge to inform their initial proposal.

Expected applicant consortium contribution:

- advisory role on the selection committee. Leveraging ability to draw on expert knowledge, and large-scale, public-domain, integrative genomic and bioinformatics datasets from publicly available data and other EU-based consortia;
- in collaboration with industrial partners, create an action plan for each target/set of targets including which target/target family is prioritized by each industrial member.

Work package 5: Generation of protein reagents, protein expression and purification for proteins on the SLC priority list

Deliverable 5a: Generation of validated functionally competent purified SLC protein. Protein expression clones, protein purification protocols, high quality recombinant antibodies; all to be made publically available.

Industry contribution:

- cDNA clones for priority human protein targets;
- cell lines for expression;
- small molecule tools (substrates, ligands, imaging agents etc.) to facilitate protein expression and/or purification;
- validated sh/siRNAs (or CRISPR reagents) for generation of knockdown cell lines for antibody validation.

Expected applicant consortium contribution:

- design of expression vectors;
- protein expression for integral membrane proteins, relevant protein complexes in multiple systems (bacteria, eukaryote), likely including multiple expression strategies (e.g. constructs of different lengths, site-directed mutants);
- purification of human proteins, human integral membrane proteins, human protein complexes;
- protein characterization (e.g. mass spectrometry to characterize novel high-priority protein complexes, and to assess relevant post-translational modifications);
- generation of high-quality, validated antibody reagents (possibility through collaboration with commercial antibody vendors);
- recombinant binder production (e.g. Fabs, darpins, camelids etc.) for high-priority proteins to facilitate assay development and protein characterization.

Although not a core aspect of this work package, upon access to these protein reagents the project may elect in certain circumstances to use these reagents in the generation of protein crystal structures – either directly as part of this project, or where mutually beneficial through collaboration with other initiatives. This will be determined by an analysis of the results and after consultation with consortium partners. It is therefore suggested that applicants ensure that they have expertise necessary to undertake the activities under deliverable 5a but also have the expertise necessary or have ready access to the expertise to undertake deliverable 5b.

Deliverable 5b (if undertaken): Protein structure data, where generated, will be deposited into the protein data bank prior to publication in papers.

Industry contribution:

- small molecule ligands to promote protein crystallization;
- access to synchrotron beamlines.

Expected applicant consortium contribution:

- infrastructure and expertise to carry out protein and protein-ligand crystallization and X-ray structure determination. Development of new, high-throughput methods to generate co-crystals of proteins and protein complexes;
- develop mechanism to access X-ray free electron laser technology as potential 'game-changer' for hard to achieve structures.

Work package 6: Generation of robust cell-based (high-throughput) and/or cell-free assay systems for all proteins on the SLC priority list

Deliverable 6a: Experimental conditions for 72 high-quality, cell-based (if not delivered in work package 3), biochemical and biophysical assays for proteins on the prioritized list, all to be made publicly available.

Industry contribution:

- cDNA clones;
- endogenous and/or engineered cell lines for expression and/or knockdown;
- small molecule ligands to facilitate validation of protein transport;
- validated sh/siRNAs (or CRISPR reagents) for generation of knockdown cell lines for antibody validation;
- define assay parameters;
- contribute assays, reagents and know-how to the partnership.

Expected applicant consortium contribution:

- develop and implement new biochemical and/or biophysical assays to measure SLC inhibition/binding;
- mass spectrometry expertise;
- additional biophysical methods suitable to this application.

Although not a core aspect of this work package, upon gaining access to these robust high-throughput, cell-based and/or cell-free assays, in certain circumstances the project may elect to engage in chemical hit identification and chemical probe generation, either directly in this project, or where mutually beneficial, through collaboration with other initiatives. This will be determined by an analysis of the results and after consultation with consortium partners. It therefore suggested that applicants ensure that they have expertise necessary to undertake the activities under deliverable 6a but also have the expertise necessary or have ready access to the expertise to undertake deliverable 6b.

Deliverable 6b (if undertaken): Well-characterized chemical probes, meeting stringent criteria for potency, selectivity, and with demonstrated on-target effects in cells.

IP requirements should match those of similar chemical tool generating consortia e.g. SGC Epigenetic Probes Consortium, i.e. with final chemical probe being unpatented, with other compounds screened and generated during probe generation to stay blinded from public domain.

Industry contribution:

- computational chemistry to select and prioritize compounds for screening;
- design and access to fragment or other bespoke libraries;
- focused screens to identify hits;
- expertise in triage and validation of screening hits;
- logistics, automation or infrastructure support of academic partners;
- design and access to fragment libraries;
- assays (e.g. selectivity screening panels) and structure determination to support probe development;
- design and synthesis of research chemical probes.

Expected applicant consortium contribution:

- mechanism to access chemical libraries from leading academic chemists and chemical biologists;
- small-scale screening of fragment and industry-partner chemical libraries;
- secondary biochemical screens to validate and prioritize hits;
- protein-ligand structure determination to support probe development;
- establish quantitative chemical probe criteria;
- explore interactions with the European Lead Factory (see Possible synergies, Section 2.a.), thereby leveraging the value of the IMI investments.

Work package 7: Definition of interactome and regulation for the SLC priority list

Deliverable 7a: Generation of interactome data for prioritized SLC proteins, ideally in endogenous cell lines in basal state and upon cellular challenge/stimulation.

Deliverable 7b: Application of bioinformatics to interactome datasets to propose regulatory mechanisms for the SLC priority list.

Industry contribution:

- endogenous and/or engineered cell lines for expression and/or knockdown;
- cDNA clones;
- validated sh/siRNAs (or CRISPR reagents) for generation of knockdown cell lines for antibody validation;
- antibody reagents;
- bioinformatics expertise and resources.

Expected applicant consortium contribution:

- mass spectrometry, proteomics expertise;
- expertise in the study of interactomes and regulatory mechanisms for integral membrane proteins;
- other 'omics' platforms suitable for application to interactome studies.

Part 3 – Integrating and sharing knowledge gained from the consortium

Work package 8: Knowledge integration, management & sharing

Deliverable: Develop mechanism to integrate all publicly available literature on the SLC family, building upon extant data sources such as: the Bioparadigms dataset (http://slc.bioparadigms.org/) or the IUPHAR Guide to Pharmacology database (http://www.guidetopharmacology.org).

Industry contribution:

- Chem-informatics analysis of hits, probes and public domain chemical probes for SLCs.

Expected applicant consortium contribution:

- bio-/chem-informatics to aid in design and dissemination of data from work packages 1-7;
- mining of this resource to facilitate target selection into SLC priority list (see work package 4);
- annotation of proposed targets with enabling resources, for example existing cell lines, substrate knowledge, interactome data, structural information, knockouts, etc.;
- electronic lab notebooks to facilitate data sharing among partnership.

Work package 9: Collaborative network outside of consortium

Deliverable: A functioning network of academic and clinical research collaborators, with a strategy to initiate collaborations, define expected outcomes, monitor progress toward the objective, and a mechanism to terminate unproductive collaborations, if necessary.

Industry contribution:

- generate a list of key opinion leaders for potential collaboration.

Expected applicant consortium contribution:

- identify a list of key opinion leaders for potential collaboration;
- develop and implement a mechanism to initiate, monitor and manage or terminate (if necessary) collaborations;
- implement a robust and sustainable mechanism to communicate results from IMI project;
- make results and research tools publically available (open access);
- make results and research tools publically available in an efficient manner and according to pertinent standards (e.g. as being defined by OpenPHACTS);
- implement a plan to partner with disease foundations, where applicable;
- implement a strategic plan to liaise with other IMI consortia, with timelines and metrics of success.

Work package 10: Project management and translation of results

Deliverable: A management structure that ensures that the project meets its deliverables, integrating input from academic and industry partners.

The management plan must describe how progress against milestones will be monitored and actions to be taken if progress against milestones is not adequate. In addition, the plan must describe an IP and data sharing strategy that allows data and reagents to be made as widely available as possible and in as timely a manner as practicable without restrictions to spur further research without prejudice to applicable rules.

A joint steering committee will govern the project in all aspects, including scientific direction, resource allocation, progress monitoring, quality assurance for all research outputs, IP etc. The joint steering committee will also clearly articulate research outputs to be made publically available, and any research outputs that might remain confidential to participating academic, SME and industry consortium members.

Industry contribution:

- senior scientist to represent company on joint steering committee;
- experts in drug discovery to manage collaborations in specific scientific areas or on specific targets;
- contributions to collaborative scientific meetings, management of internal versus external activities;
- legal contributions to manage collaborative agreements.

Expected applicant consortium contribution:

- an outstanding scientific and management plan is required to ensure the success of the consortium, to identify new scientific opportunities, and identify and build strategic partnerships with other projects (e.g. international consortia, other IMI projects);
- senior scientists to manage projects to deliverables, to disseminate the project output and to engage in collaborations to maximize impact;
- exchange of scientists among academic and industry partners to ensure that all participants benefit maximally from the collaboration;
- manage finances, valuation of deliverables, IPR, communication etc;
- disseminate results in the form of publications, meeting presentations, and via the consortium's website.

Glossary

AP-MS	Affinity-purification mass spectrometry
BirA-mediated BioID	BirA-mediated biotinylation
ChIP	Chromatin immunoprecipitation
CRISPR	Clustered regularly interspaced short palindromic repeats
DARPins	Designed ankyrin repeat proteins
DNA	Deoxyribonucleic acid
IMP	Integral membrane proteins
KO	Knock out
LC/GC-MS	Liquid chromatography/ Gas chromatography–mass spectrometry
RNA	Ribonucleic acid
SGC	Structural Genomics Consortium
SGLT2	Sodium-dependent glucose cotransporter 2
Sh/siRNAs	Short hairpin/small interfering RNA
SLC	Solute carrier
SLCO	Solute carrier organic anion transporter
SNP	Single nucleotide polymorphism
SSRI	Selective serotonin re-uptake inhibitors
WP	Work package
Deorphanization	In the context of SLC transporters we refer to the identification of endogenous substrate(s) of transporters
Interactome	In the context of SLC transporters we refer to the set of proteins which interact with a given probe SLC protein
Metabolomics	In the context of SLC transporters we refer to scientific study of chemical processes involving metabolites, usually involving mass spectrometry methods

References

[1] Cesar-Razquin A, Snijder B, Frappier-Brinton T, Isserlin R, Gyimesi G, Bai X, et al. A Call for Systematic Research on Solute Carriers. Cell. 2015;162(3):478-87.

[2] Lin L, Yee SW, Kim RB, Giacomini KM. SLC transporters as therapeutic targets: emerging opportunities. Nature reviews Drug discovery. 2015;14(8):543-60

Topic 7: Patient perspectives in medicines lifecycle

Topic details

Topic code	IMI2-2016-10-07
Action type	Research and Innovation Action (RIA)
Submission & evaluation process	2 Stages

Specific challenges to be addressed

There is a growing body of evidence showing that patient-stakeholder engagement at key decision points throughout the medicines life cycle (from early development to outcomes monitoring) can drive better innovation and process efficiency and quality. Processes and outcomes become more relevant to individual patients, patient groups, healthcare consumers in general and society at large when they are based on a mutual understanding between patients, other healthcare stakeholders and manufacturers about their respective needs.

Many initiatives have been started that focus on bringing the patient closer to the centre of medicines development, authorization and reimbursement processes in the EU [1] [2] [3]. Progress, however, remains too slow, mainly because of lack of harmonisation.

- There is no clear alignment amongst stakeholders on the nature and value of patient engagement at different points of the medicines lifecycle. This results in inconsistent engagement, often leading to the absence or under-representation of patient insights.
- There is a lack of broadly accepted tools, processes, guidance and capabilities amongst stakeholders, resulting in the use of anecdotal and/or fragmented information. For example, many patient groups lack internal resources (people, time, mobility, legal) and the general capability to engage with multiple and different types of stakeholders.
- Perceived or real differences amongst organisations' conflicts of interest rules block progress.

Therefore, there is a need to establish transparent and integrated standards that permit patient involvement during the medicines lifecycle (including associated products and services). The resolution of four specific issue groups is required to make progress: recognition of the validity and value of such engagement; metrics to demonstrate value; capability development; and rules of engagement (for further information see Scope).

Need and opportunity for public-private collaborative research

- Interaction between patients and industry is a very sensitive matter that requires a formal and neutral framework such as IMI to ensure maximum transparency and buy-in by all stakeholders.
- There should be no discussion about patient involvement without patients.
- Patient engagement happens, or should happen, across the entire value chain (from early development through reimbursement decisions to commercialisation and on-going benefit-risk assessments and tracking outcomes) and it has an impact on all R&D processes that deliver data for and via authorities. Therefore, it is important for these authorities who review data that reflects patient perspectives, to be actively involved in defining the standards and objectives for such patient engagement.
- Academic and industry research (sponsorship) is closely interconnected and thus needs similar tools, processes and guidance to engage with patients. This requires alignment of and input from all those

stakeholders in order for the tools and standards to be useful for all constituents and raise standards across the board.

- Current and new patient engagement processes in R&D, regulatory and health technology assessment (HTA) processes should require selection criteria that all stakeholders support, as well as independent scientific evaluation and value evaluation by patients.

The project will address the above needs and deliver solutions to all stakeholders in medicines R&D (e.g. patients, authorities, academia and industry sponsors/researchers) in both public and private research settings.

Scope

In the context of this proposal, the scope of the term 'patient' includes those people who have the medical issues or symptoms as well as those caring for or living with them.

This project represents an opportunity to enable patients to better reflect their perspectives – in qualitative and quantitative terms – in the medicines pathways from discovery to outcomes monitoring and beyond. The input from those who are currently under-represented, or may not normally participate in critical decision-making is of particular interest, including patients not affiliated with patient groups, vulnerable populations such as minors or the elderly. In addition, it will provide a framework and guidance for all EU stakeholders about who and how to engage, when and what information is required, to ensure adequate input from patients and healthcare consumers.

The project will specifically aim at addressing several challenges that currently hinder productive patient-stakeholder engagement:

- **Adoption of practices by stakeholder groups by creating minimum expectations for effective engagement.** There are good examples of patient engagement practice. However, the landscape is still fragmented and this project offers the opportunity to make the practices more consistent across the research sector. It will also help to align efforts to measure the impact of specific types of practices on process efficiency, quality as well as the effectiveness of processes, results and decision-making based on the practices. A blueprint representing the minimum expectations on how to engage effectively, when, and with whom, along with metrics are needed to support implementation within industry (including companies operating globally) and healthcare authorities, as well as other decision makers. This will assist in determining the resources and capabilities necessary for implementing patient engagement across the medicines lifecycle. A blueprint which includes metrics will also help patients/advocates to determine where to focus time and resources in order to gain maximum benefit.
- **Engagement capability:** All stakeholders need to have defined knowledge, capabilities and be able to sustain their involvement in order to effectively and routinely be part of the engagement processes.
- **Rules of engagement**: Co-creation involving all the key players is required to ensure that each stakeholder's perspective is considered and to achieve ethical engagement. There are practical considerations that need to be taken into account when research and health-system decision makers, patients and health advocates are engaged; these need to be more clearly defined.

The project **will not** address policy development advocacy **nor** will it duplicate any deliverables specifically addressed under other IMI and relevant non-IMI-initiatives (see Synergies with existing consortia).

A number of patient engagement initiatives that will deliver tools and recommendations are currently under way and will continue. Beyond filling obvious gaps in the engagement toolkit/practice, the project will build on existing tools and learn from good and bad experience and advance their utility.

The project's aim is not intended to set a rigid framework or over-systematise patient-stakeholder engagement but instead to provide a blueprint and tools that will enhance engagement and make it a seamless part of the R&D and decision-making processes.

Expected key deliverables

The applicant consortium will select up to three specific stages of the medicines lifecycle or gateways/decision points and address several key problems that hinder the adoption of patient-stakeholder engagement. The proposed solutions will reflect the heterogeneity of patients (including unaffiliated patients) and their needs.

- **Deliverable 1: Defining minimal expectations (blueprint) for patient engagement aligned across key stakeholders (who, when, what, how)**

By bringing key stakeholders together, this project will align and generate valuable engagement criteria that are co-created by stakeholder groups (patients, industry, academia, regulators, HTA and payer authorities) as constituting valuable patient engagement. These criteria would either be based on existing initiatives and practices or developed to cover identified gaps. The output will be a more structured framework for expectations in patient engagement activities throughout the medicines pathways. This will include considerations on what type of patient stakeholders might be included in specific types of engagements (i.e. patients, caregivers, patient advocates or general healthcare consumers), as well as define what constitutes 'representative' patient input, methods of gaining input and how to address potential barriers linked to different patient segments and/or disease areas.

- **Deliverable 2: Application of these criteria to existing frameworks and tools, to establish good patient engagement practices**

Using the criteria developed in deliverable 1, this project will (if needed map and) evaluate existing patient engagement initiatives and projects. Framework developers and key stakeholders will work collaboratively to identify and evaluate existing practices and identify gaps. By engaging the developers in the evaluation, the project will provide an opportunity for them to update their existing frameworks and tools in order to strengthen their utility and value. This deliverable will include a list of frameworks and tools that meet the criteria listed in deliverable 1, as well as suggestions of whether additional frameworks and tools are needed to address gaps. The frameworks and tools will be selected through an open call conducted by the consortium. The consortium will define the selection criteria and conditions for testing them in regular practice and decision making.

Deliverables 1 and 2 will build on the tools, methodologies and experience existing at the project start and learn from their implementation as the project progresses.

- **Deliverable 3: A set of qualitative and quantitative metrics to evaluate the impact of:**
  - Patient engagement practices, tools, methodologies and strategies (i.e. does the practice lead to usable input that can be integrated at key decision-making points within the medicines lifecycle and greater efficiency and transparency of processes and decision-making?);
  - The influence of patient input on decisions made across the medicines lifecycle from both a sponsor and health-authority perspective (i.e. does the presence of patient input bring added value and inform decision-making across R&D and healthcare delivery processes?).

A set of metrics aligned across stakeholders for assessing the impact of patient engagement will allow more consistent evaluation of patient engagement activities and generation of an evidence base as to which practices and activities may produce results with the most impact. This set of metrics shall help all stakeholders to identify and select those patient-centric activities which are representing the best match for their individual situation and purpose in drug development/lifecycle of medicines.

Applicants may choose to address all or some parts of the medicines lifecycle.

- **Deliverable 4: Co-designed recommendations on the rules of engagement and capabilities required for patients, researchers/sponsors (industry and academia, those generating the data).**

  This will include:

  - standard capabilities and a patient engagement toolbox to support patient engagement with multiple stakeholders;

- clarification of what is (not) conflict of interest, as well as appropriate disclosure to ensure transparency;
- codes of conduct relevant to patient involvement (including gaps in data privacy and informed consent that are not addressed by other projects);
- models of appropriate compensations for patients.

These recommendations will allow for more consistent management of patient engagement activities that are aligned with the ethical standards of key stakeholder groups.

- **Deliverable 5: Communication strategy and implementation to share the above outputs (and key milestones) transparently across all stakeholders groups**

An ongoing and scalable communication is deemed more helpful to move the field forward than waiting and communicating final results at the end of the project. The impact of communication will also be assessed.

- **Deliverable 6: Sustainability plan and capacity building plan to keep deliverables up-to-date over time and develop knowledge, skills and behaviour**

The project will deliver both tools and mechanisms to enable the management as well as updating of practices, resources and other deliverables. This will help to ensure they are living documents that are accessible to all stakeholders as a live resource for the long term (potentially through a 'one stop shop'). Ownership by public partners will be preferred and a model for sustainable resourcing will be delivered. Any potential web-based tool would not include patient-level data or information.

Capacity building is an essential element of long-term sustainability. The project will therefore deliver tools and recommendations on defining roles and responsibilities as well as developing the required knowledge, behaviours and skills for R&D professionals, resources (human, financial, skills) for patients to engage, clarity on roles and responsibility at each step, etc.

Expected impact

The project is expected to advance patient engagement and medicines life cycle and make it more meaningful, systematic and effective. It will facilitate and further enhance patient perspectives in the process. This will be accomplished through creating more clarity on the process and provide patients and their partners in research with the tools that facilitate smooth and useful interaction. Enhanced and systematic engagement of patients and healthcare consumers in medicines lifecycle will ultimately contribute to:

- improved and sustainable innovation and meaningful outcomes for all stakeholders;
- successfully addressing objectives of IMI to reduce attrition, speed up patient access and improve patient outcomes and experiences.

The applicants will propose a course of action with the maximum impact for the patient communities and for the quality of interactions in the medicines lifecycle.

Potential synergies with existing consortia

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

IMI projects/consortia (examples):

- **EUPATI** (www.patientsacademy.eu)

- **ADAPT SMART** (www.adaptsmart.eu)
- **PREFER** (http://imi-prefer.eu)
- **EMTRAIN** (www.emtrain.eu)
- New project on patient engagement in Alzheimer Disease (AD) trials (see IMI2 Call 5 Topic 5, expected start date Q4 2016)
- Big Data for Better Outcomes projects (see IMI2 Call 7 topic 7, expected start date Q1 2017)
- **UBiopred** (http://www.europeanlung.org/en/projects-and-research/projects/u-biopred/home)

Non-IMI initiatives:

- DIA (http://www.diaglobal.org/en/get-involved/patients)
- ISPOR (http://www.ispor.org/sigs/patientcentered/pc_engagementinresearch.aspx)
- HTAi (http://www.htai.org/interest-groups/patient-and-citizen-involvement.html)
- Patient-Centred Outcomes Research Institute (PCORI) (www.pcori.org/)
- International Consortium for Health Outcomes (ICHOM) (www.ichom.org/)
- Patient Focused Medicines Development (PFMD) (http://patientfocusedmedicine.org/)
- National Health Council (NHC) (http://www.nationalhealthcouncil.org/meaningful-patient-engagement)
- Faster Cures (http://www.fastercures.org/)
- Clinical Trials Transformation Initiative (CTTI) (http://www.ctti-clinicaltrials.org/home)
- TransCelerate (http://www.transceleratebiopharmainc.com/)
- DIA-Tufts initiative on Return on Engagement (https://www.ciscrp.org/)
- AURORA project (https://www.linkedin.com/groups/8548998/profile)

The consortium may consider setting up an advisory board that will involve key IMI and non-IMI initiatives in patient engagement/perspectives field.

Industry consortium

The industry consortium is composed of the following EFPIA companies:

- EFPIA (lead)
- MSD (co-lead)
- UCB (co-lead)
- ABPI
- Amgen
- Bayer
- GSK
- Grünenthal
- Janssen
- Lilly
- Lundbeck
- Merck
- Novo Nordisk

- Pfizer
- Roche
- Servier
- VFA

The industry will contribute to the deliverables with the following expertise:

- chief medical officers, medical affairs, scientific affairs, chief patient (engagement/affairs) officers, patient advocacy expertise;
- clinical development;
- outcomes research;
- regulatory, HTA, market access and post-marketing requirements;
- business operations;
- data and knowledge management;
- project management;
- communication;
- legal, compliance;
- policy and regulatory expertise;
- IT and social media infrastructure, translation services, and other services as appropriate.

Indicative duration of the action

The indicative duration of the action is 30 months.

Future project expansion

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

Such further work may address evaluation and implementation of new practices and tools delivered by on-going IMI and non-IMI projects in order to complement for example the patient engagement toolkit and implement education and training for stakeholder, etc.

Indicative budget

The indicative EFPIA in-kind contribution is EUR 4 250 000

The financial contribution from IMI2 is a maximum of EUR 4 500 000.

Applicant consortium

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

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

- various types of patient groups (umbrella and disease specific), healthcare-consumers groups and patient experts – with proven patient-stakeholders engagement track record and publicly-known funding/income sources; the consortium will reflect the heterogeneity of patients (including unaffiliated patients) and carers populations and will enable participation and input from the relevant groups and individuals;
- regulators, HTA and payers from national or pan-European levels;
- healthcare professionals, including general practitioners and clinicians;
- academic experts in ethics, codes of conducts, performance evaluation;
- experts in point-of-care know-how and integration;
- experts in communication and knowledge dissemination (including social media).

The size of the consortium should be proportionate to the objectives of the project and be able to reach out to patient experts/groups and countries/regions that are under-represented in patient/stakeholders engagement. It is expected that patient groups and experts and healthcare consumer groups will account for a sizeable part of the public consortium. The consortium will also run an open call for recruitment of tools and practices that will be subject to evaluation.

Suggested architecture of the full proposal

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

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

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

Glossary

AD	Alzheimer disease
HTA	Health technology assessment
R&D	Research and development
WP	Work package

References

[1] EMA, The patient's voice in the evaluation of medicines, How patients can contribute to assessment of benefit and risk, October 2013. (http://www.ema.europa.eu/docs/en_GB/document_library/Report/2013/10/WC500153276.pdf)

[2] Hoos, Anderson, Boutin et all, Partnering With Patients in the Development and Lifecycle of Medicines: A Call for Action, DIA Therapeutic Innovation and Regulatory Science, April 2015.

[3] Anderson and McCleary, On the path to a science of patient input, http://stm.sciencemag.org/content/8/336/336ps11 27 April 2016 Vol 8 Issue 336 336ps11

Topic 8: Personalised medicine approaches in autism spectrum disorders

Topic details

Topic code	IMI2-2016-10-08
Action type	Research and Innovation Action (RIA)
Submission & evaluation process	2 Stages

Specific challenges to be addressed

Autism spectrum disorders (ASD) are common and severe neurodevelopmental disorders characterised by deficits in social communication and repetitive and restricted behaviours (including sensory anomalies). It is estimated that approximately 1% of children and adults are affected by ASD world-wide; that is nearly 5.5 million patients in Europe (EU).

Currently, no effective medical treatments for the core symptoms are available and prior drug trials have been largely unsuccessful. Over the past years, major progress in the understanding of the genetics of autism, the development of *in vitro* (e.g. patient-derived induced pluripotent stem cells (iPSCs)) and genetic animal models, and identification of several neurobiological phenotypes have opened new avenues for the identification of aetiology-based treatment targets. However, these advances were accompanied by increasing recognition of a further hurdle, namely the profound phenotypic and genetic heterogeneity between patients. For example, approximately 70% of people with ASD have one or more comorbidities, including epilepsy, intellectual disability, attention deficit hyperactivity disorder (ADHD), anxiety or depression, and others. Likewise, hundreds of risk genes (for ASD and other neurodevelopmental/psychiatric disorders) have been identified, yet each explains only a small percentage of patients. Last but not least there is poor understanding and knowledge on how the condition and the needs of the patients change in the different stages of life (e.g. in children, versus adolescents, versus adults with ASD). This highlights the need to move beyond one-size-fits-all treatment approaches and to develop stratified approaches that are tailored to the specific needs and biological profiles of particular patient subgroups.

To move the field forward, it is essential to build on the lessons learned from the failure of most previous medication trials in ASD. Potential reasons include:

1) the therapeutic targets may have been incorrect;
2) the same treatment was offered to a biologically and clinically heterogeneous collection of individuals;
3) reliance on subjective self- or observer-based reports;
4) lack of objective clinical outcome measures and biomarker endpoints that relate to the underlying pathophysiology;
5) use of small-scale (i.e. underpowered) trials that do not adapt to emerging data; and/or
6) poor alignment and experience of participating sites not using industry standards of good clinical practice (GCP) and rigor.

Thus, to overcome these bottlenecks, a strategic framework for the development of stratified medicine approaches in ASD is needed, which comprises three key stages:

1) validation and qualification of stratification biomarkers (e.g. genetic, molecular, such as inflammatory markers, neuroimaging, neurophysiology) to test drug responses in relevant patient subgroups;

2) development of a European-wide clinical trials network trained to GCP standards to facilitate large-scale (adaptive) clinical trials and the demonstration that the network is 'fit for purpose' to execute studies that are pivotal for the registration of the studied compound;

3) on the basis of the clinical studies, achieve a better understanding of the translatability of molecular mechanisms and drug effects between preclinical models and iPSC lines of particular patient subgroups with ASD by aligning *in vitro* (patient-derived iPSCs) and *in vivo* models leveraged from pre-existing European and international initiatives.

Moreover, new opportunities are emerging that could lead to the development of 'targeted' pharmacological interventions for stratified patient groups. These include new approaches into the aetiology and neurobiology of ASD with particular focus on: (i) genetic variants mediating synaptic structure and functioning and (ii) differences in brain anatomy, chemistry and connectivity in this condition. The characterisation of the genotypic and phenotypic differences underlying ASD might in the future be invaluable for stratifying the large range of different individuals on the autism spectrum into genetically and/or biologically homogeneous subgroups that might respond to similar targeted interventions.

Thus, a strategic framework for the development of targeted pharmacotherapies for ASD which harnesses research findings to develop transformational tools and capacities for future clinical development is a mandatory approach for this topic.

Need and opportunity for public-private collaborative research

In a field like that of ASD, underinvested because of the complexity of the disease and of the science, no critical mass exists in one region or one sector to make progress.

Developing new stratified medicine approaches in ASD requires a concerted effort of stakeholders that includes excellence in academia, the pharmaceutical industry, patients, advocacy groups, and regulatory authorities. For example, to test translatability of drug effects (new and/or repurposed) between (genetic) animal and patient-derived *in vitro* models, close collaborations between industry and academia are needed. Validation and qualification of stratification biomarkers requires consensus between academia, industry, and regulatory authorities and a critical amount of high-quality data to support the conclusions. Development of a 'trial-ready' Europe-wide clinical network relies on the interaction between academia and clinicians, patients and their families, and advocacy groups. Hence, translating basic science into the clinic cannot be achieved by a single entity but requires the definition of common strategies, setting new standards and the necessary critical mass created by all key stakeholders both from the private and public sides.

In addition, to achieve significant impact and drive a timely game change in the field for the benefit of the patients, it is necessary to kick-start the process by building from all available assets and learnings, and combining key resources globally, mobilising stakeholders in Europe and beyond.

To this end, the proposed IMI initiative would be a powerful and unique instrument, with the capability to significantly move forward the development of an evidence-based European-wide consensus on best treatment options for patients with high unmet needs, such as ASD patients. Most critically, to maintain a specific focus on the patient, the initiative is leveraging resources from two key United States (US) based disease foundations (participating as Associated Partners to IMI2) which are driven by patients and their families.

Indeed, while both European efforts (with the key driver being the IMI project EU-AIMS) and industry experience and expertise in clinical research in ASD remain fairly limited, significant resources and knowledge are currently available in the US, on both the academic and disease foundations side. These stakeholders are ready to make their resources and expertise available to IMI in order to build the necessary capacity within Europe, fully aligned with those in the US for the conduct of future clinical trials, and in parallel help to develop a unified approach to clinical science research on ASD which currently does not exist within Europe. This initiative will, for the first time, make European experts work hand in hand with US-based ones to bring Europe to the forefront of ASD clinical research. Beyond advancing the understanding of the disease and delivering potential treatments, the action has the potential to establish Europe in a leadership position in this field.

Scope

This topic will deliver a European-wide research strategy in collaboration and alignment with US-based efforts that overcomes key bottlenecks in the development and testing of treatments for ASD. It will build the necessary capacity within Europe for the conduct of future trials, while also contributing towards a more unified approach to ASD research within Europe in the clinical sciences.

Specifically, to meet these objectives, the successful proposal will include in its workplan two parts (Part 1 and Part 2) of activities and is expected to:

- create a European-wide clinical trials network trained to good clinical practice (GCP) standards to facilitate large-scale clinical trials (Part 1);
- obtain a fully aligned and global framework for clinical trials in ASD and co-morbidities (Part 1 and Part 2) and to test the viability of the network by measuring performance metrics during the execution and completion of a number of different clinical studies (phase I-IV) from different sponsors (industry, non-industry);
- validate stratification biomarkers to enable identification of more homogeneous clinical and/or biological subgroups for clinical trials, including for co-morbidities, in particular epilepsy, but excluding psychosis/schizophrenia (Part 1);
- enhance drug discovery efforts by testing translatability of new (Part 2) and/or repurposed (Part 1) drug effects between patients with ASD with and without co-morbidities and preclinical models (back and forward translation) to enable and feed a sustainable pipeline of innovative treatments.

Importantly the key objective of this action is to create a GCP trained clinical network and to test its viability by conducting clinical trials, rather than compound testing *per se*.

Expected key deliverables

The action to be created from this topic will include Part 1 activities that will be implemented throughout the entire project duration and additional Part 2 activities (funded via release of additional budget) which will only be implemented on the basis of specific criteria being fulfilled (see budget section) and after evaluation by an independent panel of experts. The expected key deliverables for the two parts are identified below.

- A European wide clinical trials network trained to GCP standard and aligned with US efforts. The action will build on and further expand the network identified by the EU-AIMS project:
    - structure and governance of the network to oversee the coordination of activities (including training) and recruitment of ASD specialised centres, including a point of contact for all sponsors (Part 1, **critical deliverable**);
    - implement standardised processes, procedures, and performance metrics necessary for efficient initiation and execution of studies and maintenance of high-level performance across the network. In collaboration, where appropriate, with the Call 10 topic 4 on paediatric clinical trials network (Part 1);
    - test the readiness of the network by conducting ‘proof of viability studies’ pivotal for the registration of the studied compound: at least one industry or non-industry study with repurposed compound (e.g. single ascending dose (SAD), multiple ascending dose (MAD), tolerability studies etc.), (Part 1 and Part 2);
    - conduct one study with a novel industry compound in order to further validate and operationalise the network, provided that such an ASD specific compound is available within the consortium and trials can be initiated during the action term (Part 2).

- International registry and data network including data acquisition:
    - a European registry of 'deeply phenotyped' individuals willing to take part in clinical trials for ASD. The action will increase the number of deeply phenotyped patients from those in EU-AIMS to up to 2500 patients transatlantically (Part 1);
    - international 'big data' networks (e.g. linking to US efforts) around genetics/omics and other biomarker data including brain tissue banks and all ethical and legal considerations (e.g. federated approach). This will also include establishing databases of cohorts of 'deeply phenotyped' individuals with rare genetic disorders putatively linked to ASD (Part 1, **critical deliverable**);
    - smartphone (or other portable digital device) based data acquisition for unbiased data collection (Part 1).
- Tools and methodologies to increase the probability of success of clinical trials:
    - validated (by regulators) biomarkers and endpoints. The action will build on a range of biomarkers submitted by the applicant consortium and those identified in the EU-AIMS project[20] (Part 1, **critical deliverable**);
    - trial inclusion criteria that allow stratification of the clinical phenotype (Part 1);
    - objective clinical trial outcome markers, and established international collaborations (including outside Europe) for trials in ASD that help develop novel trial methodologies for selecting/replacing treatment arms and reducing placebo response rates (Part 1);
    - alignment of international efforts on obtaining early 'first in human' proof of concept for compounds (both novel (Part 2) and repurposed (Part 1 and Part 2) impacting on neural systems implicated in ASD. This will share risk for validating targets, and 'fast failing' novel or repurposed compounds.
- Eventually building on all above, deliver novel molecular systems and symptom-based approaches (e.g. that may cross clinical diagnostic boundaries) and not just a disorder-based approach to ASD, including a better understanding of the biological underpinnings of common co-morbidities (e.g. epilepsy, ADHD and intellectual disability), (a first set of conclusions to be available at the end of Part 1, final refined set by end of Part 2):
    - a global communication and dissemination strategy of the results generated by this novel model of international collaboration (Part 1 and Part 2).

Expected impact

This action will have a major impact on this field and in parallel contribute towards the Innovative Medicines Initiative 2 (IMI2) objectives[21] as outlined in Article 2 of the IMI2 Council regulation:

- develop a Europe-wide infrastructure to accelerate and tailor patient recruitment to targeted (adaptive) clinical trials;

[20] http://www.ema.europa.eu/docs/en_GB/document_library/Other/2015/12/WC500198347.pdf
http://www.ema.europa.eu/docs/en_GB/document_library/Other/2015/12/WC500198351.pdf
http://www.ema.europa.eu/docs/en_GB/document_library/Other/2015/12/WC500198348.pdf
http://www.ema.europa.eu/docs/en_GB/document_library/Other/2015/12/WC500198350.pdf
http://www.ema.europa.eu/docs/en_GB/document_library/Other/2015/12/WC500198349.pdf

[21] According to Article 2 of the IMI2 Council regulation IMI2 Objectives:
(i) increase the success rate in clinical trials of priority medicines identified by the World Health Organisation;
(ii) where possible, reduce the time to reach clinical proof of concept in medicine development, such as for cancer, immunological, respiratory, neurological and neurodegenerative diseases;
(iii) develop new therapies for diseases for which there is a high unmet need, such as Alzheimer's disease and limited market incentives,such as antimicrobial resistance;
(iv) develop diagnostic and treatment biomarkers for diseases clearly linked to clinical relevance and approved by regulators;
(v) reduce the failure rate of vaccine candidates in phase III clinical trials through new biomarkers for initial efficacy and safety checks;
http://eur-lex.europa.eu/legal-content/EN/TXT/?uri=uriserv:OJ.L_.2014.169.01.0054.01.ENG

- identify patient sub-populations for particular treatments through validation and qualification of stratification biomarkers;
- based on the above, the action will set new standards for industry and allow potential identification of personalised medicines for patients in highly characterized patient groups;
- develop a unified approach to clinical research in ASD within Europe;
- a better understanding of common vs. distinct pathophysiological mechanisms underlying ASD subgroups, i.e. genetic, neurobiological and/or accounting for clinical variables such as comorbidities, developmental stage and sex.

Finally, the integration in the IMI action of complementary activities conducted in parallel in Europe and the US will result in a significantly larger patient population studied, in the combination of clinical trial results, and parallel validation and regulatory submissions of R&D tools. All this will not only increase the probability of success, but will also contribute to significantly accelerating R&D in a very complex research field.

Background and Ownership Transfer

Under this topic, the applicant consortia may research and develop pre-existing product candidates owned by one of the beneficiaries participating in the proposal, to validate the clinical trial network. By performing such activities, clinical results that are generated from the pre-existing product candidates (or compounds) tested will be owned by the generating beneficiary(ies). These results may be improvements (or directly related) to the pre-existing product candidate.

When solely owned by the generating beneficiary, the IMI2 rules allow the consortium to establish that the ownership of such results can be transferred to the owner of the pre-existing product candidate. Considering the value of the asset and the objective of the action, the applicant consortium should be fully comfortable to establish in the consortium agreement that the ownership of clinical results generated from the pre-existing product candidate(s) tested – when and only where not jointly owned according to Article 26.2 of the IMI2 Model Grant Agreement – will be transferred to the initial owner of the pre-existing product candidate(s) at no additional cost, when requested so by the pre-existing product candidate owner.

When jointly owned by the generating beneficiaries according to Article 26.2 of the IMI2 Model Grant Agreement, the decision on the terms of transferring their ownership shares to a single owner with access rights for the other participants can only take place after the results have been generated.

Potential synergies with existing consortia

Applicants should take into consideration, while preparing their short proposal, existing relevant national and European networks, projects in public health, European infrastructures, and collaborative research projects such as:

- **EUROSIBS** (The European Babysibs Autism Research Network: http://www.eurosibs.eu),
- **ASDEU** (Autism Spectrum Disorders in the European Union: http://asdeu.eu/autism-europe/)
- **ECRIN** (http://www.ecrin.org/).

Synergies and complementarities should be considered, building from achievements, and incorporating when possible, data and lessons learnt while avoiding unnecessary overlapping and doubling of efforts from initiatives such as and not limited to:

- **IMI EU-AIMS** [1] (European Autism Interventions – A Multicentre Study for Developing New Medications, the most successful IMI project to date according to Thomson Reuters - http://www.eu-aims.eu/) as infrastructure, scientific and regulatory knowledge by building on its ASD cohorts profiling and ongoing clinical studies (i.e. the baby sibling study and the naturalistic observational study in children and adults: further information available at: http://www.eu-aims.eu/clinical-network/ ;

https://www.autismresearchcentre.com/project_32_leap ; http://www.downs-syndrome.org.uk/download-package/eu-aims-leap-research/ ;

- IMI2 Call 10 topic 4 “Creation of a pan-European paediatric clinical trials network”;
- **IMI StemBANCC** (http://stembancc.org/);
- **IMI EPAD** (http://ep-ad.org/);
- **IMI RADAR-CNS** (http://www.radar-cns.org/);
- **IMI eTRIKS** (https://www.etriks.org/);
- **H2020 COSYN** (Comorbidity and Synapse Biology in Clinically Overlapping Psychiatric Disorders, http://cordis.europa.eu/project/rcn/199728_en.html).

The interactions and synergies will be facilitated by the EFPIA partners of the industry consortium that are also partners of these projects.

This IMI2 action clinical studies should, in addition, be complementing and aligned with ongoing efforts in the US, most notably those by :

- the National Institute of Mental Health (NIMH, i.e. https://www.nimh.nih.gov/health/topics/autism-spectrum-disorders-asd/index.shtml), Autism Biomarkers Consortium for Clinical Trials (http://ycci.yale.edu/researchers/autism/), National Database for Autism Research (https://ndar.nih.gov/), Autism Centers of Excellence (https://www.nichd.nih.gov/research/supported/Pages/ace.aspx)
- the Simons Foundation Autism Research Initiative (SFARI : https://sfari.org/resources)
- Autism Speaks (https://www.autismspeaks.org/).

Industry consortium

The consortium consists of EFPIA companies and Associated Partners.

The industry consortium is composed of the following EFPIA companies:

- F. Hoffmann-La Roche Ltd (lead)
- Janssen
- Novartis
- UCB Biopharma
- TEVA

Additional companies expressed interest and may join the action at stage 2 of the call process or during action execution.

The following IMI2 JU Associated Partners will contribute to the action:

- Autism Speaks
- Simons Foundation Autism Research Initiative (SFARI)

Additionally, the funded IMI2 action will receive an important scientific contribution from the National Institute of Mental Health (NIMH) by virtue of the signature of a memorandum of understanding (MoU) with the selected consortium.

Indicative duration of the action

The indicative duration of the action is 60 months.

The action should be designed to comprise of two distinct sets of activities (Part 1 and Part 2; see Figure 1). The work-plan of Part 2 may have to be adapted in light of the results from Part 1. This might include, as relevant, a modification of the consortium composition and an action extension of 12 months.

Applicants have to be aware that the triggering of the Part 2 activities (and related IMI2 JU contribution) will have to be endorsed by a panel of independent experts (action review) on the basis of the successful completion of critical deliverables upon reaching the first regulatory milestone (e.g. submission of a validated biomarker for EMA and/or FDA regulatory qualification) and the availability of relevant compounds, tracers and/or other assets, currently at the pre-proof of concept stage from the EFPIA companies, the Associated Partners, or the public partners necessary for the implementation of the activities.

However, in case an industry compound is available before a biomarker is fully validated by the consortium and discussions with the regulators indicate the value to proceed with the clinical trial, this may also trigger the start of Part 2, subject to positive opinion of the panel of independent experts.

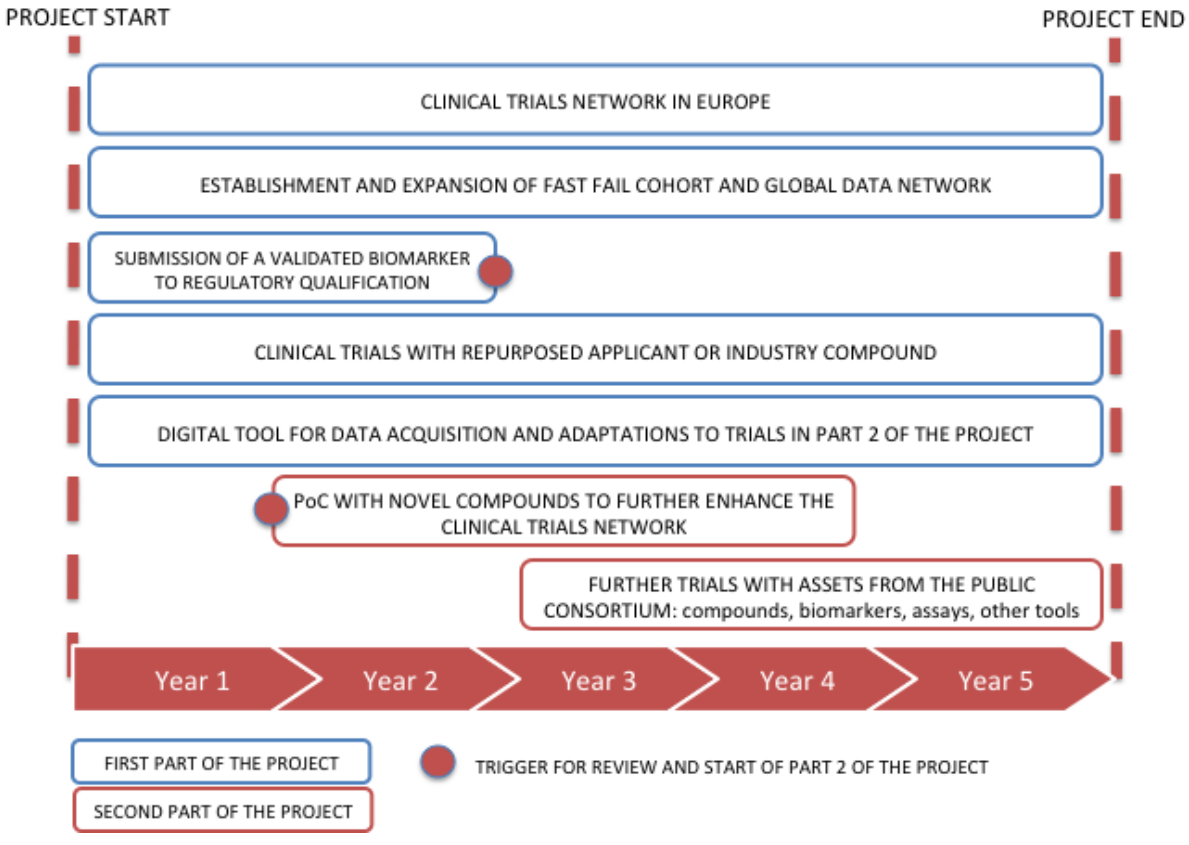

Figure 2: Simplified schematic depicting key deliverables and trigger points for the initiation of Part 2 funding (with indicative timing)

Indicative budget

The total financial contribution for IMI2 is a maximum of EUR 55 000 000.

IMI2 JU contribution for Part 1 activities is a maximum of EUR 35 000 000.

IMI2 JU contribution for Part 2 activities is a maximum of EUR 20 000 000.

All activities financed by IMI2 JU will be implemented in Europe.

For Part 1 activities of the action, the indicative EFPIA in-kind contribution is EUR 2 500 000.

For Part 2 of the action, the indicative EFPIA in-kind contribution will be up to EUR 15 000 000, subject to availability of relevant compounds, currently in pre-proof of concept stage, biomarkers and other assets from EFPIA partners. All the appropriate legal considerations will have to be met and suitable confidentiality and non-use agreements established upfront with the recipient beneficiaries prior of the start of the action.

The indicative IMI2 Associated Partners in-kind contribution is EUR 53 000 000.

In total, for Parts 1 and 2 of the action the indicative in-kind contribution from EFPIA and Associated Partners will be EUR 55 500 000 up to EUR 70 500 000.

Due to the global nature of the participating partners, and given the scope of the topic, a large component of the in-kind contribution will be provided from non-EU/H2020 Associated Countries; as contributions will come from US-based Associated Partners of IMI2 who will contribute critical resources, knowledge, experience and expertise not readily available in Europe, for the successful implementation of this action, in addition to EFPIA companies based in Switzerland.

Applicant consortium

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

The applicant consortium is expected to address all the research objectives and make key contributions to the deliverables in synergy with the industry consortium and complementing the contributions of the participating EFPIA and IMI2 Associated Partners which will join the selected applicant consortium in preparation of the full proposal for stage 2.

The applicant consortium should be able to demonstrate the full scope of expertise in order to address effectively and meet all goals outlined in this topic. This may require mobilising, as appropriate: expertise ranging from clinical and biomarker to regulatory and logistical (clinical network); data and knowledge management; project management and professional communication expertise; and inclusion of patients and patient organisations, with SME participation also encouraged. The size of the consortium should be assessed in a feasibility assessment (assessment to be part of the documentation by the applicant consortium) in order not to exceed or fall short of critical mass.

It may also require mobilising, as appropriate, the following resources: a relevant clinical network covering the largest possible number of European countries; relevant biomarkers that have already been endorsed via EMA qualification advice; networking and linkage to patients and patient organisations.

Suggested architecture of the full proposal

The applicant consortium should submit a short proposal which includes their suggestions for creating the full proposal architecture, taking into consideration the industry and IMI2 Associated Partners participation including their contributions, assets and expertise.

The work plan of the short/full proposal has to be designed including two parts with the Part 2 activities to be implemented only after successful achievement (as endorsed by a panel of independent expert evaluators) of critical milestones (see expected key deliverables and budget section). Thus applicants should design their work packages to insure timely achievement of such milestones and accordingly of all deliverables of Part 1 and Part 2 of the action.

Importantly, applicants are requested to design their activities for Part 1 and Part 2 keeping within the maximum budget allocated to each part (see indicative budget section). This information should be clearly included in the short/full proposal.

Applicants have to insure the inclusion of the necessary interaction points between work packages. In particular full integration between European and non-European studies is a must for the success of this new model of IMI2 initiative. The *modus operandi* for this integration will have to be clearly addressed in the full proposal and demands a high level of interconnection between work packages.

In the spirit of the partnership, and to reflect that IMI2 Call topics are built upon 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 strategy on the translation of the relevant action outputs into regulatory, clinical and healthcare practice. A plan for interactions with regulatory agencies/health technology assessment bodies with relevant milestones and resources allocation should be proposed to ensure this (e.g. qualification advice on the proposed methods for novel methodologies for drug development).

Sustainability

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

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

Work package 1: Governance and project management (Part 1 and Part 2)

The goals of this work package are:

- grant management;
- project management;
- communication and dissemination;
- legal and IP related activities.

Work package 2: Validation of stratifications markers in infants, children and adults with ASD, including regulatory work (Part 1 and Part 2)

The goals of this work package are:

- fluid biomarkers;
- imaging and electroencephalogram (EEG)/electromyogram (EMG);
- clinical endpoints;
- genomics/proteomics.

Work-package 3: Clinical network development and sustainability

The goals of this work package are:

- good clinical practice (GCP) standardisation and training (Part 1);
- study ready and fast fail cohorts (Part 1 and Part 2);
- European Medicines Agency (EMA) and U.S. Food and Drug Administration (FDA) alignment (Part 1 and Part 2);
- sustainability strategy development (pipeline and network), including monitoring of proper integration of data and resources internationally, and mitigation strategies (Part 1).

Work package 4: Drug testing

The goals of this work package are:

- efficacy studies with repurposed (Part 1) and innovative (Part 2) approaches in patients using a stratified medicines approach as developed on the basis of pre-existing and/or innovative markers identified in work package 2.

Work package 5: Stakeholder engagement (Part 1 and Part 2)

The goals of this work package are:

- outreach to European policy makers;
- payer/reimbursement;
- educational programme across Europe;
- regulatory alignment United States (US)/European Union (EU).

NOTE: The EU-AIMS project has successfully finalised a quality assurance (QA) procedure; this has resulted in important guidance for any new molecular entity (NME) in the field of neurodevelopmental disorders [2]. This guidance will be of influence to any regulatory agency in the world. Within the framework of the IMI2 action described here, the intention of the regulatory work package is to align EMA and FDA using qualification procedures. Relevant budget has to be allocated for these activities.

Work package 6: Data analysis and modelling (Part 1 and Part 2)

The goals of this work package are:

- tissue and data repository;
- patients' big data international networks;
- legal, ethical and societal issues.

Nature of the anticipated indicative industry and Associated Partners consortium in-kind contribution and available assets for all work packages

Industry and Associated Partners will contribute to activities both for Part 1 and 2 of the action: the Associated Partners contributions are fully available at the start of the action and have to be considered for all activities of the action. The industry contributions as relevant novel compounds, biomarkers and other assets from EFPIA partners, and dependent upon their stage of development[22], will be available for the Part 2.

Applicants should consider these suggested contributions and their timing when designing the workplan, in order to integrate them in the most appropriate work packages.

- F. Hoffmann-La Roche Ltd contributions will focus, in addition to taking scientific leadership of the action, on a focused approach to specific agenda items of the action. These relate in particular to those areas where Roche has built expertise over the past years by running Phase 2 programmes with two NME's in clinical development within the neurodevelopmental disorders space. Therefore, the focus will be on the development of biomarkers for stratification purposes and the development of the clinical trial network. In addition, the feasibility is currently assessed to share the data of the placebo arms of the Phase 2 results of Basimglurant in patients with Fragile-X.
- TEVA will establish synergies across its relevant scientific programmes and internal resources to support and contribute towards the goals of the IMI2 autism action, including the expertise, experience and support from TEVA internal scientific leadership. Specifically, they will contribute towards the development of patient registries in key countries within Europe.
- Janssen is actively developing a system of tools and technologies to optimize clinical trials for ASD. This includes mobile and web-based tools, as well as biosensors. Janssen's contributions will focus on development of putative biomarkers of ASD, and the development of a clinical trials network for ASD. In-kind knowledge contributions of scientific and technical expertise and advice will be provided. This advice will be supported with key learnings and data from ongoing research studies related to the system under development at Janssen, as well as expertise in clinical drug development. This includes active expert attendance and participation in consortium meetings and initiatives, document-based review and writing, and other collaborative activities.
- UCB Biopharma contributions will focus on the following aspect of the action that capitalize on previous experience and expertise in the company: a) understanding the biological pathways that are shared between autism and epilepsy considering the extensive data are emerging on the shared contribution of genetic risk factors between epilepsy and autism and the fact that epilepsy is a highly prevalent condition in autism patients; b) testing molecular imaging biomarkers that interact with synaptic vesicle proteins that are relevant to the current understanding of the underlying neurobiological substrate of autism patients.
- Novartis Pharma AG will contribute preclinical and clinical expertise to various work packages with biological data, and with results from potential future clinical studies in areas of interest to explore the personalised medicines stratification approaches in autism spectrum disorders.
- SFARI will focus on contributing to the IMI2 action by making available data or bio-specimens from any of the autism resources they have developed. These are among others their rich clinical/genomic databases from their patient cohorts including the Simons Simplex Collection (SSC), Simons Variation in Individuals Project (Simons VIP), Simons Foundation Powering Autism Research for Knowledge (SPARK) and Autism BrainNet. These resources will be available to develop international 'big data' networks around genetics/omics and other biomarker data including brain tissue banks and to develop novel molecular/ systems and symptoms based approaches, and determine the biological underpinnings of common

[22] Since neither the nature of these compounds, the stage of development which the programme would be in at the set milestone, nor the target population (and therefore size of the trial), can be anticipated before the validation of the relevant biomarkers, it is not possible to determine the exact level of these potential contributions. Nevertheless, as an example, the estimated average per-patient clinical trial costs, in 2013, for central nervous system trials was $36'000 (http://phrmacdn.connectionsmedia.com/sites/default/files/pdf/biopharmaceutical-industry-sponsored-clinical-trials-impact-on-state-economies.pdf)

co-morbidities (e.g. intellectual disability, epilepsy, and ADHD). SFARI will also contribute to develop objective clinical trial outcome markers and establish international collaborations to develop novel trial methodologies for selecting/replacing treatment arms and reducing placebo response rates. SFARI is financially and intellectually contributing toward the Foundation for the National Institutes of Health (FNIH) Autism Biomarker Consortium for Clinical Trials (ABC-CT) and is also internally developing novel outcome measures for clinical trials that will be shared as part of their contribution to the IMI2 action. SFARI is also willing to contribute Arbaclofen if a clinical trial of Arbaclofen is performed as part of the action. SFARI is fully prepared to provide in-kind contributions to allow fulfilment of the objectives of the selected proposal and achieve successfully all Part 1 activities. Their expertise will be also very valuable to facilitate Part 2 activities driven by the industry.

- Autism Speaks proposes to make contributions to the IMI2 action to establish and maintain synergy between its most relevant signature scientific programmes and resources, and those that promise to be developed by achieving the goals of the IMI2 JU. In addition, their in-kind contribution to the IMI2 JU will include the expertise, experience and support from Autism Speaks internal scientific leadership. Thus they will be key partners in all Part 1 activities of the action. Their expertise will be also very valuable to facilitate the Part 2 activities driven by the industry.
- National Institute of Mental Health (NIMH). Via the establishment of a memorandum of understanding (MoU) NIMH would continue and extend the synergy with the Longitudinal European Autism Project (LEAP: https://www.autismresearchcentre.com/project_32_leap) by contributing in the new IMI2 action to validate stratification biomarkers to enable identification of more homogeneous clinical and/or biological subgroups for clinical trials. The proposed roles and responsibilities of NIMH are: providing expertise, experience and feedback on lessons learned and data generated by the NIMH funded ABC-CT project (U19 MH108206, James McPartland, PI http://ycci.yale.edu/researchers/autism/). The objectives of the ABC-CT project are to evaluate neurophysiological (eye tracking and EEG), lab-based measures (Noldus Ethovision) of social impairment, and clinician and caregiver assessments of social communicative function in children with ASD (6-11 years of age). The 24-week study will assess performance characteristics (test-retest reliability) of the measures and their utility, individually or in combination, as stratification markers for use in ASD clinical trials. The ABC-CT study will provide an independent replication of several of the neurophysiological markers already developed by the LEAP study and will generate a dataset that is complementary to the new IMI2 action study. The ABC-CT study will determine whether one or more markers can be used to stratify/select subjects for inclusion in clinical trials. All data produced by the NIMH trial and the European based trial will be shared to a public repository for integration among all partners of the IMI2 action.

The industry in-kind contribution is anticipated to increase during the course of the action, including Part 1. The topic text is not prescriptive on the types of tools and/or assets that can be used to achieve the objectives of the action. In order to allow the best tools and assets available to be considered, the resultant full consortium will determine what available additional tools, beyond those brought forward by and within the capabilities of the applicant consortium, would best facilitate the objectives of the project and can be provided by industry, e.g. for the translation/back translation research. The nature and amount of this contribution can only be determined at the stage of preparation of the full proposal and could include, for example (and not limited to) cell lines, animal models, bioinformatics platforms, etc.

Further tools and assets that can be made available to the applicant consortium and not included in the above

In addition to the proposed in-kind contribution, certain proprietary tools and assets (developed previously by the industry) will be shared with the consortium beneficiaries to achieve the objectives of the action. Examples of such proprietary tools and assets may include (but are not limited to): data from placebo arms of a number of clinical phase programmes with compounds within the neurodevelopment disorder space i.e. data from adolescent and adult patients with fragile X syndrome (FXS) (e.g. randomized, double-blind, 12- week, parallel group, placebo-controlled study of efficacy and safety in patients with Fragile X Syndrome); data from paediatric patients with fragile X syndrome (e.g. randomized, double-blind, parallel-group, placebo-controlled, 12-week study to evaluate tolerability and safety in pediatric patients with FXS); data from adolescents with

symptoms associated with ASD (e.g. randomized double-blind, placebo controlled study to evaluate efficacy in children and adolescents with irritability associated with autistic disorder), etc.

In addition, reference compounds and the radiolabelling precursor for the synaptic vesicle transporter (synaptic vesicle glycoprotein 2A (SV2A)) positron emission tomography (PET) tracer which visualizes synaptic density in human brains and has already been tested in man will be made available. Another resource that can be provided is access to pre-existing treatment registries, cognitive testing, samples (e.g. blood, stool) and demographics from 150 ASD patients.

Furthermore, experience and data from ongoing research studies related to the mobile and web-based tools, technologies currently under development within the industry; and pre-clinical data, models, cell lines and samples, where relevant, which could complement the expertise/tools from the successful applicant consortium, will be made available from internal industry sources.

Glossary

ABC-CT	Autism Biomarkers Consortium for Clinical Trials
ADHD	Attention deficit hyperactivity disorder
ASD	Autism spectrum disorders
ASDEU	Autism Spectrum Disorders in the European Union
^{11}C	Carbon -11
COSYN	Comorbidity and Synapse Biology in Clinically Overlapping Psychiatric Disorders
ECRIN	European Clinical Research Infrastructure Network
EEG	Electroencephalogram
EFPIA	European Federation of Pharmaceutical Industries and Associations
EMA	European Medicines Agency
EMG	Electromyogram
EPAD	European Prevention of Alzheimer's Dementia Consortium
eTRIKs	Delivering European Translational Information & Knowledge Management Services
EU	European Union
EU-AIMS	European Autism Interventions – A Multicentre Study for Developing New Medications
EUROSIBS	The European Babysibs Autism Research Network
FDA	Food and Drug Administration
^{18}F	Fluorine-18
FNIH	Foundation for the National Institutes of Health
FXS	Fragile X syndrome
GCP	Good clinical practice
IMI2 JU	Innovative Medicines Initiative 2 Joint Undertaking
iPSCs	Induced pluripotent stem cells
LEAP	Longitudinal European Autism Project
LENA	Language Environment Analysis
MAD	Multiple ascending dose
MoU	Memorandum of understanding

NIMH	National Institute of Mental Health
NME	New Molecular Entity
PET	Positron Emission Tomography
QA	Quality Assurance
SAD	Single Ascending Dose
SFARI	Simons Foundation Autism Research Initiative
Simons VIP	Simons Variation in Individuals Project
SPARK	Simons Foundation Powering Autism Research for Knowledge
SSC	Simons Simplex Collection

Reference

[1] Nature Reviews, Drug Discovery, 11, 2012 (http://www.nature.com/nrd/journal/v11/n11/full/nrd3881.html)

[2] Nature Reviews, Drug Discovery, 15, 2015 (http://www.nature.com/nrd/journal/v15/n1/pdf/nrd.2015.7.pdf)

Conditions for this Call for proposals

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

The following conditions shall apply to this IMI 2 JU Call for Proposals:

Applicants intending to submit a Short proposal in response to the IMI2 Call 10 should read this topics text, the IMI2 JU Manual for submission, evaluation and grant award and other relevant documents (e.g. IMI2 model Grant Agreement).

Call Identifier	**H2020-JTI-IMI2-2016-10-two-stage**
Type of actions	**Research and Innovation Actions (RIA)**
Publication Date	**21 December 2016**
Stage 1 Submission start date	**4 January 2017**
Stage 1 Submission deadline	**28 March 2017 (17:00:00 Brussels time)**
Stage 2 Submission deadline	**14 September 2017 (17:00:00 Brussels time)**
Indicative Budget	
From Industry consortia (EFPIA companies and IMI2 Associated Partners)	EUR 174 140 000
From the IMI2 JU	EUR 173 890 000

Call Topics

IMI2-2016-10-01	The indicative contribution from EFPIA companies will be EUR 10 504 000 The indicative IMI2 Associated Partners contribution will be 2 956 000 The financial contribution from IMI2 will be a maximum of EUR 13 460 000	Research and Innovation Action. Two-stage submission and evaluation process. Only the applicant consortium whose proposal is ranked first at the first stage is invited for the second stage.
IMI2-2016-10-02	The indicative contribution from EFPIA companies will be EUR 6 000 000 The financial contribution from IMI2 will be a maximum of EUR 6 000 000	Research and Innovation Action. Two-stage submission and evaluation process. Only the applicant consortium whose proposal is ranked first at the first stage is invited for the second stage.

IMI2-2016-10-03	The indicative EFPIA in-kind contribution will be EUR 11 230 000 The financial contribution from IMI2 for each subtopic will be: **Subtopic 3A PROMs:** The financial contribution from IMI2 will be a maximum of EUR 4 250 000 **Subtopic 3B BIOM:** The financial contribution from IMI2 will be a maximum of EUR 4 140 000 **Subtopic 3C CPP:** The financial contribution from IMI2 will be a maximum of EUR 2 840 000	Research and Innovation Action. Modified two-stage submission and evaluation process. At stage 1, applicant consortia to this topic will submit short proposals to address one of the three subtopics. Applicants can submit proposals to any of the subtopics. If applicant consortia wish to submit for more than one subtopic, separate short proposals should be submitted. Applicants are not obliged to apply for all. At stage 2, the winning consortium from each subtopic shall merge into a single consortium with the industry consortium.
IMI2-2016-10-04	The indicative contribution from EFPIA companies will be EUR 67 000 000 The financial contribution from IMI2 will be a maximum of EUR 67 000 000	Research and Innovation Action. Two-stage submission and evaluation process. Only the applicant consortium whose proposal is ranked first at the first stage is invited for the second stage.
IMI2-2016-10-05	The indicative contribution from EFPIA companies will be EUR 4 700 000 The financial contribution from IMI2 will be a maximum of EUR 4 700 000	Research and Innovation Action. Two-stage submission and evaluation process. Only the applicant consortium whose proposal is ranked first at the first stage is invited for the second stage.
IMI2-2016-10-06	The indicative contribution from EFPIA companies will be EUR 12 000 000 The financial contribution from IMI2 will be a maximum of EUR 12 000 000	Research and Innovation Action. Two-stage submission and evaluation process. Only the applicant consortium whose proposal is ranked first at the first stage is invited for the second stage.
IMI2-2016-10-07	The indicative contribution from EFPIA companies will be EUR 4 250 000 The financial contribution from IMI2 will be a maximum of EUR 4 500 000	Research and Innovation Action. Two-stage submission and evaluation process. Only the applicant consortium whose proposal is ranked first at the first stage is invited for the second stage.

IMI2-2016-10-08	The indicative contribution from EFPIA companies will be EUR 2 500 000 The indicative IMI2 Associated Partners contribution will be EUR 53 000 000 The financial contribution for IMI2 will be a maximum of EUR 55 000 000.	Research and Innovation Action. Two-stage submission and evaluation process. Only the applicant consortium whose proposal is ranked first at the first stage is invited for the second stage.

List of countries and applicable rules for funding

By way of derogation[23] from Article 10(1) of Regulation (EU) No 1290/2013, only the following participants shall be eligible for funding from the Innovative Medicines Initiative 2 Joint Undertaking:

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

b) which fall within one of the following categories:

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

   ii. secondary and higher education establishments;

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

c) the Joint Research Centre;

d) international European interest organisations;

In accordance with Article 10(2) point (a) of the Regulation (EU) No 1290/2013, in case of participating legal entity established in a third country, that is not eligible for funding according to point (a) above, funding from the IMI2 JU may be granted provided the participation is deemed essential for carrying out the action by the IMI2 JU.

Admissibility conditions for grant proposals, and related requirements

Part B of the General Annexes[24] to the H2020 Work Programme shall apply *mutatis mutandis* for the actions covered by this Call for proposals.

For this Call, the page limit for a stage 1 – Short proposal is 30 pages. The page limit for a stage 2 – Full proposal is 70 pages.

[23] Pursuant to the Commission Delegated Regulation (EU) No 622/2014 of 14 February 2014 establishing a derogation from Regulation (EU) No 1290/2013 of the European Parliament and of the Council laying down the rules for participation and dissemination in 'Horizon 2020 — the Framework Programme for Research and Innovation (2014-2020)' with regard to the Innovative Medicines Initiative 2 Joint Undertaking

[24] http://ec.europa.eu/research/participants/data/ref/h2020/other/wp/2016-2017/annexes/h2020-wp1617-annex-ga_en.pdf

Eligibility conditions

Part C of the General Annexes to the H2020 Work Programme 2016-2017 shall apply *mutatis mutandis* for the actions covered by this Call for proposals.

In addition, under the two-stage submission procedure of this Call for proposals the following additional condition applies:

- The participants from EFPIA constituent entities and affiliated entities, and other Associated Partners if any, which are pre-defined in the topics under the section 'Industry consortium' of a Call for proposals do not apply at the stage 1 of the Call. The applicant consortium selected from the stage 1 of the Call for proposals is merged at the stage 2 with the EFPIA constituent entities or their affiliated entities and other Associated Partners.[25]

Types of action: specific provisions and funding rates

Part D of the General Annexes to the H2020 Work Programme 2016-2017 shall apply *mutatis mutandis* for the actions covered by this Call for proposals.

Technology Readiness Levels (TRL)

Part G of the General Annexes to the H2020 Work Programme 2016-2017 shall apply *mutatis mutandis* for the actions covered by this Call for proposals.

Evaluation rules

Part H of the General Annexes to the H2020 Work Programme 2016-2017 shall apply *mutatis mutandis* for the actions covered by this Call for proposals with the following additions:

Award criteria and scores

Experts will evaluate the proposals on the basis of "Excellence", "Impact" and "Quality and efficiency of the implementation" according to the stage of the evaluation procedure, as follows:

Type of action ***Evaluation stage***	**Excellence**	**Impact**	**Quality and efficiency of the implementation**
RIA and IA ***1st stage***	The following aspects will be taken into account, to the extent that the proposed work corresponds to the topic	The following aspects will be taken into account, to the extent to which the outputs of the project should contribute at	The following aspects will be taken into account: ▪ coherence and

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

evaluation	description in the Call for proposals and referred to in the IMI2 annual work plan: ▪ clarity and pertinence of the proposal to meet all key objectives of the topic; ▪ credibility of the proposed approach; ▪ soundness of the concept, including trans-disciplinary considerations, where relevant; ▪ extent that proposed work is ambitious, has innovation potential, and is beyond the state of the art; ▪ mobilisation of the necessary expertise to achieve the objectives of the topic, ensure engagement of all relevant key stakeholders.	the European and/or international level: ▪ the expected impacts of the proposed approach as mentioned in the Call for proposals; ▪ added value from the public-private partnership approach on R&D, regulatory, clinical and healthcare practice as relevant; ▪ strengthening the competitiveness and industrial leadership and/or addressing specific societal challenges; ▪ improving European citizens' health and wellbeing and contribute to the IMI2 objectives[26].	effectiveness of the outline of the project work plan, including appropriateness of the roles and allocation of tasks, resources, timelines and approximate budget; ▪ complementarity of the participants within the consortium (where relevant) and strategy to create a successful partnership with the industry consortium as mentioned in the topic description in the Call for proposal; ▪ appropriateness of the proposed management structures and procedures, including manageability of the consortium.
RIA and IA ***2nd stage evaluation***	The following aspects will be taken into account, to the extent that the proposed work corresponds to the topic description in the Call for proposals and referred to in the IMI2 annual work plan and is consistent with the stage 1 proposal: ▪ clarity and pertinence of the proposal to meet all key objectives of the topic; ▪ credibility of the proposed approach; ▪ soundness of the concept, including trans-disciplinary considerations, where	The following aspects will be taken into account, to the extent to which the outputs of the project should contribute at the European and/or international level: ▪ The expected impacts of the proposed approach as mentioned in the Call for proposals; ▪ added value from the public-private partnership approach on R&D, regulatory, clinical and healthcare practice as relevant; ▪ enhancing innovation capacity and integration of new knowledge;	The following aspects will be taken into account: ▪ coherence and effectiveness of the project work plan, including appropriateness of the roles and allocation of tasks, resources, timelines and budget; ▪ complementarity of the participants within the consortium (where relevant); ▪ clearly defined contribution to the project plan of the industrial partners (where relevant);

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

	relevant; ▪ extent that proposed work is ambitious, has innovation potential, and is beyond the state of the art; ▪ mobilisation of the necessary expertise to achieve the objectives of the topic, ensure engagement of all relevant key stakeholders.	▪ strengthening the competitiveness and industrial leadership and/or addressing specific societal challenges; ▪ improving European citizens' health and wellbeing and contribute to the IMI2 objectives;[26] ▪ any other environmental and socially important impacts; ▪ effectiveness of the proposed measures to exploit and disseminate the project results (including management of IPR), to communicate the project, and to manage research data where relevant.	▪ appropriateness of the management structures and procedures, including manageability of the consortium, risk and innovation management and sustainability plan.

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

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

For the evaluation of first-stage proposals under a two-stage submission procedure, the threshold for the two first criteria ‘excellence’ and ‘impact’ is 3. The proposals will also be evaluated for the ‘quality and efficiency of the implementation’ criterion but with no threshold. There is no overall threshold.

For the evaluation of second-stage proposals under a two-stage submission procedure the threshold for individual criteria is 3. The overall threshold, applying to the sum of the three individual scores, is 10.

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

The full evaluation procedure is described in the IMI2 Manual for submission, evaluation and grant award in line with the H2020 Rules for Participation[27].

Under the two-stage evaluation procedure, and on the basis of the outcome of the first stage evaluation, the applicant consortium of the highest ranked short proposal (first stage) for each topic will be invited to discuss with the relevant industry consortium the feasibility of jointly developing a full proposal (second stage). The applicant consortia of the second and third-ranked short proposals (first stage) for each topic may be invited for preliminary discussions with the industry consortium if the preliminary discussions with the higher ranked proposal and the industry consortium fail. In such case, the applicant consortium and the industry consortium shall be responsible for jointly notifying the IMI2 JU if the preparation of a joint full proposal is not feasible. This notification must be accompanied by a joint report clearly stating the reasons why a joint full proposal is

[27] http://www.imi.europa.eu/sites/default/files/uploads/documents/IMI2_CallDocs/Manual_SubEvalAward_IMI2_v1.4_Oct2016.pdf

considered not feasible. Upon acknowledgement and after consideration of the specific circumstances, the IMI2 JU may decide to invite the next-ranked applicant consortium in priority order, i.e. the second ranked proposal is contacted only after failure of preliminary discussions with the first ranked, and the third ranked after the second ranked.

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

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

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

Indicative timetable for evaluation and grant agreement

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

Budget flexibility

Part I of the General Annexes to the H2020 Work Programme 2016-2017 shall apply *mutatis mutandis* for the actions covered by this Call for proposals.

Actions involving financial support to third parties

Part K of the General Annexes to the H2020 Work Programme shall apply *mutatis mutandis* for the actions covered by this Call for proposals.

Submission tool

Proposals in response to this Call for proposals must be submitted on-line, before the Call deadline, by the coordinator via the Electronic Submission Service of the Participant Portal:

http://ec.europa.eu/research/participants/portal/desktop/en/home.html

No other means of submission will be accepted.

Others

For proposals including clinical trials/studies/investigations, a specific template to help applicants to provide essential information on clinical studies in a standardised format is available under:

http://ec.europa.eu/research/participants/data/ref/h2020/other/legal/templ/h2020_tmpl-clinical-studies_en.pdf

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

Ethical issues should be duly addressed in each submitted proposal to ensure that the proposed activities comply with ethical principles and relevant national, Union and international legislation. Any proposal that contravenes ethical principles or which does not fulfil the conditions set out in the H2020 Rules for Participation, or in the IMI2 JU Call for proposals shall not be selected.[28]

Part L of the General Annexes of the Horizon 2020 Work Programme 2016-2017 shall not apply for the actions covered by this Call for proposals. Nevertheless, in order to ensure excellence in data and knowledge management consortia will be requested to:

1) disseminate scientific publications on the basis of open access[29] (see 'Guidelines on Open Access to Scientific Publications and Research Data in Horizon 2020');
2) include a data management plan outlining how research data will be handled during a research project, and after it is completed, as part of the full proposal (see Guidelines on Data Management in Horizon 2020 providing guidance for the collection, processing and generation of research data). In order to ensure adherence to the legislation concerning protection of personal data, controlled access digital repositories and data governance will need to be considered;
3) use well-established data format and content standards in order to ensure interoperability to quality standards. Preferably existing standards should be adopted. Should no such standards exist, consideration should be given to adapt or develop novel standards in collaboration with a data standards organisation (e.g. CDISC);
4) disseminate a description of resources[30] according to well-established metadata standards such as the Dublin Core (ISO15836) in order to make the resources included and generated by the IMI actions discoverable for metrics and re-use.

Full proposals shall contain a draft plan for the exploitation and dissemination of results.

Consortium agreements

In line with the Rules for Participation and Dissemination applicable to IMI2 actions[31] and the IMI2 model grant agreement, participants in IMI2 actions are required to conclude a consortium agreement prior to grant agreement.

[28] Article 19 of *Horizon 2020 Framework Programme*, and Articles 13 and 14 of the *Horizon 2020* Rules for Participation
[29] Article 43.2 of Regulation (EU) No 1290/2013 of the European Parliament and of the Council laying down the rules for participation and dissemination in *Horizon 2020 - the Framework Programme for Research and Innovation (2014-2020)* and repealing Regulation (EC) No 1906/2006
[30] Examples of resources are (a collection of) biosamples, datasets, images, publications etc.
[31] Regulation (EU) No 1290/2013 of 11 December 2013 and Commission Delegated Regulation (EU) No 622/2014 of 14 February 2014.