IMI2

13th Call for proposals

Annex III to the 2nd amended IMI2 JU Annual Work Plan approved by the IMI2 JU Governing Board on 28 November 2017 per Decision n° IMI2-GB-DEC-2017-25

Document reference: IMI2/INT/2017-02702

Contents

Introduction

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

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

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

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

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

The IMI2 Strategic Research Agenda (SRA)[4] is the main reference for the implementation of research priorities for IMI2 JU. The scientific priorities for 2017 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.

Applicants consortia, during all stages of the evaluation process, must consider the nature and dimension of the IMI2 JU programme as a public-private collaboration.

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

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 JU Manual for evaluation, submission and grant award[6], and the IMI2 evaluation criteria.

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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; the definition of 'affiliated entities' within the meaning of Article 2(1)(2) of Regulation (EU) No 1290/2013 applies mutatis mutandis. Where established in an EU Member State or an associated country, are eligible for funding.
[4] http://www.imi.europa.eu/sites/default/files/uploads/documents/About-IMI/research-agenda/IMI2_SRA_March2014.pdf
[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/apply-for-funding/call-documents/imi2/IMI2_ManualForSubmission_v1.6_October2017.pdf

Applicants should refer to the specific templates and evaluation procedures associated with the topic type: Research and Innovation Actions (RIA), Coordination and Support Actions (CSA).

Topic 1 : Assessment of the uniqueness of diabetic cardiomyopathy relative to other forms of heart failure using unbiased pheno-mapping approaches

Topic details

Topic code	IMI2-2017-13-01
Action type	Research and Innovation Action (RIA)
Submission and evaluation process	2 stages

Specific challenges to be addressed

Diabetes contributes to the development of heart failure (HF) indirectly by promoting the progression of coronary artery disease and directly through the development of cardiomyopathy. Thus, diabetic patients have a 2.5-fold greater risk for HF as compared to those without diabetes. Epidemiological studies have reported a 4-fold higher prevalence of diabetes mellitus in HF patients (20%) compared to age-matched populations without HF (5%) which rises up to 40% in hospitalised HF patients. Over the last decades it became clear that there is a relationship between diabetes and HF, although not all patients with diabetes develop cardiomyopathy or evolve toward HF.

Traditionally, heart failure is divided into two types based on ejection fraction:

1) heart failure with reduced ejection fraction (HFrEF) or systolic heart failure caused by left ventricular systolic dysfunction, which manifests when the ejection fraction is less than 40%;
2) heart failure with preserved ejection fraction (HFpEF) also known as diastolic heart failure or heart failure with unaltered ventricular contractility and normal ejection fraction. In this type of HF, the ventricle typically fails to adequately relax and, therefore, does not fill completely with blood in the relaxation phase.

Diabetic cardiomyopathy is considered as a distinct form of heart failure that occurs in diabetic patients in absence of coronary artery disease, long standing hypertension, valvular or familial heart disease. It relies on a diagnosis of exclusion based on the presence of symptomatic cardiomyopathy, a long history of diabetes with many exclusion criteria as referred above. The main feature of diabetic cardiomyopathy is left ventricular diastolic dysfunction with impaired relaxation that impedes the efficiency of passive filling during diastole, preserved left ventricular contractility, increased filling pressure with or without cardiac hypertrophy. It is more frequent in obese females with poor glycaemic control. Diabetic cardiomyopathy shares many commonalities with HFpEF and hypertrophic cardiomyopathy (HCM). Although its pathogenesis is yet to be clearly defined, diabetic cardiomyopathy is increasingly recognised as a clinically relevant entity.

Therefore, the overall objective of this topic is to determine whether diabetic cardiomyopathy is unique and distinct from the other forms of heart failure such as HFpEF or HCM by performing unbiased statistical clustering analysis from a dense phenotyping of these patient populations. Similar methodology has recently been used to identify phenotypically distinct and more homogeneous HFpEF segments. This approach would facilitate a molecular taxonomy of diabetic cardiomyopathy which is widely accepted in the scientific community and could be applied in the clinics for differentiation from other forms of heart muscle disorders already at disease onset, thereby enabling an optimised and individualised treatment of patients. Furthermore, a better comprehension of the underlying mechanisms and clinical manifestations of diabetic cardiomyopathy will also allow the development of more translatable and predictable preclinical models to support target and drug discovery.

Need and opportunity for public-private collaborative research

The purpose of this topic is to bring a sufficient level of funding and multi-stakeholder commitment to comprehensively and definitively address the compilation of a set of jointly agreed phenotype criteria enabling the classification and new definition of diabetic cardiomyopathy. The leading edge of this IMI2 JU topic is to make use of extant heart failure cohorts, with or without diabetes, and then prospectively access clinical and imaging data, as well as samples that meet carefully considered criteria. This unprecedented effort will be transformative for the field and is the type of effort needed to gain consensus acceptance by those carrying out basic research into diabetes and heart failure and by clinical investigators.

The magnitude of the issue is such that it can only be addressed by a major public-private-partnership involving a variety of stakeholders, including those primarily involved in understanding the clinical parameters and molecular mechanisms of disease who have a complementary experience and expertise, as well as regulators. This is a topic which cannot be successfully administered by an individual research group or a company but will require a broad consortium to be successful.

- Pharmaceutical companies contribute expertise in diabetes and cardiovascular drug discovery and development, including an understanding of regulatory, economic, and logistical challenges facing drug development for disease prevention and modification. They bring unique expertise in biomarker discovery, data analysis, assay development, and prospective clinical trial design. Furthermore, companies may provide biological samples from control and standard therapy arms of clinical trials.
- Small- and medium-sized enterprises (SMEs) are expected to contribute specific methodologies or technical platforms to foster efficiency and innovation within the project.
- Academic investigators contribute expertise in a range of methods to discover and validate molecular phenotypic biomarkers from human tissues and bio-fluids (e.g. by multi-omics and genetics/epigenetics analyses), to assess clinical and imaging phenotypes, and to analyse the relationship of molecular phenotypic biomarkers with clinical/imaging evaluation of disease development and progression.
- Hospitals, clinical research centres, and practicing physicians with access to patients with diabetes and heart failure will allow prospective assessment of these patients and contribute to the understanding of epidemiology, pathophysiology, clinical, imaging and biochemical phenotypes and provide bio-banked samples that may be used in combination with novel molecular biomarkers to discriminate patients with diabetic cardiomyopathy from other heart failure forms.
- The taxonomy and new classification will need to find acceptance by global regulators and other public bodies, including payers. It will be crucial for the success of the project to interact and integrate these stakeholders as early as possible. This can be achieved by integrating them as participants into the project or, if appropriate, within advisory bodies.

Scope

The overall goal of the proposed topic is to assess the uniqueness of diabetic cardiomyopathy and to unveil the underlying mechanisms of cardiomyopathy in diabetic patients and the impact on cardio-vascular mortality in this population, which may finally allow the clustering of patients into an independent cohort. In consequence, this improved understanding of the clinical manifestations and diagnosis of diabetic cardiomyopathy as well as the linkage between the onset and disease progression with a specific signature will enable patient stratification at an early stage of the disease by clustering of patients into an independent cohort.
The scope of the collaborative research for diabetic cardiomyopathy can be envisioned to ideally encompass objectives, outlined below:

- definition of the inclusion criteria for patients with preserved ejection fraction (EF > 50%) and diastolic dysfunction of four different origins including:
    - non-ischemic diabetic cardiomyopathy,

- non-diabetic HFpEF,
- idiopathic HCM,
- type 2 diabetes mellitus (T2DM) with no HF or cardiomyopathy;

- enrollment of patients according to pre-defined inclusion criteria into the four different patient groups;

  A cohort of patients shall be enrolled from registries and prospective clinical trials running at academic centers or EFPIA partners according to the pre-defined and jointly agreed inclusion criteria. Deep pheno-mappingof patients will be done prospectively at baseline. Additionally, blood, plasma and urine samples will be taken for multiple omics and genetics/epigenetics analysis.
  It is estimated that approximately 1000 patients per patient group need to be investigated at baseline in order to achieve statistical significance of cluster discrimination. Since the initiation of the sample analyses is dependent on a phenotype overlap of less than 10 % across the different clusters (see below), study recruitment and deep phenotyping shall be completed within three years.
- application of non-invasive imaging technologies (transthoracic echocardiography, speckle tracking echo-cardiography (STE), doppler echocardiography and magnetic resonance imaging (MRI) to detect subclinical myocardial dysfunctions;
- assessment of cardiac, endothelial and metabolic functions in all patient groups;
- unsupervised machine-learning applied to the dense phenotypic data with the goal to identify more homogeneous and differentiated clusters;
- analysis of patients' lipidomic, metabolomic, proteomic and transcriptomic profiles in blood, plasma or urine samples, if pheno-mapping of the different clusters shows discriminative phenotypes;

  A phenotype overlap of less than 10 % is being considered as criterion for the initiation of multi-omics and genetics/epigenetics analyses of baseline samples. A go/no go decision will be taken during the course of the project based on the ability to significantly differentiate and cluster newly defined diabetic cardiomyopathy from other patients in the cohort. The expectation of the multi-omics/genetic analysis is to discover a panel of novel biomarkers that (i) predicts cardiac function decline in T2DM patients, (ii) allows for early preventative life style changes, (iii) facilitates tailored therapies to slow disease progression and (iv) enables the discovery of new pathophysiological pathways responsible for diabetic cardiomyopathy or heart failure and complications. Traditional biomarkers associated with cardiomyopathy and heart failure will be monitored to determine whether the novel biomarkers offer greater predictive value for each newly defined cluster.
- system biology data analysis for disease modelling;
- compilation of existing pre-clinical models for diabetic cardiomyopathy which will serve as a "state-of-the-art" reference;
- translation of clinical results back into pre-clinical settings to improve the knowledge on translatable preclinical models for diabetic cardiomyopathy and develop relevant and reliable *in silico*, *in vitro* and *in vivo* models based on disease modelling.

  The proposed action's duration allows in-depth systematic evaluation of collected clinical parameters for pheno-mapping and molecular analysis of biological samples from registries and prospective patient cohorts. Further, the obtained insights will be integrated both into novel to-be-established and existing pre-clinical models.

Expected key deliverables

The expected deliverables should be achieved during the five years duration of the funded project.

Through a network of clinical databases and laboratories, efforts to enable the classification of diabetic cardiomyopathy and validation of relevant biomarkers and imaging modalities, in addition to parallel efforts towards pathway/target identification for future therapeutics development shall be initiated. These will include the following aspects:

- definition of jointly agreed inclusion criteria/parameters that will be used for initial patient enrollment;
- successful patient enrollment into the four groups (1000 patients/group) to ensure successful deep phenotyping and prospective assessment of phenotyping markers including clinical, imaging and biological ones;
- applied unsupervised machine learning algorithms to deep phenotyping in order to identify patients with diabetic cardiomyopathy and distinguish them from other heart failure populations;
- identification of causal mechanisms and pathways responsible for diabetic cardiomyopathy resulting from the comparative evaluation of the four clusters;
- better understanding of the disease biology of diabetic cardiomyopathy based on disease modelling that will lead to the development of more translatable and predictive preclinical models;
- pavement of the way for implementing this new classification by communicating value proposition to target audiences (i.e. global regulators, patients, healthcare practitioners and payers).

Expected impact

In terms of research and development (R&D), clinical, regulatory, healthcare practice and patient management:

- proposals are expected to define and assess key phenotypes that characterise diabetic cardiomyopathy and could serve to establish patient diagnosis and ultimately prognosis;
- the stratification of patients into the diabetic cardiomyopathy cluster based on pheno-mapping, supported by biomarkers specific for this group will be transformative for the clinical management of these patients;
- furthermore, novel pre-clinical models with improved knowledge on the translatability to humans will profoundly enable drug development for the treatment of diabetic cardiomyopathy beyond blood glucose control.

Overall, a better comprehension of the mechanisms and clinical manifestations of diabetic cardiomyopathy will allow the development of more translatable and predictable preclinical models supporting target and drug discovery in academia and industry. The molecular taxonomy of diabetic cardiomyopathy to be developed will enable innovative and individualised treatment options for patients.

In terms of strengthening the competitiveness and industrial leadership in Europe the applicants could also include the relevant expertise from the small- and medium-sized enterprises (SMEs).Their involvement might offer a complementary perspective to industry and the academia, and help deliver the long-term impact of the project.

Potential synergies with existing consortia

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

Currently, there are no synergies with completed or ongoing IMI/IMI2 JU projects.

Consortia like **DIRECT** (http://www.direct-diabetes.org), **RHAPSODY** (https://imi-rhapsody.eu) and **BEAt-DKD** (http://www.imi.europa.eu/projects-results/project-factsheets/beat-dkd) are also investigating T2DM patients. However, their scientific goals are addressing different aspects of research. The focus of DIRECT and RHAPSODY is the identification of novel biomarker panels predictive for glycaemic deterioration / disease progression of pre-diabetes and early onset of T2DM, and treatment response that can be applied for patient stratification, whereas the BEAt-DKD consortium is assessing biomarkers for diabetic kidney disease.

Industry consortium

The industry consortium is composed of the following EFPIA companies:

- Sanofi (lead)
- Bayer
- Lilly

The industry consortium will contribute the following expertise and assets:

The industry consortium will bring expertise in methodologies for the merging, harmonisation and meta-analyses of existing clinical, imaging and biomarker data as well as systems biology and disease modelling. This will include expertise in biomarker evaluation, bioinformatics and statistical expertise and possibly technology for measuring specific biomarkers when appropriate. Additional contributions will include diabetes and heart failure clinical trial and regulatory expertise. Furthermore, it is envisaged that data, results and samples from control arms of ongoing clinical trials may be provided to the consortium.

EFPIA participants have also indicated interest in providing in-kind contributions that will entail efforts at 'back-translation' into preclinical models to help in validating appropriate animal model(s) and biomarkers of diabetes cardiomyopathy.

Indicative duration of the action

The indicative duration of the action is 60 months.

Indicative budget

The indicative EFPIA in-kind contribution is 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.

The financial contribution from IMI2 JU is a maximum of EUR 6 700 000.

Applicant consortium

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

To address the ambitious objectives of the topic adequately, the funded project is expected to establish a multidisciplinary network that will include scientists, physicians and imaging specialists, who are recognised experts in heart failure and diabetes and contribute expertise in developing and maintaining the clinical database that is relevant to an in-depth characterisation of the patients enrolled into the four cluster groups. Furthermore, expertise in clinical research recruitment including access to clinical research centres with registries and ongoing prospective trials shall be provided.

Such a network should be capable of mobilising following capabilities to make the following types of contributions:

- access to clinical cohorts of heart failure patients with or without diabetes from registries or prospective clinical trials to ensure the enrolment of 1000 patients per group within the first phase of the project;
- availability of key non-invasive imaging technologies to assess subclinical myocardial dysfunctions;
- development of a structured database that allows the joint analysis of complex datasets;
- strong experience in unsupervised machine learning;
- capability of systems biology analysis by vertical integration of phenotype, clinical, multi-omics and genetics/epigenetics datasets;
- in-depth expertise in pre-clinical models relevant to diabetic cardiomyopathy;
- experience in communication with global regulators, patients, practitioners and payers, who may be members of a to be established advisory board.

The participation of SMEs, in particular, with the following expertise would be highly appreciated:

- machine-learning
- data management
- image analysis
- imaging technologies
- metabolomics analysis
- lipidomics analysis
- project management in the context of IMI2 JU/H2020 projects.

Consequently, partners providing medical record-based information (e.g. data from registries) as project background must be mindful that they, as background contributor, should have sufficient title to said background to authorise its use within the project pursuant to the IMI2 JU IP and legal framework[7] Consideration should also be given to any additional information that may be introduced after the start of the project but is not listed as project background at the start date.

The applicants need also to take into consideration that the sharing of data and samples within the consortium should be allowed and be in conformity with the applicable data privacy laws and laws regarding ethical matters.

Suggested architecture of the full proposal

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

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

In the spirit of the partnership, and to reflect how IMI2 JU call topics are built on identified scientific priorities

[7] Regulation No. 1290/2013 (11th December 2013) laying down the rules for participation and dissemination in Horizon 2020 (H2020 RfP); Council Delegation Regulation (EU) No. 622/2014 (establishing a derogation from Regulation (EU) 1290/2013 (Delegated Act); Council Regulation (EU) No. 557/2014 (establishing the Innovative Medicines Initiative 2 Joint Undertaking).

agreed together with EFPIA beneficiaries/large industrial beneficiaries, these beneficiaries intend to significantly contribute to the programme and project leadership as well as project financial management.

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

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

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

Work package 1 – Consortium management, administration, integration and dissemination

Work package 2 – Clinical study

The goals of this work package will be as follows:

- definition of inclusion criteria for the different patient groups;
- enrollment of patients according to pre-defined inclusion criteria from registries and prospective clinical trials.

Work package 3 – Imaging technologies

The goal of this work package will be as follows:

- application of non-invasive imaging technologies to detect subclinical myocardial dysfunction in diabetic cardiomyopathy patients.

Work package 4 – Data management and machine learning

The goals of this work package will be as follows:

- data centralisation in a unique, scalable and secured database for data analysis;
- system biology approach for data analysis using data from multiple sample analysis (work package 5);
- unsupervised machine-learning for clustering on phenotypic differences beyond diabetes.

Work package 5 – Multiple sample analysis

The goals of this work package will be as follows:

- proteomics, lipidomics, metabolomics, transcriptomics and genetics/epigenetics analyses;
- analysis starts after go/no go decision depending on a phenotype overlap of less than 10% across the different clusters.

Work package 6 – Disease modelling

The goal of this work package will be as follows:

- systems biology analysis based on imaging and omics data generated in work packages 3 and 5.

Work package 7 – Preclinical models

The goals of this work package will be as follows:

- identification of existing pre-clinical models for diabetic cardiomyopathy;

- development of relevant and reliable *in silico*, *in vitro* and *in vivo* models based on disease modelling.

Topic 2 : Genome-Environment Interactions in Inflammatory Skin Disease

Topic details

Topic code	IMI2-2017-13-02
Action type	Research and Innovation Action (RIA)
Submission and evaluation process	2 stages

Specific challenges to be addressed

Inflammatory skin diseases affect a significant percentage of our global population. Atopic Dermatitis (AD) affects approximately 10% of children and 3% of adults worldwide. Psoriasis (Pso) affects approximately 2% of our population. These diseases remain poorly understood with limited understanding of their mechanism, endotypes, ontology and co-morbidities, affecting the quality of effective treatments. While there may be aspects of these diseases that overlap, others show little or no similarities e.g. their associated co-morbidities are generally quite distinct with Pso being linked with arthritis, psychiatric disorders, metabolic syndrome and cardiovascular sequelae while AD is associated with rhinitis, asthma, food allergy as well as cardiovascular complications. As a result, there is an immediate need for sophisticated, in-depth investigations of these diseases that address transformative topics. These studies include, but are not limited to, the impact of environmental factors (e.g. via the microbiome) interacting with genomic factors and studies that help elucidate molecular pathways of disease in a comprehensive, patient-driven manner. To this end, the challenge is seeking to define the key heterogeneous and homogeneous aspects of AD and Pso, both within each disease and across their shared biology. Such characterisation can include clinical hallmarks, patient epidemiology and reported outcomes, and assessment of molecular signatures. Expanding our current knowledge to understand unique endotypes of inflammatory skin diseases will help give rise to more precise, targeted treatments that can yield long lasting reductions in disease burden and improved patient quality of life, fulfilling unmet medical needs in patient care.

Need and opportunity for public-private collaborative research

The proposed topic addresses a complex issue related to human diseases. This can only be adequately addressed by a combination of collaboration and specialised expertise, which would be impossible in the setting of a single organisation or institution. Specific contributions to a collaborative effort would likely be:

- Pharmaceutical companies possess access to clinical trial samples related to Pso and AD, and the expertise in specialised technologies that can be applied;
- Academia has the clinical expertise and patient access (both retrospective and prospective) needed, as well as unique, state-of-the-art technologies;
- Patients and caregivers, as well as advocacy groups related to these diseases, provide important inputs into the real-world issues related to inflammatory skin diseases;
- Small- and Medium-sized Enterprises (SMEs), businesses with appropriate interests and Contract Research Organisations may contribute to centralised development of key output information and deliverables.

Scope

The action to be generated from this topic is expected to lead to a step change in our understanding of the molecular mechanism and ontology of the two main inflammatory skin diseases: AD and Pso. Elucidating the molecular pathways of these inflammatory skin conditions over time will give rise to novel and meaningful therapeutic targets for specific patient populations and help address the complex patterns of co-morbidities. In addition, this work will identify biomarkers that will enable robust, efficient and meaningful patient management.

These objectives should be achieved both via a retrospective assessment of Pso and AD patients that can aid in defining key endotypes of disease and the disease commonalities and uniqueness, as well as via access to ongoing prospective studies that will embrace novel approaches and hypotheses relating to defining these. It is expected that reliable access to robustly defined clinical information and specimens will be vital to the overall scope.

Expected key deliverables

1) Identify shared and distinct disease mechanisms of AD and Pso:
   - Establish a BioResource that includes patient samples (blood, skin tissue) reflective of baseline status as well as longitudinal samples of patients under standard of care;
   - Investigate patient-centred outcomes of AD and Pso (e.g. disease progression, quality of life evaluations, patient reported outcomes), particularly taking advantage of patient samples obtained from ongoing longitudinal studies;
   - Investigate the genetic and epigenetic profiles as AD, Pso and healthy controls of these patient samples;
   - Investigate the transcriptome of AD, Pso and healthy controls;
   - Investigate environmental factors (e.g. microbiome) of AD, Pso and healthy controls;
   - Investigate commonalities and differences in samples (e.g. skin biopsies, peripheral blood mononuclear cells PBMCs) from patients with varying levels of disease severity;
   - Apply cutting edge technical approaches to samples obtained from ongoing prospective collections/trials, including single cell profiling, high dimensional immune subset analysis and advanced bioinformatics analysis.
2) Establish a new disease ontology by defining distinct and overlapping inflammatory skin disease endotypes and co-morbidities:
   - Investigate characteristics/pathways associated with disease;
   - Investigate characteristics/pathways associated with disease progression;
   - Investigate how environment (microbiome) interacts with genomic features to drive disease;
   - Develop a molecular understanding of how these factors interact in disease;
   - Investigate the impact on co-morbidities (existing registries):
     - For Pso these would include: arthritis, cardiovascular sequelae (MI, Stroke), metabolic syndrome (insulin resistance) and psychiatric disorders (depression).
     - For AD these would include: rhinitis, food allergy, asthma and other potential comorbidities such as new cardiovascular complications.
3) Identify molecular, immunological and microbial biomarkers that inform prognosis and response to therapy of patients suffering from inflammatory skin disease. Such deliverables should be capable of improving diagnosis and directed care decisions and might include:
   - Identify markers that predict disease severity;

- Identify markers that predict response to treatment;
- Identify how endotypes differ in response to therapy;
- Identify how endotypes differ in prognosis.

Expected impact

Currently, Pso and AD represent diseases difficult to treat and they significantly impact quality of life and medical health care costs for patients. This topic aims to comprehensively address aspects of disease endotypes, underlying pathobiology, and factors contributing to initiation, exacerbation and severity of disease, as well as response to therapy. Consequently, there are broad impacts relevant to the IMI2 goals that include:

- Research and Development (R&D) Process: using a patient-centred approach through comprehensive characterisation of skin disease heterogeneity, it is expected that new understandings into pathobiological processes will be established that should help drive future therapies, as well as stimulate new levels of understandings into skin biology and how it is regulated during homeostasis, disease, and repair.
- Regulatory Pathways and Health Technology Assessment: establishment of comprehensive disease endophenotyping will improve directed care decisions and future clinical trial design, including biomarkers, quality of life considerations, and patient enrolment suitability.
- Clinical and healthcare practices: understanding of early life events and environmental influences over disease progression and severity will support improvement in physician recommendations and management of patients.

The topic expected impact is to establish, and support access to, a world-leading analysis of skin disease, as comprehensively addressed from the perspectives of AD and Pso. This should be achieved through studying unprecedented patient numbers, a robust depth of data available (e.g. clinical, transcriptomic, response to treatment etc.), state-of-the-art approaches to studying the disease biology and central accessibility for users of the BioResource.

- In terms of strengthening the competitiveness and industrial leadership in Europe impact will be significantly enhanced by also including the relevant expertise from the Small- and Medium-sized Enterprises (SMEs).Their involvement might offer a complementary perspective to industry and the academia, and help deliver the long-term impact of the project.

Potential synergies with existing Consortia

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

While there are no current consortia aimed at the scope of this topic, the proposal has potential synergies with immune-related initiatives such as IMI **U-BIOPRED** (http://www.europeanlung.org/en/projects-and-research/projects/u-biopred/home) examining asthma (potential synergy with AD outcomes), and with a number of other disease specific consortia looking at microbiome regulation over disease (e.g. the Inflammatory Arthritis Microbiome Consortium as well specifically the finalised MAARS consortium: http://www.maars.eu/).

Industry consortium

The industry consortium is composed of the following EFPIA companies:

- Sanofi (lead)
- Boehringer Ingelheim

- Pfizer
- UCB

The industry consortium will contribute the following expertise and assets:

Contributions include prospective clinical study samples and/or data based on samples from atopic dermatitis and/or psoriasis trials; generating, processing and analysing RNA and other –OMICS data, precision immunology based studies incl. and as well as fluorescence-activated cell sorting (FACS), immunohistochemistry (IHC) data and methods. It also includes bioinformatics experts and data management activities as well as translational and clinical expertise. Further details are listed in the section “Suggested architecture of the project”.

Indicative duration of the action

The indicative duration of the action is 60 months.

Future Project Expansion

Potential applicants must be aware that the Innovative Medicines Initiative 2 (IMI2) Joint Undertaking, may publish at a later stage another call for proposals restricted to those projects already selected under this topic in order to enhance and progress the results and achievements by extending their duration and funding to prospectively progress the findings within this consortium.
Consortia will be entitled to include other beneficiaries as they see fit. In the context of this topic, such future expansion refers specifically to progress with translation and validation of key results and findings of this consortium (e.g. disease ontologies, biomarker candidates).

Indicative budget

The indicative industry in-kind contribution is EUR 8 300 000.

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

The financial contribution from IMI2 JU is a maximum of EUR 10 500 000.

Applicant consortium

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

The applicant consortium is expected to address all the 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 should be comprised of expertise in three key areas: clinical characterisation and patient access (incl. samples and/or data from on-going prospective collections/trials for atopic dermatitis and/or psoriasis), biological specimen-based profiling, and advanced informatics. Consequently, the consortium would likely involve partners who bring expertise in access to and use of medical record-based information; this can be from ongoing clinical care sites and from ongoing clinical trials provided by the industry consortium (see above).
For a successful project, these samples and data will need to be accessible to the whole consortium.

Since access to clinical information and specimens is critical to the overall success of defining endotypes and the consortium goals, applicants should demonstrate their capacity (e.g. patient consent or waiver to consent)

and quality to provide access to these. Applicants may involve academic medical centres with existing materials, biobanks, or organisations planning or actively participating in clinical trials and able to obtain consent. Building from previous efforts to define disease endotypes (e.g. as performed with asthma [1]), it is anticipated that access to large numbers of patients will be important to establish the power needed to define endotypes (e.g. 190 asthma patients were used to define a subgroup with high periostin [2]). Value is seen in both cross-sectional and longitudinal approaches but longitudinal data (e.g. patients before and after therapy) is seen as high value.

Consequently, partners providing medical record-based information as project background must be mindful that they, as background contributor, should have sufficient title to said background to authorise its use within the project pursuant to the IMI2 JU IP and legal framework. Consideration should also be given to additional information that may be introduced after the start of the project but is not listed as project background at start date.

Biological profiling will encompass partners with skills in transcriptomics, genetic sequence determination (e.g. SNP variance), microbial characterisation from human samples, proteomics, lipidomics, advanced immune cell phenotyping (e.g. single cell characterization), metabolomics and other specialist technologies. Advanced informatics will coordinate in-depth analysis of the input data to establish endotypes and would require expertise in big-data handling and include machine-based learning, cluster mapping and advanced algorithm development. Skills in molecular epidemiology, clinical science, and integration of biological profiling with such datasets, will also be considered valuable to the consortium.

The applicant consortium must demonstrate significant experience, possibly through the participation of an experienced SME, in both Advanced Analytical approaches and strong Data Management practices. Advanced Analytical approaches will require the coordination of in-depth analysis of the input data to establish endotypes and would require expertise in big-data analysis and include machine-based learning, cluster mapping and advanced algorithm development. Strong Data Management experience is considered to be a critical strength of the successful applicant and therefore the applicants must be able to demonstrate previous experience of managing/coordinating a multi-centre multi-node clinical-research data-generation activity of comparable scope. Essential experience should also include the legal and ethical challenges associated with integrating multi-centre patient-derived data, as well as physical data-processing/ data-management and data management practices (privacy, security). Crucial will also be a demonstrable ability to deliver analytical platforms to facilitate the above mentioned Advanced Analytical approaches for a range of scientific/medical and analytical communities.

The applicant consortium is expected to include resources for project administration, management and communication.

In addition to industry and academic partners, SMEs can be of great benefit to IMI projects and strengthen the competitiveness and industrial leadership of Europe. Their involvement might offer a complementary perspective to industry and the academia, and help deliver the long-term impact of the project. For these reasons, applicants should consider engaging SMEs throughout the proposal. Under this topic, the contribution of SMEs would be considered especially beneficial in the context of professional data management and orchestrating data collection, analysis and availability to the rest of the consortium in a centralised, scalable and sustainable manner.

Given the nature of the key deliverables it is also expected from the applicant consortium that they provide experience and interaction in communication with Global Regulators, Patients, Practitioners and Payers, who may be members of a to be established Advisory Board.

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. Further details are listed below in the outline of the contributions from the different companies as well as the outline of the applicant consortium.

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

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

Industry contribution

The EFPIA participants are companies with extensive, ongoing interests in skin diseases and have come together to address this topic in a collaborative manner aligned with the goals of the IMI programmes. The contributions are framed across the needs of the work-flow and include management support, methodological expertise and training, access to specimens and samples and data-management and data control. The specifics of each partner are as follows:

- Sanofi (lead)

  Sanofi aim to provide the overall scientific leadership needed to support the programme and to ensure the work is of the highest novelty and innovation. Sanofi will also support the alliance management needed to support the successful execution of this project (including project monitoring and problem resolution) to meet expectations, goals and timelines. From a non-administrative contribution, Sanofi proposes to provide access to advanced, precision based technologies and bioinformatic capabilities. Sanofi will also provide clinical and translational expertise and access to resources that are necessary for regulatory oversight and ethics.

- Boehringer Ingelheim

  Boehringer Ingelheim will provide contributions that will financially support data generation and input in the form of postdoctoral scientists embedded within members of the consortium. This will provide training and career development for individuals. In addition, Boehringer Ingelheim also will support work packages that utilise immune cell assays, both as activities on prospective samples being collected by the consortium, as well as retrospective samples using appropriate methodologies.

- Pfizer

  Through access to samples from ongoing prospective clinical trials within their own programmes, Pfizer will support the work packages aimed at using advanced technologies (e.g. single cell analysis from skin, lipidomics, epigenetics) that cannot be performed on retrospective samples. Pfizer will also provide contributions to the clinical and molecular profiling needs important to assessing endotypes of AD and Pso.

- UCB

  UCB will provide Full Time Equivalent (FTE) support that will be important for the clinical and molecular profiling needs of the program. UCB will also provide support for the data management and capture needs of the programme.

Expected Applicant consortium contribution

The Applicant consortium contributions include access to existing samples relevant to the skin disease topic (especially AD and/or Pso), as well as access to *de novo* samples from ongoing collection. They will provide access to clinical epidemiology information related to skin diseases through comprehensive medical records. They will provide highly specialised techniques of relevance to the overall topic and science of skin and inflammation, including microbiome assessment, and bulk and/or single-cell analysis of transcriptomics, lipidomics, metabolomics; inclusion of precision-based approaches to this is considered a strength. The

applicant consortium can provide state-of-the-art approaches to studying skin biology, including 3D organotypic cultures. The applicant consortium contribution should also include advanced modelling of human diseases based on multi-parameter data streams

Reference

[1] Lötvall J, Akdis CA, Bacharier LB, Bjermer L, Casale TB, Custovic A, Lemanske RF Jr, Wardlaw AJ, Wenzel SE, Greenberger PA. Asthma endotypes: a new approach to classification of disease entities within the asthma syndrome. J Allergy Clin Immunol. 2011 Feb;127(2):355-60. doi: 10.1016/j.jaci.2010.11.037.

[2] Matsusaka M, Kabata H, Fukunaga K, Suzuki Y, Masaki K, Mochimaru T, Sakamaki F, Oyamada Y, Inoue T, Oguma T, Sayama K, Koh H, Nakamura M, Umeda A1, Ono J, Ohta S, Izuhara K, Asano K, Betsuyaku T. Phenotype of asthma related with high serum periostin levels. Allergol Int. 2015 Apr; 64 (2): 175-180.

Topic 3: The value of diagnostics to combat antimicrobial resistance by optimising antibiotic use

Topic details

Topic code	IMI2-2017-13-03
Action type	Research and Innovation Action (RIA)
Submission and evaluation process	2 stages

Specific challenges to be addressed

Antimicrobial-resistant (AMR) bacterial strains killed 25 000 people in the EU in 2007 and cost the economy €1.5 billion a year. Many antibiotics that were once thought to put an end to infectious diseases are no longer working. Huge amounts of antibiotics are prescribed and consumed unnecessarily in almost all healthcare systems. The misuse of antibiotics has created a huge global health crisis. Prudent use of antibiotics is urgently required in order to protect the efficacy of our currently available antibiotics. We can reduce their unnecessary use in many ways; nevertheless diagnostics have the potential to provide more targeted, accurate use of antibiotics which is in the best interest of patients and the wider population. Diagnostics play a critical role in guiding treatment in infectious diseases. However, the value of diagnostics as a critical component of antimicrobial stewardship programmes is not fully established throughout Europe, with guidelines, funding and policy varying in each country. This hinders the adoption and use of currently available diagnostic tests by health professionals, as well as the development of advanced or innovative diagnostic tools. Therefore, a pan-European approach is required, to demonstrate the medical, economical and public health value of diagnostics for combating AMR: rapid and reliable characterisation of pathogens and their antibiotic resistance characteristics along with host susceptibility biomarkers. One way to determine the full value of diagnostics, and the optimal means of addressing the multitude of obstacles for their creation, valuation and deployment, is to analyse all these aspects in a standardised clinical trial network.

The overuse of antibiotics and the underuse of diagnostics occur within the entire breadth of healthcare: primary care, as well as hospitals with acute care, rehabilitation facilities and long-term care facilities, where most of the emerging antibiotic-resistant pathogens can be found. In Europe, 30-50% of antibiotics are prescribed unnecessarily, according to estimates from the European Centre for Disease Prevention and Control (ECDC). It is also well-described that the largest volume of antibiotics for human use is prescribed in the community setting (e.g. physician offices, clinics), most often for respiratory complaints and suspected respiratory tract infections – and over half of the time unnecessarily. Better diagnostic capabilities and more aggressive antimicrobial stewardship are amongst the top five unmet medical needs in strategies to combat antibiotic-resistant infections.

One of the most convincing means of demonstrating the value of diagnostics is to conduct prospective clinical trials and data collection which evaluate their impact in real-life patient-care settings. Due to the need for large numbers of patients in such analyses, a network of well-defined patient-care settings is necessary to carry out the type and extent of studies needed to demonstrate the value of diagnostics. The goal for setting up a network of clinical sites is to assess the impact of ‘standardised care and management algorithms’ using well-defined diagnostics in a proscribed manner in a well-defined and common infectious syndrome, compared to ‘usual care’. The choice of the targeted infectious disease is expected to be community-acquired acute respiratory tract infection (CA-ARTI) since it best reflects an area of importance where the over-prescribing of antibiotics is most flagrant. Possible outcomes which could be measured include, among others: i) doses or days of antibiotics prescribed, ii) proportion of patients not receiving antibiotics, iii) development of antibiotic-resistant colonisation post antibiotic therapy, iv) selection of pathogens with a resistant phenotype during or post therapy, v) emergence of antibiotic resistance among ‘normal’ intestinal flora during or after therapy.

There is currently a dearth of studies which can provide the evidence of the value of diagnostics in well-characterised situations, and the lack of such evidence has been a hindrance for diagnostic innovation. Furthermore, the current financial framework (i.e. inadequate reimbursement of diagnostics, reimbursement based on technology rather than medical value) does not encourage innovation related to *in vitro* diagnostic tests. The current *in vitro* diagnostic business model – focused on technology used, lab activity measures, and complexity indicators – is antiquated, and should change to focus on patient outcomes and health-economic benefits to incentivise the creation and utilisation of high-medical-value diagnostics. Moreover, regulatory approval has historically been based on analytical performance, rather than on clinical effectiveness. Inserting patient-based benefits into the regulatory process would advantage diagnostics which confer the most benefit to individuals and the healthcare system.

More background information is available in the following list of publications:

[1][2][3][4][5][6][7][8][9][10][11][12][13][14][15][16][17][18][19][20][21][22][23][24][25][26][27][28][29][30][31][32][33][34][35][36][37][38][39][40][41][42][43][44][45][46][47][48][49][50][51][52].

Need and opportunity for public-private collaborative research

The urgent action to address the escalating problem of antibiotic resistance requires cooperation amongst industry, academia, patients and patient groups, policymakers, public health experts and healthcare decision-makers in order to implement critical solutions, including impactful diagnostics, which will allow preserving the efficacy of the antibiotics currently available or in development. Multiple diagnostics already exist which can be used to accurately and efficiently guide and improve antibiotic prescribing, but they are under-utilised across Europe. A public-private project is required to address the barriers which prevent the uptake and development of diagnostics for antimicrobial stewardship, which include studies, policy development, funding and reimbursement formulae and schemes, physician education and patient awareness, psychosocial factors, appropriate and innovative assessment (e.g. modern HTA which uses latest technology-specific methods of health technology assessments that include economic and health outcomes in order to assess comprehensively the value of these technologies and not only the clinical effectiveness), and disparate regulatory requirements.

Scope

The main objective of this action is to understand, demonstrate, and quantify the value of diagnostics and the obstacles to their adoption and use in the framework of a Standardised Care Network in order to combat antimicrobial resistance (AMR) by optimising antibiotic use in Europe.

The overuse of antibiotics and the underuse of diagnostics occur within the entire breadth of healthcare. It is a major issue especially in the 'community' setting (e.g. non-hospital clinics, private physician offices, para-medical clinics) where the majority of human antibiotics are used, most of which are inappropriately and unnecessarily prescribed. It is crucial to demonstrate both the economic and clinical value of diagnostics to health systems and purchasers. Governments and healthcare systems need to understand the wider value of diagnostics – including how their use can help them to achieve reductions in AMR and healthcare costs.

Health economic models for the use of diagnostics must be developed to:

- address the costs and benefits of the use of diagnostics and their impact on antibiotic prescribing;
- propose funding models (e.g. research incentives, reimbursement framework, adoption motivation) which would facilitate the development, introduction, deployment and use of diagnostics into routine medical care.

A global roadmap, aligned with the essential diagnostics list from the World Health Organisation (WHO) (likely to be disclosed at the end of 2017) must be defined to promote the use and development of diagnostic tools that would have distinct and clearly defined objectives: (i) avoiding unnecessary antibiotic use; (ii) optimising patient treatment and antibiotic use; (iii) identifying high-risk patients and/or pathogens for targeted and personalised antibiotic therapy; (iv) using diagnostics in clinical trials for supporting the development of new

anti-infective approaches (prophylactic or therapeutic); (v) boosting innovation for new diagnostic development.

This project aims at providing clinical evidence to demonstrate the medical value, healthcare benefit and economic viability of diagnostic tests for combatting antibiotic resistance and improving patient outcome in conditions such as community-acquired acute respiratory tract infection (CA-ARTI).

Four objectives need to be addressed in this project:

Objective 1

The first objective is to establish a health-economic framework to assess and demonstrate the impact – for individual patients and public health in general – of increasing the use of diagnostics to reduce or optimise antibiotic prescription and ultimately combat the development of antibiotic resistance.

The framework should build on existing evidence from extensive research work and literature in the field as well as experiential knowledge and expertise from key stakeholders in, for example, traditional and innovative value-based evaluation methods, reimbursement schemes, research incentives, evaluation models, policies etc. Results should be disseminated in an adapted way to all stakeholders, including policymakers, clinicians and patients.

Objective 2

The second objective is to establish a Standardised Care Network (pre-existing or new) in order to conduct clinical trials evaluating the value of diagnostics. This network should include high-, medium- and low-antibiotic-use countries in Europe with an antibiotic stewardship programme in place. At a minimum, it should include five high-income EU countries representing a large population base, and five upper or lower middle-income countries from the EU Member States and H2020 Associated Countries. A business model must be constructed which will assure the sustainability of the Standardised Care Network after the IMI project completion. In addition, within this network, a bank of appropriate clinical specimens – properly annotated and curated – must be kept for the duration of the project and a model proposed to sustain the biobank *a posteriori* in cooperation with the diagnostics industry.

Objective 3

A third objective is to design and implement clinical studies to demonstrate the value of diagnostics in the optimal management of community-acquired acute respiratory tract infections (CA-ARTIs), by using the outputs, measures and deliverables defined in the health-economic framework (Objective 1). The study must use combinations of 'host-based' and 'pathogen-based' diagnostic tests in order to determine the optimal testing algorithm for reducing inappropriate antibiotic use and the subsequent development of antibiotic-resistant bacteria (colonisation and/or infection).

Objective 4

The fourth objective is to explore, define and attempt to resolve the many aspects which prevent the more widespread adoption of diagnostics when delivering healthcare to the population. Focus will be necessary on patient and healthcare provider education, psychological, ethical, organisational and social barriers in order to understand and address this complex issue.

Expected key deliverables

Main deliverables include (i) a defined framework to assess and demonstrate the value of diagnostics to optimise antibiotic therapy and reduce antibiotic resistance, taking into account all expected evidences from key stakeholders; (ii) a sustainable Standardised Care Network representing the different countries mentioned above and encompassing the entire range of healthcare establishment from community clinics to long-term care, able to collect and share thorough information on pathogen, patients status, treatment regimen and outcome; (iii) comprehensive clinical studies on the value of diagnostics in community-acquired acute respiratory tract infection (CA-ARTI) by using outcomes and measures specified in the framework; and (iv) a definition and better understanding of the psychosocial aspects preventing widespread adoption of

diagnostics during healthcare delivery, focusing on education, psychological, organisational, ethical and social barriers, as well as pragmatic obstacles.

- A framework has to be set up for demonstrating how the use of diagnostics can help to achieve reductions in antibiotic use and the emergence of AMRs. It requires a precise and shared methodology agreed and defined with main stakeholders to:
  1. benchmark the standard of care and identify the most promising opportunities for improvement,
  2. specify the required clinical evidence for the adoption of the best practice and define measurable clinical outcome and success parameters,
  3. describe necessary standards and quality controls to allow the use of the generated evidence for IVD registration,
  4. review the current regulatory environment and recommend improvements for product approvals to accelerate their time to market,
  5. propose funding models facilitating the introduction and application of diagnostics into primary care,
  6. develop a health economic model acceptable to payers for establishing value-based reimbursement for innovative diagnostics,
  7. develop an education and dissemination programme to facilitate the implementation of the framework.

- Standardised Care Network comprising high-, medium- and low-antibiotic use countries in Europe, including at least five high-income EU countries that represent a large population base and five upper or lower middle-income countries from the EU Member States and H2020 Associated Countries, should be established to:
  1. perform extensive characterisation of clinical samples and pathogens isolated from patients,
  2. create and maintain a biobank of samples associated with a database and repository of information,
  3. propose an information flux architecture for data sharing and analysis,
  4. define a business concept to sustain the infrastructure for future rapid benchmarking and translation of innovative diagnostics and/or other process changes.

- A multi-country and multi-centre clinical study must be designed and conducted on the value of diagnostics in community-acquired acute respiratory tract infection (CA-ARTI) in order to:
  1. establish the optimal combination of pathogen-based and host-based diagnostics to achieve the outcomes being measured,
  2. define measurable clinical and other outcomes as well as success parameters to support quantification of the clinical impact and value of diagnostics.

- A thorough exploration and analysis of the psychosocial obstacles preventing widespread adoption of diagnostics when delivering healthcare to the population should be conducted to:
  1. define the psychosocial obstacles related to adoption of diagnostics by healthcare providers and patients, and,
  2. provide pragmatic solutions to each of the obstacles outlined, as well as evidence-based methods for their resolution within a European framework.

Expected impact

Expected impact will be the reduction of antibiotic use and AMR resulting in improved patient care through better routine use of diagnostics. It should be adapted according to national/regional requirements and maintained based on a sustainable business model beyond the proposed funding period. A decrease of antibiotic-prescribing rates should further happen in countries involved in the study. This would happen thanks

to a raised awareness of health professionals and patients on the necessity to effectively replace empiric therapy by avoidance of antibiotics where unnecessary and definitive targeted therapy when required, particularly for acute respiratory tract infections (ARTIs) with short-term health benefits for patients, short-term economic benefits for the healthcare system, and mid-term / long-term benefits on reducing antibiotic resistance.

The main expected impacts should be: (i) optimum use of diagnostic tests in CA-ARTI for achieving improved patient outcomes, reduction in the inappropriate use of antibiotics, and decrease in the incidence of key antibiotic-resistant pathogens; (ii) wide dissemination of evidence-based conclusions that will sensitise the medical and patient communities, as well as decision makers, to the clinical and economic value of diagnostics; (iii) incorporation of guidance using diagnostic tests and testing algorithms in national and international guidelines; (iv) assistance to regulatory bodies to facilitate adoption of diagnostic tests into wider routine practice; (v) assistance to health technology assessment (HTA) bodies to enable appropriate, fit-for-purpose assessment of the clinical value of diagnostics; (vi) reform of pricing policies (including reimbursement) related to diagnostic tests, according to the demonstrated or anticipated medical value and health outcomes.

New health economic models demonstrated through the project will lead to new pan-European guidelines and algorithms to facilitate the widespread introduction, deployment, adoption and reimbursement of existing and new diagnostics to guide appropriate antibiotic use and reduce unnecessary antibiotic prescribing. Economic models will illustrate to governments, third-party payers and healthcare providers the economic feasibility and benefits of utilising diagnostics to guide appropriate antibiotic prescribing in various healthcare settings.

This evidence should then be published, disseminated, and adopted in order to sensitise the medical, political, regulatory and patient communities to the value of diagnostics in the targeted condition, and promote adoption of the diagnostic tests and testing algorithms into national and international guidelines. Additionally, it is expected that interactions will occur with European (and other) regulatory bodies to assist in the timely approval of diagnostic tests for quick introduction into routine clinical practice.

Health technology assessment (HTA) bodies will be also consulted separately and/or via EUnetHTA Joint Action 3 (European network for Health Technology Assessment, http://www.eunethta.eu) in order (i) to facilitate future, fit-for purpose assessments of the clinical value of diagnostics and (ii) to enhance, improve and reformulate information on the financial decision of diagnostic tests according to their medical value and the health outcomes which they confer.

Applicants should indicate how they will strengthen the competitiveness and industrial leadership of Europe by, for example, engaging suitable small and medium-sized enterprises (SMEs). They can benefit from this project in many ways: (i) choice of their diagnostic for the trial; (ii) clarification of HTAs and other aspects of diagnostic implementation which benefits all diagnostic companies; (iii) connect to laboratories for easier access to blood samples from patients across Europe and clinical data from multi-site European studies, tools that are normally beyond the reach of small companies; (iv) set-up and deployment of education programs; (v) exploitation/expansion opportunities: possibility of spin-off creations, trademark, licensing deals, results implementation by industry, sustainability plans, commercialisation, patent applications, increase in company size/workforce, etc.

Potential synergies with existing consortia

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

For example, the initiatives listed below might be relevant in that respect:

- **COMBACTE-Net** and **New Drugs for Bad Bugs (ND4BB) programme** (www.combacte.com): This IMI project has established large clinical investigator site and laboratory networks comprising more than 800

clinical sites and more than 600 laboratories across more than 40 European countries. Where possible, this project could build upon the established ND4BB networks and explore synergies. Applicants should note however that there is no requirement to include partners currently engaged in ND4BB in their proposal, but partners should be chosen to best match network needs and the objectives of this call topic.

- **DRIVE-AB**: The IMI project DRIVE-AB (Driving re-investment in R&D and responsible use of antibiotics) (http://drive-ab.eu/) is assessing the present and future burden of antibiotic resistance, defining the value of new antibiotics, and proposing new economic models for antibiotic development, bearing in mind innovation, stewardship, and access.
- **ND4ID** (http://www.nd4id.eu/): the H2020 project ND4ID (New Diagnostics for Infectious Diseases) is addressing the current shortcomings in the training of IVD researchers through an inter-sectorial, multidisciplinary and translational approach by transversal researchers to close the apparent gap between the clinical perspective and the technological perspective on IVDs.
- **ECRIN** (The European Clinical Research Infrastructure Network - http://www.ecrin.org/) is facilitating clinical research in Europe.
- **Enpr-EMA** (European Network of Paediatric Research at the European Medicines Agency - http://www.ema.europa.eu/ema/index.jsp?curl=pages/partners_and_networks/general/general_content_000303.jsp).
- **PREPARE** (Platform for European Preparedness Against (Re-)emerging Epidemics - www.prepare-europe.eu) and its associated GRACE network.
- Upcoming **pan-European Paediatric Clinical Trials Network** (part of the 10th Call for proposals of IMI2 JU)
- The UK Department of Health project Innovate UK AMR is focused on creating an infrastructure that will fast-track the research, development, evaluation and commercialisation of new drugs, diagnostics and vaccines, also, establishing a global multi-centre clinical trials network for drugs, diagnostics and vaccines, with a focus on antibiotic resistance.
- **CARB-X** (http://www.carb-x.org/) mostly devoted to drug development, but new diagnostic technologies are in scope.
- **JPIAMR** http://www.jpiamr.eu/: The scientific research agenda and recommendations of JPIAMR are aligned with the objectives of this project. Synergies with JPIAMR should therefore be explored.
- **Joint action Antimicrobial Resistance and Health Care Associated Infections** (European Commission, 3rd Health Programme - http://ec.europa.eu/chafea/health/actions-2016.html).
- Results and learnings of the following past EC-funded projects (now completed) might potentially be useful:
    - **C4L** (http://cordis.europa.eu/project/rcn/102035_en.html) developed rapid diagnostic tests to link antibiotic prescription with evidence-based diagnosis. Combining the Multiplex Ligation-dependent Probe Amplification (MLPA) and microfluidic technologies allows determination of viral or bacterial origin, as well as bacterial resistance mechanisms.
    - **PARCIVAL** (https://www.up2europe.eu/european/projects/partner-network-for-a-clinically-validated-multi-analyte-lab-on-a-chip-platform_15872.html) developed an integrated and automated multi-analyte lab-on-a-disk platform for the fast and reliable sample-in / answer-out diagnosis of highly infectious respiratory pathogens, resistance patterns and biomarkers for individual severity of the infection.
    - **ROUTINE** (http://cordis.europa.eu/project/rcn/104172_en.html) developed a test that integrates sample preparation, DNA amplification and a fluorescent-based read-out on one platform to allow direct detection of bacteria causing upper respiratory tract infection and the associated antibiotic resistances within 30 min.
    - **RiD-RTI** (http://cordis.europa.eu/project/rcn/104050_en.html) developed and evaluated diagnostic tools for the rapid (< 2 hrs) diagnosis of pneumonia. The diagnostics products are ‘near patient’, reliable, cost-effective and user friendly allowing for detection, identification, and quantification (for selected targets) and molecular drug susceptibility testing of RTIs.

- **RAPP-ID** (https://www.uantwerpen.be/en/projects/rapp-id/) developed some of the technologies and innovations needed to speed up the development of rapid diagnostics tests such as a prototype of a breath sampler for influenza and a prototype of the ventilator-associated pneumonia (VAP) test (development of chips which help isolate the DNA of these bacteria from aspirates of VAP patients).

Industry consortium

The industry consortium is composed of the following EFPIA partners:

- bioMerieux (lead)
- Janssen Diagnostics
- Abbott (rapid diagnostics division)

In addition, the industry consortium includes the following IMI2 JU Associated Partners[8]:

- Accelerate Diagnostics
- Bio-Rad
- BD
- The Wellcome Trust

The Wellcome Trust has an interest to better demonstrate the value of diagnostics (both clinical and economic value) to health systems and purchasers. This evaluation can serve as the evidence base to inform a coordinated international advocacy. The Wellcome Trust aims to stimulate the development of new ways for diagnostics to be delivered into care pathways, and trail blaze diagnostics development which can be used in low- and middle-income countries (LMICs). The Wellcome Trust participates in the present topic as Associated Partner to IMI2 JU, contributing EUR 3 400 000.

The industry consortium will provide financial and/or in-kind contributions that altogether address the following area:

- pathogen and host-based assays and equipment
- clinical design and medical affairs expertise
- point-of-care data connectivity solutions, software and expertise
- data analytics (e.g. diagnostic biostatistics and bioinformatics)
- market access / pricing / reimbursement expertise
- health economics
- biobanking capabilities and pathogen characterisation (e.g. antibiotic susceptibility testing, clinical annotations)
- training facilities and modules (assays, data privacy).

[8] Moreover, MedTech Europe (http://www.medtecheurope.org/), as the European trade association of medical technology industries, will support this project in a role of an informal advisor.

Indicative duration of the action

The indicative duration of the action is 48 months.

Indicative budget

The indicative in-kind and financial contribution from EFPIA partners and IMI2 JU Associated Partners is EUR 6 800 000.

This contribution comprises an indicative EFPIA in-kind contribution of EUR 1 945 000 and an indicative IMI2 JU Associated Partners in-kind and financial contribution of EUR 4 855 000, of which EUR 3 805 000 financial contribution to the beneficiaries receiving JU funding in the selected action.

The financial contribution from IMI2 JU is a maximum of EUR 6 800 000.

The total financial contribution available to applicants for proposed activities in relation to the objectives of this action is therefore EUR 10 605 000. Therefore, applicants may allocate up to EUR 10 605 000 in the budget of their short proposals.

Applicants should however note that the final allocation of the financial contribution will be further discussed during the preparation of the full proposal for stage 2 between the applicant consortium selected at stage 1, the EFPIA partners and the IMI2 JU Associated Partners (full consortium).

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 satisfies the following conditions and mobilises, as appropriate, the following expertise or capabilities:

- health economists experienced in diagnostic studies;
- experience and know-how in conducting clinical trials including clinical operations and clinical programme management;
- access to a large population suffering from CA-ARTI across all age groups and differing healthcare environments (i.e. community, acute-care, rehabilitation, long-term care, home care);
- physicians and other healthcare providers experienced 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;
- payers / prescribers / regulatory organisations able to actively contribute to the development and standardisation of study procedures and processes (e.g. creation of study documents, patient/parent information);
- psychologists, social workers, educators and other social science experts skilled in the analysis of psychosocial barriers to health intervention implementation;
- expertise in advocacy;
- expertise in 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.

Applicant consortia will be expected to include experts and sites in a 'community' setting such as non-hospital clinics, private physician offices, para-medical clinics, etc. (where the majority of human antibiotics are used), as well as hospitals, rehabilitation facilities and long-term care facilities (where most of the emerging antibiotic-resistant pathogens can be found).

SMEs can be of great benefit to IMI projects and, inter-alia, strengthen the competitiveness and industrial leadership of Europe. Their involvement might offer a complementary perspective to industry and the academia, and help deliver the long-term impact of the project. For these reasons, applicants should consider engaging SMEs throughout the proposal. SMEs could provide in particular, but not exhaustively: (i) diagnostic tests, regulatory registered or in the registration process, including novel validated biomarkers; (ii) services, information systems or software for data sharing, storage and analysis; (iii) infrastructures, logistics and services for bio-banking and deep characterisation of pathogens or samples; (iv) project management and dissemination tools including set-up of education programs and training modules to advocate on the value of diagnostic to combat AMR.

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

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

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

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

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

It is anticipated that industry contribution would include:

- project management support (project design and continuous follow-up);
- legal expertise, health economics expertise;
- clinical operations, data management, and clinical expertise to support regular review of deliverables;
- training and support of professionals to use/run new diagnostic assays;
- co-leadership to contribute to consortium governance structure and meetings.

Work package 1 – Implementation of diagnostics

It aims at designing and testing a framework for establishing a sustainable infrastructure for the evidence based translation of innovative diagnostics into standard-of-care. The framework should assess and demonstrate the value of diagnostics both for individual patients and for public health. The framework should build on the available evidence and utilise an extensive consultation with key stakeholders.

A diagnostic test needs to provide the clinician with sufficient information to decide on the most appropriate antibiotic strategy or to deviate from prescribing antibiotics altogether. This need differs between various infectious diseases, between different clinical settings and between geographies within Europe and beyond. The project team and public/private partnership should elaborate further on a roadmap including the points outlined below.

- **User requirement specifications** outlining the minimal and optimal requirements of a diagnostic test from an end-user perspective. A separate document could be generated per clinical setting specifying regional differences with clear indication on how the specifications drive clinical utility. Such a document requires an extensive outreach to the various stakeholders, integrating their viewpoints. A number of case studies can be used to anchor these concepts in concrete examples.
- **Proposals of clinical algorithms** for use of diagnostics within various clinical settings. Such use should be based on what is considered 'responsible use' of antibiotics and should integrate in a first instance the result of one or more diagnostic tests with the results of the clinical evaluation of the patient. To this end, the different viewpoints held by different stakeholders should be mapped and linked to current and future (ideal) diagnostic concepts.

This study should reveal shortcomings in the currently available diagnostic tests – even if currently underused, which should feed a technological roadmap, aligned with the essential diagnostics list from WHO, addressing both bioassay content (host and pathogen biomarkers, probes, antibodies, metabolic substrates, etc.) and device/instrument gaps. Indeed, investments into novel technologies that might result in new returns could be considered to incentivise new technology development.

Key tasks:

1. establish a consulting network including physicians, European in vitro diagnostics (IVD) regulators, HTA and other assessment programmes, reimbursement experts, third-party payers, health economists, medical educators and psychosocial experts;
2. undertake a systematic review of the existing (peer-reviewed) literature and ongoing European AMR-related activities;
3. analyse the implementation process for innovative diagnostics into standard of care in CA-ARTI, describe key hurdles and propose actions to systematically drive their evidence based implementation, especially;
4. provide a description of the framework for a rapid evidence based implementation of innovative diagnostics into routine based on a Standardised Care Network;
5. facilitate the decisions regarding the implementation of the best practice process into routine with the key stakeholders;
6. establish and define the measurable clinical and other outcomes and success parameters with which to measure the clinical impact and value of diagnostics;
7. establish a list of shortcomings of currently available tests and propose high level requirements for new products that further improve the practice to tackle AMR challenge in CA-ARTI.

Work package 2 – Establishment of a Standardised Care Network

The purpose is to establish a Standardised Care Network (pre-existing or new) in order to conduct clinical trials evaluating the value of diagnostics. This network should include high-, medium- and low-antibiotic-use countries in Europe, including countries with and without an antibiotic stewardship programme in place. The network should include at least five high-income EU countries that represent a large population base and five upper or lower middle-income countries from the EU Member States and H2020 Associated Countries. A

business model must be constructed which will assure the sustainability of this network after the IMI2 JU project completion.
In addition, within this network, a bank of appropriate clinical specimens – properly annotated and curated – must be kept for the duration of the clinical trial, and a sustainability plan should be proposed.

Key tasks:

1. define and set-up a network of well-defined patient-care settings, in order to demonstrate and quantify the value of diagnostics for CA-ARTI management:
   - covering countries mentioned above,
   - encompassing the entire range and spectrum of healthcare establishments from community clinics to long-term care, including physician offices,
   - being coordinated and led through a single entity or group and providing a one-stop point of access,
   - establishing and sharing standardised care procedures and algorithms both for usual care and prospective clinical trial to generate data that feed criteria and evidences specified in work package 1,
   - leveraging or synergising with existing European networks or clinical research infrastructures (IMI, others) in a collaborative effort to shorten set-up time and expand access to patients and samples;
2. conduct multi-center prospective/randomised clinical trials in order to demonstrate and quantify the value of diagnostics for CA-ARTI and their impact in real-life patient-care settings:
   - respecting the frame of clinical studies defined in work package 4,
   - comparing use of novel diagnostics and procedure with usual care in a standardised manner,
   - ensuring relevant patient and sample data collection and storage in agreement with work package 3 requirements;
3. perform extensive characterisation of clinical samples and pathogens isolated from patients:
   - including both isolated pathogens, commensal flora and patient (host) sample analysis,
   - using reference (phenotypic) and state-of-the-art deep characterisation methods (whole genome sequencing, mass spectrometry, epidemiological tools) for pathogen analysis (identification, antibiotic resistance),
   - evaluating host status and response (immune profile, biochemical and genetic markers),
   - covering all antibiotic resistance traits encountered and allowing the identification of new markers or mechanism of resistance;
4. create and maintain a biobank of samples, clinical specimens and pathogens isolated from patients:
   - constituting a comprehensive collection of microorganisms and primary clinical samples with high quality standards (redundancy, traceability, storage),
   - constantly curated and updated based on latest results (new samples, patient follow-up) to allow reliable analyses (statistical performance, regulatory evaluation);
5. propose and validate a scheme and business model to allow the created Standardised Care Network to be sustainable and permanently accessible in Europe for further studies with an emphasis on diagnostics for infectious diseases in order to reduce global antibiotic use and AMR, and so:
   - broadening diagnostic evaluation to other clinical situations,
   - allowing long-term analysis of diagnostic value (patient outcome, infection and resistance recurrence).

Work package 3 – Data Analysis

The purpose is to provide tools and organisation suitable for the analysis of the data from the clinical study undertaken in the Standardised Care Network, including surveillance data, 'best practices' which are based on optimal patient outcomes, and all of the outcomes, measures and deliverables outlined in work package 1.

Key tasks:

1. establish a database and repository of information:
   - gathering results and information obtained in clinical studies (work package 4) performed in the Standardised Care Network (work package2),
   - containing all detailed information on isolated pathogens (identification, resistance traits, epidemiology, prevalence),
   - interfaced with laboratory / hospital information system,
   - connected with patient electronic record / retrieving key (anonymised) information relevant for the project,
   - collecting treatment information related to patient care (drug prescribed, treatment regimen, posology, antibiotic stewardship),
   - consolidating health-care associated expenses by category (hospital stay duration, cost of antibiotic treatment, complementary care, cost of testing…),
   - providing inter-operability features to allow connections between laboratory information systems and partners, and favoring information exchange across laboratories of the consortium),
   - with a user interface suitable for clinicians and healthcare professionals of the network to load, consult or extract information;
2. allow (meta) data analysis including:
   - data mining relevant to evidence and criteria expected from work package 1,
   - extraction of information of clinical studies managed in work package 4;
3. propose a data flux information architecture suitable for:
   - future decision-support tools to implement optimal treatment and management of patient for healthcare professionals,
   - clinical context use to implement / optimise use of diagnostic solutions.

Work package 4 – Clinical study on the value of diagnostics in community-acquired acute respiratory tract infection (CA-ARTI)

The objective is to design and implement clinical studies to demonstrate the value of diagnostics in the optimal management of community acquired – acute respiratory tract infections (CA-ARTIs), by using the outcomes, measures and deliverables outlined in work package 1 within the Standardised Care Network of Work package 2. The studies must use combinations of 'host-based' and 'pathogen-based' diagnostic tests in order to determine the optimal testing algorithm for reducing inappropriate antibiotic use and the development of antibiotic-resistant bacterial strains.

Key tasks:

1. design a multi-country and multi-centre clinical study within the Standardised Care Network as set out in work package 2, to demonstrate the value of diagnostics in the optimal treatment of community acquired – acute respiratory tract infections (CA-ARTIs);
2. implement the clinical study with the following objectives:

- evaluate the impact of the use of diagnostics in relation to their impact on antibiotic prescribing rates,
- assess the defined measurable clinical outcome and success parameters (clinical utility) which will be derived from the results of work package 1,
- include combinations of 'host-based' and 'pathogen-based' diagnostic tests,
- evaluate and test the implementation process for new devices (change management and sustainability) as derived from work package 1,
- include parameters to evaluate the health economic models as derived from work package 1;

3. implement a system for collecting, monitoring and validating measurable / data as set out above;
4. periodically report the status, results to date and progress;
5. analyse, interpret and publish the results of the study in a peer-reviewed journal.

Work package 5 – Education & advocacy

Key stakeholders who can influence practice, policy and prescribing culture must be made aware of the available research, evidence, clinical utility and societal value (i.e. optimisation of antibiotic prescription and reduction of subsequent antibiotic resistance) of diagnostics. A thorough exploration and analysis of the obstacles preventing widespread adoption of diagnostics when delivering healthcare to the population should be conducted. The social, ethical, organisational, environmental, economic, and psychological factors, that influence the perception and adoption of new diagnostic technologies and their delivery into health systems, should be identified. With the input and help from behavioural and social sciences this work package should address barriers for acceptance of diagnostic tests and help understanding motivational factors which may help overcoming hurdles to effectively use these tests in patient management. This work package should also study how patients and populations can be empowered to become value-conscious beneficiaries of diagnostic tests. Coordinated education and awareness raising will facilitate this.

Regulation and policy can largely influence the development and use of IVD tests regarding AMR. Currently, a coordinated advocacy effort is missing to help all stakeholders (regulators, payers, policymakers, others) to define a new framework that incentivises the use of diagnostics. IVD industries and non-industry actors have a common interest in providing evidence to policymakers resulting from the different activities of the project.

The European Commission has published a new AMR Action Plan and most countries are defining or have defined their national AMR plans. A coordinated public-private action through an advocacy platform is needed to analyse existing policies, identify examples of good practice and evidence regarding diagnostics and surveillance of AMR, discuss with stakeholders and establish concrete recommendations. Advocacy actions should not only target the European level, and collaboration with international associations and initiatives should be envisaged. A public-private partnership will efficiently address the barriers which prevent the uptake of diagnostics and their use in antimicrobial stewardship, which include policy, funding, awareness and disparate regulatory requirements. Economists, public health bodies, healthcare groups and other public bodies are all required to demonstrate independently from industry the value and benefits of rapid diagnostics in antimicrobial stewardship, in order to guide policy, awareness campaigns and funding models.

The advocacy effort performed for middle-income countries from the European continent could be extended to low and middle-income countries (LMICs).

Key tasks:

1. mapping of stakeholders and policies;
2. establishment of an advocacy platform;

3. analysis of existing policies and good practice;
4. sharing of evidence provided in other work packages;
5. organisation of events and meetings with stakeholders and decision makers;
6. analysis of the many obstacles preventing widespread adoption of diagnostics;
7. education and communication programme for all stakeholders.

Work package 6 – Project management

The objective is to establish a framework to optimise resources and ensure delivery of results in due time and/or mitigate the risks associated to the project, maximising interaction and cross-fertilisation across the various work packages.

Project management should furthermore ensure the strategic alignment of efforts to key deliverables. It should also oversee, coordinate, manage and facilitate the project and its work packages among the consortia members and with IMI2 JU.

Key tasks:

1. set-up a joint governance structure for the project;
2. define charters and clear accountabilities;
3. provide coordination and support to work package leaders;
4. define work plan, timelines, deliverables, dates, adherence to budget and review progress;
5. identify project interdependencies, stakeholders, risks and mitigation plan;
6. verify that partners are committed and engaged;
7. ensure meetings and interactions between work packages, sub-groups, and consortium governance;
8. ensure internal and external communication.

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Topic 4: Mitochondrial Dysfunction in Neurodegeneration

Topic details

Topic code	IMI2-2017-13-04
Action type	Research and Innovation Action (RIA)
Submission and evaluation process	2 stages

Specific challenges to be addressed

Neurodegenerative diseases such as Parkinson's disease (PD) are of growing public health concern in developed countries, and the need for novel effective treatments continues to increase. Neurodegenerative diseases take many forms, reflecting the degeneration of different populations of neurons at different times and from distinct causes, but many of them also share common features. Amongst the commonalities are bioenergetic failure and oxidative stress, both of which reflect the dysfunction of mitochondria within neural and glial cells [1][2][3][4]. As such, a detailed understanding of mitochondrial dysfunction in the brain in the context of ageing, injury by misfolded protein toxicity, and genetic factors associated with neurodegeneration holds much promise for the development of therapeutic interventions that could impact multiple neurodegenerative disease states.

While mitochondria are found in most cell types, they have a distinct involvement in the brain and in neurodegeneration and especially in neuronal cells. Indeed, in diseases caused by mutations in the mitochondrial genome (thus in principle systemic, in all cells), the typical disease phenotype is dominated by neuronal dysfunction [5]. In addition, many mitochondrial toxins (such as rotenone or 3-nitroproprionic acid) delivered systemically result in selective injury to the central nervous system [6][7]. Thus, while the brain may be selectively vulnerable to mitochondrial dysfunction, this also implies that the nervous system may preferentially benefit from mitochondrial-targeted therapeutics.

Mitochondria are not static organelles. They constantly undergo fission and fusion; their genome also replicates in post-mitotic cells; and they move to different cellular locations up to the end of the neuronal axon [8-10]. Neuronal injury has been associated with cessation of mitochondrial movement and sometimes dramatic alterations in mitochondrial morphology [11], but the impact of altered mitochondrial structure and function on neurodegenerative disease is yet to be fully elucidated. Some of the key modifiers of mitochondrial dynamics have been identified, such as fission and fusion promoting proteins [10][12], as well as proteins that regulate mitochondrial movement [13][14][15][16][17], but the specific role of these proteins in the context of neurodegeneration has not been established.

Mitochondrial dysfunction may be due to abnormal respiratory function, biogenesis, dynamics (axonal transport, fission, fusion) or mitophagy. It can affect several different cellular activities, including abnormal cellular energy generation encompassing oxidative phosphorylation, the citric acid cycle and beta-oxidation. On the other hand, dysfunction can emerge from perturbations in key functions which are energetically distinct yet intimately related to mitochondrial function as they ensure overall cellular metabolic health. Examples are iron-sulphur cluster biogenesis, organisation of the Endothelial Reticulum (ER)-mitochondria network, mitochondrial quality control (mitophagy), and synthesis of mitochondrial proteins and lipids [1]. It is widely believed that neuronal health is reliant on the proper positioning of the mitochondrial network within long axonal projections, and therefore insults to the ever-adapting nature of mitochondrial networks are seen as a key turning point in the aetiology of many neurodegenerative indications [18].

The overall aim of this topic is to develop an unprecedented appreciation of the evolution of mitochondrial dysfunction in models of PD in order to understand if dysfunction is a driver of disease progression. A key goal is to develop an unprecedented appreciation of mitochondrial function in an *in vivo* model of neurodegenerative disease, which is currently lacking. Other challenges to be addressed within this topic are

to quantitatively dissect changes in mitochondrial function in *in vitro* and *in vivo* models (including brain slices) and through mechanistic computational models of PD; and to understand the impact on the degeneration of neurons and/or glia. There is a growing appreciation of the impact of glial cells (astrocytes, oligodendrocytes and microglia) in neurodegeneration, so this topic may include investigations of mitochondrial dysfunction in several cell types [19]. There is also the opportunity to investigate mitochondrial function in neural cells derived from human sources, both from patients and unaffected individuals [20]. Identification of the key molecular drivers of mitochondrial dysfunctions in the disease models will provide a unique scaffold to enable the discovery and development of new therapeutics to halt neurodegenerative disease progression. It is anticipated that the topic will lead to the identification of key molecular drivers which will provide a foundation for the identification and validation of new drug targets, facilitating innovative therapeutic approaches within the neurodegeneration field. Moreover, mitochondrial abnormalities serve as a connecting theme between several neurodegenerative diseases, with a direct link to several processes known to be impaired in neurodegeneration such as bioenergetics and misfolded protein toxicity [21]. Therefore, the learnings are anticipated to also feed into the understanding of the role of mitochondrial dysfunctions in other neurodegenerative diseases such as Alzheimer's disease (AD).

Need and opportunity for public-private collaborative research

Neurodegenerative diseases are complex entities that demand cross-disciplinary investigation. Successful development of methodologies and technologies will require quantitative assessment of mitochondrial dysfunction *in vitro* and *in vivo*; identification of mitochondrial dysfunction in robust neurodegenerative disease models; and the understanding of the impact this dysfunction has on disease progression. These insights will enable significant advances in strategies to expand the repertoire of targets and encourage renewed investment to develop treatments for neurodegenerative disorders.

It is beyond the reach of a single company or institution to fully understand the magnitude and complexity of the roles of mitochondria in health and disease. Because of the scale and scope of this endeavour, success will require the collaboration of a cross-functional/cross-institutional consortium of academic, small- and medium-sized enterprises (SMEs)/biotech and industrial scientists covering a large variety of scientific expertise.

State of the art *in vitro* and *in vivo* models (brain slice cultures, transgenic and models based on the 'prion-like hypothesis') developed in industry and already used in the research and development (R&D) process, along with creative new disease models and novel methodologies to quantify mitochondrial dysfunction from academia and innovative SMEs, will create synergies that would otherwise likely be unobtainable.

Scope

The overall scope of the project generated by this topic is to identify and understand the impact of mitochondrial dysfunction in *in vitro* and *in vivo* models of neurodegenerative diseases, incorporating core characteristics of neurodegeneration such as protein misfolding. Understanding if dysfunction is a driver of disease progression, and the detailed mechanisms responsible for it, will enable the exploration of novel targets for therapeutic approaches to neurodegenerative diseases.

The scope will be reached by a scientifically robust strategy building on established and innovative PD models, and the appropriate technology experience within the consortium. More specifically, this will include addressing the following objectives:

In vitro

- In established and innovative *in vitro* models of PD in neurons, microglia, oligodendrocytes and/or astrocytes, understand the impact of mitochondrial dysfunction (such as respiratory function, biogenesis, trafficking, fission, fusion and mitophagy) on the development/severity of the disease phenotype and identify key molecular drivers of these dysfunctions. Assessment of correlation between morphology and function should be included to ease later interpretation of morphological observations *in vivo*.

- Among others, the *in vitro* phenotype would ideally include a demonstration of mitochondrial dysfunction induced by α-synuclein or tau in a humanised model system such as induced pluripotent stem cells (iPSCs) which allow the study of both neurons and glia (astrocytes, oligodendrocytes and microglia) individually, but also in co-cultures to study interactions and cross-talk. These cellular models would then be further developed into a robust model for therapeutic target identification. Models could potentially include organotypic slice cultures including those incorporating prion-like spreading of misfolded proteins. Assessment of correlation between morphology and function should be included to ease later interpretation of morphological observations *in vivo*.
- Neurodegeneration is a phenomenon directly associated with ageing, yet most *in vitro* cell-based models use neonatal tissues as a source of primary cells. Moreover, iPSCs essentially have their biological clock reset, thus eliminating elements of ageing in the model. Incorporating a component affecting mitochondrial ageing as a model variable would be a valuable addition to the *in vitro* approach.

In vivo

- In a well characterised, robust *in vivo* PD model, investigate if mitochondrial dysfunction can be identified. Understand the impact of these changes on disease progression such as neuronal and synaptic health, as well as the potential for their therapeutic modulation. While many *in vivo* models of PD exist, convenient models using transgenic animals already aged before the start of the project or injection of fibrillary forms of disease-associated proteins as a seeding mechanism to trigger neurodegeneration would be the most appropriate [22]. These models typically develop disease pathology over a time frame suitable for the studies proposed here.
- ***In silico***

  Reconstruct a mechanistic computational model of mitochondrial function to account for the gene products of each gene associated with mitochondria [23] and closely associated organelles. Integrate the experimental data from the *in vitro* and *in vivo* experiments to generate control and neurodegenerative computational models. Quantify the relative contribution of abnormal respiratory function, biogenesis, dynamics (axonal transport, fission, fusion), and mitophaghy to mitochondrial dysfunction.

Key deliverables

The applicants should develop a translational framework for the study of mitochondrial dysfunction *in vitro* and *in vivo* that will provide mechanistic insight into the role of mitochondria on disease pathology progression. This should be achieved by the delivery of the following.

- Development of robust tools and assays to study and quantitatively address mitochondrial dysfunction in well characterised *in vitro and in silico* models of neurodegenerative and trauma-associated nervous system diseases, and *in vivo* models of neurodegeneration, with an emphasis on PD.
- Identification of mitochondrial dysfunction in established and well-characterised models using *in vitro, in silico* and *in vivo* approaches.
- Understanding the role of the mitochondrial dysfunction identified on disease progression/severity.
- Validation of the experimental robustness of the mitochondrial dysfunction identified and the quantitative detection of the endpoint. This is a pre-requisite for application of the model system in pharmaceutical research.
- Identification of the mitochondrial dysfunction in each of the cellular populations involved in the disease: neurons and glia.
- Understanding of the role of misfolded proteins and unfolded protein response associated with PD on mitochondrial dysfunction, *in vitro* (including organotypic brain slice cultures) and *in vivo*.
- Identification of key molecular drivers of mitochondrial dysfunction promoting neurodegenerative diseases. This will provide an unprecedented foundation for the pharmaceutical industry to identify and validate innovative drug targets in the field of neurodegeneration.

- Establishment of a European multidisciplinary research platform of excellence of mitochondrial dysfunction in neurodegeneration facilitating the understanding of neurodegenerative disease aetiology, thus ensuring the sustainability of project outcomes.

Expected impact

Progressive neurodegenerative diseases represent a large and growing burden. Despite a considerable investment in research aimed at understanding and treating neurodegeneration, the lack of disease-modifying therapies remains notable. Recognising this gap, the treatment of neurodegenerative disease is a clearly-identified goal of IMI2 JU, and the expected impact of the project to be generated by this topic is closely aligned with the overall goal.

There is considerable evidence implicating mitochondrial dysfunction in the pathogenesis of a number of progressive neurodegenerative diseases, including Parkinson's disease, but no efficacious treatments have been developed based on this knowledge.

By developing a set of validated cellular assays, organotypic brain slice models and *in vivo* tools, the project will remove an important barrier that has limited the systematic exploration of mitochondrial dysfunction in neurodegenerative disease. A clear identification of the specific mitochondria dysfunctions (such as respiratory function, biogenesis, trafficking, fission, fusion or mitophagy) contributing to neurodegeneration will enable the discovery of novel targets for intervention.

By taking advantage of recent advances in the understanding of mechanisms that control mitochondrial dynamics and using innovative technologies to access mitochondrial dysfunction (e.g. axonal transport and fusion/fission in highly relevant model systems), this approach should provide unprecedented insights into the causal link between mitochondrial dysfunction and neurodegeneration.

SMEs can be of great benefit to IMI2 JU projects and, inter alia, strengthen the competitiveness and industrial leadership of Europe. Their involvement might offer a complementary perspective to industry and academia, and help deliver the long-term impact of the project. For these reasons, applicants should consider engaging SMEs throughout the proposal.

The project learnings will strongly aid neurodegenerative disease understanding and the identification of novel targets, giving academics/SMEs/pharmaceutical companies new options for treatments of diseases with mitochondrial dysfunction, such as PD. Moreover it would encourage a renewed investment in developing drugs for neurodegenerative disorders for which there is a high unmet medical need. In particular, biotech SMEs will be able to 'stress-test' their technologies in a non-competitive, open innovation environment, which will greatly facilitate the development of novel and important therapeutics.

Thus, it can be anticipated that the results of the project will benefit patients and society through the accelerated discovery of new drugs and therapies for neurodegenerative diseases.

Potential synergies with existing consortia

While preparing their short proposal, applicants should take into consideration 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 overlaps and duplication of efforts and funding.

The project generated from this topic in particular should, among others, consider:

IMI/IMI2 JU projects

- **IMPRiND**: Inhibiting Misfolded protein Propagation in Neurodegenerative Diseases (https://www.imprind.org/)

Relevant with regard to both *in vitro* and *in vivo* model systems for spreading and seeding processes in PD and AD

- European Lead Factory (https://www.europeanleadfactory.eu/) – relevant for assays, and targets for NDDs
- **EBiSC**: European Bank for induced pluripotent Stem Cells (https://www.ebisc.org/)

Relevant with regard to IPSC lines from patients

- Michael J. Fox Foundation: **LRRK2 Cohort Consortium** (https://www.michaeljfox.org/page.html?lrrk2-cohort-consortium

Relevant for samples, cellular and animal models

- Michael J. Fox Foundation: **Parkinson's Disease Research Tools Consortium** (https://www.michaeljfox.org/page.html?tools-consortium)

Relevant for cellular and animal models of protein misfolding in PD

- **MIND MAPS**: Molecular Imaging of Neurodegenerative Disease – Mitochondria, Associated Proteins & Synapses consortium (https://mitochondrialdiseasenews.com/2017/04/05/imanova-mrc-funding-mind-maps-study/)

Relevant for imaging mitochondrial dysfunction in patients with AD and PD

- H2020 project **SYSMEDPD**: Systems Medicine of Mitochondrial Parkinson's Disease (http://sysmedpd.eu/)

Relevant for cellular and animal models of protein misfolding in PD

Ongoing and planned activities of the Joint Programming Neurodegenerative Diseases: Pre-clinical research on Parkinson's disease - relevant for cellular and animal models of protein misfolding in PD, and research on mitochondria in neurodegeneration to ensure complementarity and avoid duplication (http://www.neurodegenerationresearch.eu/?s=mitochondria)

- H2020 project **MEFOPA**: European Project on Mendelian Forms of Parkinson's Disease (http://cordis.europa.eu/result/rcn/149388_en.html)

Relevant for cellular and animal models of protein misfolding in PD.

Industry consortium

The industry consortium is composed of the following EFPIA companies:

- Teva (lead)
- UCB
- H. Lundbeck A/S

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

- Parkinson's UK

The industry consortium will contribute the following expertise and assets:

- Access to *in vivo* and *in vitro* disease models:
    - Well established *in vivo* α-synuclein seeding models in wild type (WT) rodents, including: the SNCA-OVX Tg mouse model (expressing human α-synuclein (SNCA) locus WT α-synuclein at disease-relevant levels) [24], pre formed fibrils (PFF) mouse and rat model [25, 26] and an α-synuclein rat model (AAV-A53T-α-synuclein rats; showing protein aggregation, dystrophic axonal morphology and progressive loss of dopaminergic neurons in the substantia nigra pars compacta and glial

responses) [27, 28], including assay protocols, seed material based on recombinant α-synuclein fibrils, and α-synuclein pathology endpoint analysis.
    - Well established α-synuclein seeding models in WT or F28 (human α-synuclein expressing mice) [25, 26] primary neurons, assay protocols, seed material based on recombinant α-synuclein fibrils, pregnant F28 mice for establishment of the cultures and α-synuclein pathology endpoint analysis.

- Access to iPSC lines, iPSC neuronal progenitors and protocols for differentiation into neurons and into glia, including microglia. Protocols and tools for viral transduction and siRNA knockdown of proteins in iPSC neurons.
- Access to human tissue samples for validation studies from a collection of ~1 000 PD cases and 200 controls from which formalin fixed and flash frozen brain tissue is available.
- Evaluation of consistency and robustness of mitochondrial dysfunction key molecular endpoints to ensure future application for target identification/validation.
- Industry will also support communication, dissemination and project management.

Indicative duration of the action

The indicative duration of the action is 36 months.

Indicative budget

The indicative industry in-kind contribution is EUR 3 288 000.

This contribution comprises an indicative EFPIA in-kind contribution of EUR 3 120 000 and an indicative IMI2 JU Associated Partners in kind contribution of EUR 168 000.

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

The financial contribution from IMI2 JU is a maximum of EUR 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 the research objectives and to make key contributions to the defined deliverables in synergy with the industry consortium which will join the selected applicant consortium in preparation of the full proposal for stage 2.

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

- Expertise in using *in vivo* models of PD, and the capability to enable easy transfer of industry models to the applicant laboratories. This includes necessary animal facilities and handling experience.
- Expertise using *in vitro* models of PD, including access to models which exhibit a robust and well characterised disease phenotype with a strong link to the pathology in patient brains, i.e. protein aggregation. The applicant laboratories must have relevant cell culture facilities and strong know-how on the proposed model systems (primary cultures, organotypic brain slice cultures or iPSCs) regardless of whether the model system is already running in their laboratories or they will be transferred from an industry partner.
- The use of *in vitro* and/or *in vivo* PD models that involve introduction of seeding proteins to trigger disease processes may be an advantage.

- Expertise in the evaluation of key elements of mitochondrial function *in vitro*, including bioenergetics, ROS production, biogenesis, fission, fusion and mitophagy.
- Expertise in, and tools for, *in vitro/in vivo* imaging for the investigation of mitochondrial morphology and trafficking. This could include expression of mitochondrial-targeted fluorescent proteins in relevant cell populations.
- Know-how and tools for manipulation of mitochondrial function. For morphology this could be through the expression of proteins such as DRP1, mitofusin 2, OPA1 or Miro or other tools. Small molecules would also be helpful.
- Know-how and an innovative mind-set for the development of new tools and assays to study and quantitatively address mitochondrial dysfunction in *in vitro* and *in vivo* models of PD.
- Expertise in multi-scale mechanistic modelling of biochemical networks.
- Expertise in approaches to model mitochondrial ageing and/or trauma in *in vitro* models; expertise in the evaluation of the role and influence of the different cell populations affected by the disease: neurons and glia (astrocytes, oligodendrocytes and microglia).
- Expertise in communication, dissemination, project management and coordination of research activities.
- Applicants should indicate how they will strengthen the competitiveness and industrial leadership of Europe by, for example, engaging suitable SMEs. Thus, participation of SMEs with relevant know-how and standardised technologies and assays is strongly supported

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 full consideration the deliverables, and the contributions and expertise of the industry consortium.

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

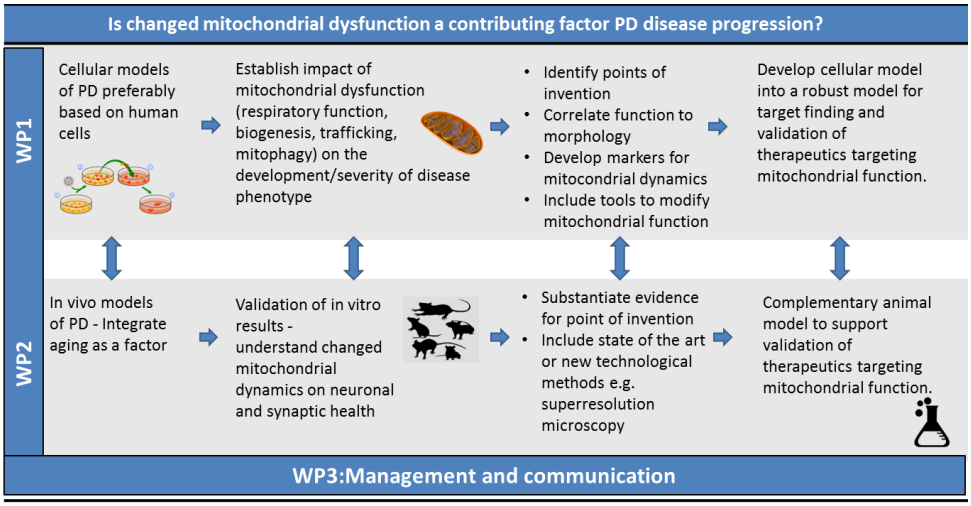
The final architecture of the full proposal will be defined by the participants in compliance with the IMI2 JU rules and with a view to the achievement of the project objectives. The allocation of a leading role within the consortium will be discussed in the course of the drafting of the full proposal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

All beneficiaries are encouraged to discuss the project architecture and governance and the weighting of responsibilities and priorities therein.

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

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

It is suggested to organise the work plan into three main themes, each corresponding to a specific work package (WP):



Work package 1 – Evaluation of mitochondrial dysfunction in cellular models of Parkinson's disease

- Identification of specific mitochondria dysfunctions (respiratory function, biogenesis, trafficking, fission, mitochondrial DNA maintenance, fusion or mitophagy) in established *in vitro* PD models which exhibit a robust and well characterised disease phenotype with a strong link to the pathology in the patient brains, i.e. ex. protein aggregation.
- Establishment of quantitative detection of the mitochondrial dysfunction endpoints and demonstration of robustness of the parameters. This could ideally include implementation of tools (proteins, reagents) modulating the relevant mitochondrial functions.
- Understanding the role of the mitochondrial dysfunction identified on disease phenotype progression/severity. Potentially, understand the contribution of mitochondrial damage due to misfolded proteins. The latter would include the establishment of relevant tools and cellular models exhibiting relevant manifestations of ageing.
- Identification and quantification of the relative contribution of key molecular drivers of the mitochondrial dysfunctions identified using data-driven, mechanistic computational modelling of mitochondria. Prediction of targets to ameliorate mitochondrial function *in vitro*.
- If relevant, transfer of model systems from industry partner/s to applicant consortium partner/s.
- As necessary, development of new robust tools and assays to study and quantitatively address mitochondrial dysfunction *in vitro*.
- In innovative organotypic brain slice models of PD, including those incorporating prion-like spreading of misfolded proteins, understand i) the impact of mitochondrial dysfunction on the development/severity of the disease phenotype; and ii) the reciprocal impact of intracellular protein misfolding on mitochondrial dysfunction. Assessment of the correlation between morphology and function should be included to ease later interpretation of morphological observations *in vivo*.

With these methods in hand, the goal is to provide a detailed characterisation of the contribution of mitochondrial dysfunctions to PD-related degeneration of the relevant cell types. Identification of the key molecular drivers of the dysfunctions identified is of particular interest. Tools modulating the abnormal mitochondrial parameters, such as fission or mitophagy, may provide the opportunity to identify mitochondrial targets for therapeutic intervention. Moreover, it would be advantageous to have the opportunity to understand the contribution of mitochondrial damage due to misfolded proteins, trauma and ageing to neurodegenerative disease progression and severity.

The industry contribution will include contributions of cellular models, tissue from animal models and protocols as well as the development of mitochondria dysfunction assays and quantitative detection of mitochondrial functional levels. Technologies to be contributed may include high content screening, bioenergetics assays and iPSC derived models.

The expected Applicant consortium contribution will include development of novel tools and models to assess the impact of ageing, trauma and misfolded proteins on the manifestation of mitochondrial dysfunction, as well as the development of additional novel mitochondrial dysfunction assays.

Work package 2 – Evaluation of mitochondrial dysfunction using *in vivo* models of Parkinson's disease

- Identification of specific mitochondria dysfunctions (respiratory function, biogenesis, trafficking, fission, fusion or mitophagy) in robust and well established *in vivo* PD models, e.g. *in vivo* seeding models. This would imply following the changes in mitochondrial function over the course of the development of the neuropathology to understand if a sub-acute time course could be identified, and then allow mitochondrial dysfunction to be tracked before and during the development of neurodegeneration.
- Establishment of quantitative detection of mitochondrial dysfunction endpoints and demonstration of robustness of the parameters. This could ideally include the development of ways to modify the parameters either genetically or pharmacologically.
- Understanding the role of the mitochondrial dysfunction identified on disease phenotype progression/severity.
- Identification of key molecular drivers of the mitochondrial dysfunctions identified.
- If relevant, transfer of model systems from EFPIA partners to Applicant consortium partners.
- If required, development of new, robust tools and assays to study and quantitatively address mitochondrial dysfunction *in vivo*. It could for example be methods for imaging of mitochondrial dynamics in mouse models.

The industry contribution will include the contribution of animal models of neurodegenerative diseases, with a focus on seeding models of disease, together with relevant protocols and the assessment of mitochondrial functional endpoints in these models.

The expected Applicant consortium contribution will include the development of tools and assays to quantitatively assess mitochondrial dysfunction endpoints *in vivo*, and implementing them to enable longitudinal of mitochondrial function in relevant models of diseases and correlation to disease phenotype and severity.

Work package 3 – Project and data management.

- Define work expectations of different work streams, deliverables, dates and activities and review progress regarding adherence to budget, timelines and quality (by all consortium members).
- Ensure legal and contractual management.
- Ensure the set-up of a joint governance structure (by all consortium member).
- Ensure appropriate communication/dissemination within the consortium and with the external scientific community and the public.
- Develop and manage communication via avweb portal and other social media tools with a repository of key documents.
- Quality assessment of documents.
- Define project interdependencies, stakeholders and risks.
- Ensure ethics management.

The industry contribution will include co-leading this work package, including management of legal, contractual, ethical and quality assessment aspects, and developing and executing a detailed communication and dissemination plan, all to be achieved in partnership with all remaining consortium members, who will also work together to define the governance structure and full work plan.

The expected Applicant consortium contribution will include co-leadership and input to all structures and activities needed for decision-making, monitoring and project management, and jointly develop the governance structure and full work plan.

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Topic 5: Support and coordination action for the projects in the neurodegeneration area of the Innovative Medicines Initiative

Topic details

Topic code	IMI2-2017-13-05
Action type	Coordination and Support Action (CSA)
Submission and evaluation process	2 stages

Specific challenges to be addressed

Dementia affects over 47 million people globally. As populations age, this figure is projected to increase to 75.6 million by 2030, and more than triple by 2050. The overall number of people living with dementia in European Union countries is expected to rise from 9.6 million in 2015 to nearly 15 million in 2035[9]. The disease places a huge and growing burden on health and social care systems as well as on the families and carers of those affected. Yet despite decades of research and large investments, there is still neither treatment nor cure for the disease and success in clinical trials remains elusive.

There are significant medical, scientific, ethical, regulatory, and operational issues around the question of what can be done to support biomedical research and health innovation for the delivery of the required diagnostics and disease-modifying treatments for Alzheimer's disease (AD) and other dementias.

After the G8 meeting in London in December 2013[10], a significant increase was observed in the number of initiatives focused on advancing the field of dementia research. While geographically diverse, these initiatives are mostly either of public-private nature with the aim to optimise pre-competitive collaboration and knowledge generation or large collaborative public efforts which deliver innovative results that would benefit from further translation into practice (see figure 1). The Innovative Medicines Initiative (IMI) projects 'European Medical Information Framework' (**EMIF -** http://www.emif.eu/), 'Organising mechanistic knowledge about neurodegenerative diseases for the improvement of drug development and therapy' (**AETIONOMY -** https://www.aetionomy.eu/en/vision.html) and 'European prevention of Alzheimer's dementia consortium' (**EPAD -** http://ep-ad.org/) stated their willingness for collaboration in March 2015, creating the IMI Alzheimer's Research platform[11]. After that, and in just the first three years of its activities, IMI2 JU implemented eight new projects in the area of neurodegeneration and more are in the pipeline. These initiatives have been launched either via the Strategic Governing Group Neurodegeneration (**SGG ND -** https://www.imi.europa.eu/about-imi/governance/strategic-governing-groups#strategic-governing-groups-collapsible-3), or as part of platforms such as the Remote assessment of disease and relapse (**RADAR -** https://www.radar-cns.org/ and http://ec.europa.eu/research/participants/portal/desktop/en/opportunities/h2020/topics/imi2-2017-12-01.html) and Big Data for Better Outcomes (**BD4BO -** http://bd4bo.eu/).

These diverse initiatives now cover the research and development (R&D) value chain from bench to bedside (see figure 1). Although several of these initiatives have started leveraging on one another, an operational coordination of the activities promoted by all these actors is missing, and despite the growing number of

[9] http://www.oecd-ilibrary.org/social-issues-migration-health/health-at-a-glance-europe-2016/dementia-prevalence_health_glance_eur-2016-20-en
[10] https://www.gov.uk/government/publications/g8-dementia-summit-global-action-against-dementia/g8-dementia-summit-global-action-against-dementia-11-december-2013
[11] http://www.imi.europa.eu/news-events/press-releases/innovative-medicines-initiative-alzheimers-disease-projects-launch-joint

initiatives, there are no agreed metrics to show their value in advancing research and removing bottlenecks toward the delivery of innovative treatments to patients.

There is a constant need for strengthening the information flow and enhancing the exchange of experience on on-going and future European and international research and innovation activities concerning neurodegeneration, at IMI level and beyond, as well as for maintaining continuous dialogue between all stakeholder groups and initiatives to allow an evaluation on how the investment is impacting the area.

Effective and efficient collaboration and coordination among the IMI/IMI2 JU portfolio of projects in the area of neurodegeneration and related national, European and global initiatives is the key success factor for the important public-private investment to achieve its full impact, as also highlighted at a recent meeting hosted in Brussels by the IMI2 JU[12].

It also is evident that projects share several areas of common interest (e.g. modelling and simulation, imaging) and have developed best practices that would be very useful for other ongoing and upcoming initiatives, but due to the silo-like structure of the individual initiatives, the opportunity for real and effective cross-fertilisation is limited and based on the 'good will' of enthusiastic individuals. Indeed this has been the case with the IMI Alzheimer's Research Platform, which links three projects which have some specific complementarities, however now the portfolio of IMI projects has grown significantly and it is much more diverse in scope and focus, creating the need for a more tailor-made and structured support structure.

Projects would also benefit from support (including access to learnings from other projects) towards the submission of results for regulatory and/or health-technology assessment (HTA) to ensure that important results can impact regulatory practice and the healthcare system in a timely manner. Often the data to support a regulatory/HTA submission are only fully available in the very final phase of the projects, or even after their official end, which may hamper their submission and subsequent follow up.

A significant challenge in collaboration is the burden required to develop agreements and good practices for sharing and reuse of data, biological tools (e.g. cell lines) and other materials, activities that are normally either not or only minimally resourced under individual initiatives and can be labour intensive and require expertise (e.g. legal, ethical) not always readily available for each project.

All projects face the challenge of sustainability of their results, and the lack of a source of advice and support in finding/choosing relevant solutions beyond the project lifetime. There is therefore a clear need for support to ensure that collaboration and coordination become intentional and structural to the portfolio of projects in the IMI strategic area of neurodegeneration, by providing the necessary resources and framework.

Last but not least, there would be a very high value in having a framework to facilitate collaboration and coordination of the many initiatives focused on neurodegeneration, in and beyond IMI, and to develop some metrics to show their value in advancing research and removing bottlenecks toward the delivery of innovative treatments to patients.

[12] http://www.imi.europa.eu/news-events/events/collaboration-alzheimers-disease-beyond

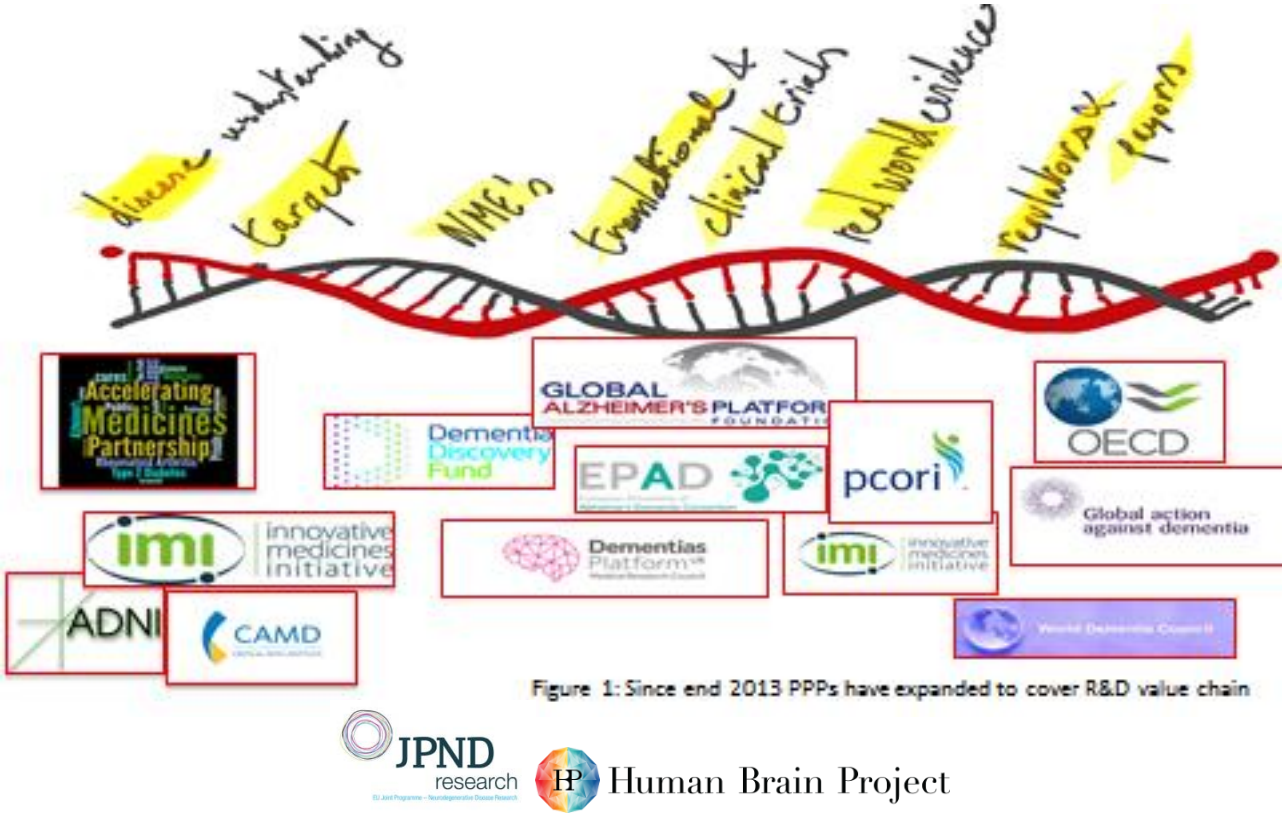

Figure 1: Since end 2013 PPPs have expanded to cover R&D value chain

Scope

The overall scope of the coordination and support action is to provide the necessary overall framework and resources to achieve effective and efficient coordination and collaboration among the ongoing and future projects in the IMI strategic area of neurodegeneration. This will include:

- developing a framework to coordinate and support the operational alignment of the IMI neurodegeneration research portfolio, including a process to ensure that projects make appropriate use and can access existing infrastructures;
- providing expert advice and other support to facilitate sharing of and access to data, biological tools and other materials among projects;
- providing expert advice and support in preparing for regulatory and/or HTAs interactions (e.g. legal support, access to relevant expertise, funding to pay submission fees) to ensure that appropriate regulatory input is provided when most valuable and also beyond the timeframe of a project;
- establishing and managing workshops designed to share common approaches/best practices across IMI projects and beyond;
- developing a framework to coordinate and efficiently support the operational alignment of IMI-led actions with other relevant partnerships and initiatives at national, European and global levels (e.g. DPUK[13], DZNE[14], JPND[15], CAMD[16], NIH/AMP[17], WHO[18], GAP[19], World Dementia Council[20]);

[13] DPUK – D ementias Platform UK: https://www.dementiasplatform.uk/
[14] DZNE – Forschungszentrum für neurodegenerative Erkrankungen: http://www.dzne.de/home.html

- creating a platform to enable the mapping of partnerships and collaborative efforts that have supported over the past years research in Alzheimer's disease to capture their contributions and identify the remaining gaps and develop metrics and benchmarks to measure value, including socio-economic impact;
- developing outreach and engagement actions with other international/national/regional initiatives including patient organisations to promote and increase the value of trans-national and international research collaborations;
- communicating and disseminating joint activities and initiatives in the field of neurodegenerative diseases;
- seeking alignment and coordination on issues of common interest such as ethical, legal and social implications of clinical neurodegenerative disease (especially Alzheimer's disease) research, where several learnings are already available but disperse.

Expected key deliverables

- An operational platform to coordinate and support the activities of the IMI neurodegeneration projects, including new relevant IMI2 JU actions and international collaborations. Ensure that cross-project dependencies/synergies are operationally supported enabling actual delivery on them. Such platforms should be developed including consideration for self-sustainability beyond the funding of this action.
- Relevant support to enable timely and effective interaction with regulatory authorities and HTAs.
- A series of guidelines and good practices for the access and sharing of data, biological tools and other materials among projects, as well as a resource to facilitate the process.
- An advisory board and an up-to-date and dynamic catalogue of potential solutions for sustainability of project results.
- A series of workshops and relevant proceedings to share common approaches/best practices across IMI projects.
- Metrics and benchmarks to measure success.
- A public depository (to be self-sustainable after the end of the action) for protocols, deliverables, white papers, etc. produced by the action and by relevant IMI projects to insure their optimal dissemination to the wider scientific community.
- A relevant programme of outreach activities.
- Joint white papers to provide an aligned and educated perspective of all key stakeholders on key issues in the area of neurodegeneration research, including regulatory and HTA perspectives.
- A map of the partnerships and collaborative efforts that have supported over the past years research in Alzheimer's disease to capture their contributions and identify the remaining gaps.

Expected impact

The expected impact would be:

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[15] JPND – Neurodegenerative Disease Research: http://www.neurodegenerationresearch.eu/
[16] CAMD – Coalition Against Major Diseases: https://c-path.org/programs/camd/
[17] NIH/AMP – National Institutes of Health / Accelerating Medicines Partnership: https://www.nih.gov/research-training/accelerating-medicines-partnership-amp
[18] WHO – World Health Organization: http://www.who.int/en/
[19] GAP – Global Alzheimer's Platform: http://globalalzplatform.org/
[20] World Dementia Council: https://worlddementiacouncil.org/

- enhancing impact of the individual projects by creating structural synergy and collaboration;
- an enhanced visibility of IMI's significant public and private investment in the area of neurodegeneration; ensuring that the results of relevant IMI projects are developed optimally for the benefit of patients and health systems including strategies for sustainability and uptake;
- an optimisation of the impact of IMI projects' activities in neurodegeneration toward the achievement of the IMI2 JU Council Regulation objectives and in particular those aiming to:
    - increase the success rate in clinical trials of priority medicines identified by the World Health Organisation;
    - where possible, reduce the time to reach clinical proof of concept in medicine development, such as for cancer, immunological, respiratory, neurological and neurodegenerative diseases;
    - develop new therapies for diseases for which there is a high unmet need, such as Alzheimer's disease;
    - develop diagnostic and treatment biomarkers for diseases clearly linked to clinical relevance and approved by regulators.
- an analysis of the scientific results and achievements delivered by various partnerships in neurodegeneration so far, and an understanding of their translation into more efficient and faster development of new medical products in this area and of critical factors for a successful translation;
- an overview and a framework to inform future collaborative research globally and facilitate the translation to innovative treatments for patients.SMEs can be of great value to IMI projects and, inter-alia, strengthen the competitiveness and industrial leadership of Europe. Their involvement might offer a complementary perspective to industry and the academia, and help deliver the long-term impact of the project. For these reasons, applicants should consider engaging SMEs throughout the proposal.

Potential synergies with other consortia

Applicants should take into consideration, while preparing their short proposal, relevant national, European (including research projects, research infrastructure initiatives, projects and joint actions funded through the Programme for the Union's action in the field of health (2014-2020) such as EUnetHTA Joint Action 3), and non-European initiatives. Synergies and complementarities should be considered in order to incorporate past achievements, available data and lessons learnt where possible, thus avoiding unnecessary overlap and duplication of efforts and funding.

The action will have to build strong links with the portfolio of IMI projects in the area of neurodegeneration[21] to ensure that the activities are in good synergy with those potentially already ongoing within individual initiatives.

It is also expected to leverage and build on efforts and lessons learnt from other initiatives and organisations at national, European and global levels (e.g. DPUK, DZNE, NIH/AMP, JPND, CAMD, WHO, GAP, World Dementia Council, among others).

Finally the action should build synergies and complementarities with other relevant coordination activities in IMI and H2020:

CSA HCO-10-2018 topic in the SC1 work programme that was recently pre-published (https://www.horizon2020.services/calls/)

IMI2 DO-IT (http://bd4bo.eu/index.php/portfolio/do-it/)

[21] http://www.imi.europa.eu/projects-results/project-factsheets

IMI2 ADAPT-SMART (http://adaptsmart.eu/)

Industry consortium

The industry consortium is composed of the following EFPIA companies:

- Janssen (lead)
- Eli Lilly
- Roche
- Takeda
- Sanofi

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

- Parkinson's UK

The industry consortium will contribute the following expertise and assets:

- contribution to project and meeting management;
- measurement and analytical tools;
- regulatory affairs;
- data privacy law and related legal aspects;
- medical affairs and healthcare communication;
- contribution to website management;
- data/knowledge management, repository of knowledge;
- experts time in different relevant scientific areas.

The industry consortium will also provide their expertise in the conduct and follow up of management tasks to secure this overall programme platform (including any IT system to help the work of the platform and the communication between partners) as well as provide the necessary resources for programme management, e.g. from defining strategic priorities to the organisation of meetings / workshops / teleconferences.

Indicative duration of the action

The indicative duration of the action is 36 months.

Indicative budget

The indicative industry in-kind contribution is EUR 1 200 000.

This contribution comprises an indicative EFPIA in-kind contribution of EUR 1 056 000 and an indicative IMI2 JU Associated Partner in kind contribution of EUR 144 000.

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

The financial contribution from IMI2 JU is a maximum of EUR 1 200 000.

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 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 expertise in:

- project management and coordination;
- organisation and logistics of workshops and international meetings;
- knowledge and expertise in legal, ethics and data privacy aspects of sensitive, personal-level data management and biological tools management , including intellectual property (IP) considerations;
- data hosting and maintenance;
- regulatory science;
- health economics;
- medical/scientific writing;
- outreach and communication targeted for the different stakeholders and public at large;
- development of effective communication tools including websites and social media, platforms to create awareness of the programme and disseminate findings;
- expertise to create training and communication materials based on results of the programme.
- Additionally, applicants should indicate how their proposal will strengthen the competitiveness and industrial leadership of Europe by, for example, engaging suitable 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.

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

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

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

Work package 1 – Platform for coordination and collaboration (including sustainability)

This work package will focus on:

- set up and maintenance of a website including relevant webpages tailor made for the different stakeholders, with special attention to patients;

- implementation of the operational platform to coordinate and support the activities of the IMI neurodegeneration projects and international collaborations. Ensure that cross-project dependencies/synergies are operationally supported, enabling actual delivery on them;
- running of workshops and production of relevant proceedings to share common approaches/best practices across IMI projects;
- establishment and maintenance of a public depository for protocols, deliverables, white papers, etc. produced by the action and by the IMI projects to ensure their optimal dissemination to the wider scientific community;
- establishment of an advisory board and set up and maintenance of an up-to-date and dynamic catalogue of potential solutions for sustainability of project results.

Industry consortium contribution:

- strong programme management skills;
- expertise in value-based healthcare, real-world evidence (RWE);
- network with leaders of IMI projects (BD4BO and others);
- governmental affairs and public policy.

Expected applicant consortium contribution:

- strong programme management skills, including road mapping tools;
- experience in coordinating projects of similar complexity/ scale/ sustainability;
- expertise in initiatives related to health outcomes and value-based healthcare.

Work package 2 – Support for regulatory and/or HTA interactions

This work package will focus on:

- establishment of a resource (including all relevant support and best practices) to enable timely and effective interaction with regulatory authorities and HTAs.

Industry consortium and applicant consortium contribution:

The types of resources will be similar from both sides of the consortium since we anticipate there will be a need for a variety of specific roles, including information/knowledge management skills, project management, business analysis, healthcare systems expertise, expertise in outcome definition, measurement tools, etc. for standardisation of methodologies across diseases, Health Economics and Outcomes Research (HEOR) expertise, knowledge about health funding models and various coordinating activities.

Work package 3 – Communication, dissemination and outreach

This work package will focus on:

- alignment of dissemination and communication strategies across the projects;
- joint white papers to provide an aligned and educated perspective of all key stakeholders on key issues in the area of neurodegeneration research, including regulatory and HTA perspectives;
- creation of material for internal and external communication;
- setting up of social media platforms and inventory of communication;
- support publication and other dissemination activities of IMI neurodegeneration projects' findings, including through training activities;

- a relevant programme of outreach activities.

Work package 4 – Mapping and impact analysis

This work package will focus on:

- analysis of the socio-economic impact of the IMI portfolio in neurodegeneration including in EU countries with different economic status;
- implementation and maintenance of a map of the partnerships and collaborative efforts that have over the past years supported research in Alzheimer's disease to capture their contributions and identify the remaining gaps.

Industry consortium contribution:

- communication (communication strategies, media, social media);
- website set up and management;
- science writers;
- events organisation;
- stakeholder engagement expertise at national and EU level with all relevant stakeholders, including but not limited to HTAs, regulators, payers, patients, medical societies, and providers;
- organisation of multi-stakeholder meetings, workshops or forums to foster stakeholder engagement.

Expected applicant consortium contribution:

- communication strategies and tools;
- health economics impact analysis;
- development/adaptation of tools, models and methods for monitoring and measuring impact
- science writers;
- creating communication materials;
- creating training materials and delivering trainings;
- appropriate resource and expertise from HTAs, regulators, payers, providers, patient organisations, medical societies and other appropriate stakeholders;
- organisation of multi-stakeholder meetings, workshops or forums to foster stakeholder engagement, especially with additional healthcare systems' stakeholders beyond the consortium.

Work package 5 – Standards and guidance for the use and reuse, access, and sharing of human samples, biological tools and data

This work package will focus on:

- implementation of a resource, including expert advice, sharing of learnings, writing of guidelines and other support, to facilitate sharing of and access to data, biological tools and other materials among projects;
- development of minimum standards (templates) for ICFs for clinical studies and other research studies;
- development of guidance documents to facilitate the work with the generated ICF templates, including their terminology and application, and provision of guidance on related aspects of data privacy laws and regulations (e.g. concept of anonymisation) for IMI/IMI2 projects and non-IMI related addressees;

- development of standards, training and educational guidance on aspects of data privacy laws and regulations, data protection mechanisms and consequences of their application for IMI/IMI2 projects as well as non-IMI related addressees (e.g. patients).

Industry consortium contribution:

- legal expertise in connection with data privacy and related legal matters.

Expected applicant consortium contribution:

- knowledge and expertise in legal, ethical and data privacy aspects of sensitive, personal- level data management from several angles: 1) from an academic perspective as well as from the perspective of groups of academic research organisations; 2) from the perspective of healthcare SMEs, in particular biobanking SMEs or health-IT companies; 3) from the perspective of national and international supervisory/regulatory authorities dealing with data protection in the healthcare context on a regular basis (ideally one participant from each interest groups);
- understanding of patient and physician concerns such as in patient organisations and medical associations;
- ethical considerations as relevant in ethics committees.

Topic 6 : A sustainable European induced pluripotent stem cell platform

Topic details

Topic code	IMI2-2017-13-06
Action type	Research and Innovation Action (RIA)
Submission and evaluation process	2 stages

Specific challenges to be addressed

Since their introduction in 2007 [1] human inducible pluripotent stem cells (human iPSCs) have been rapidly and broadly incorporated into research to understand their potential for disease and are a very powerful tool for translational research. This has substantiated interest to incorporate this resource into drug discovery pipelines, prospective patient stratification, recruitment for clinical trials and post-clinical drug assessment of safety issues following rare event reporting. In addition, human iPSCs can potentially provide unlimited autologous cells for therapy and therefore hold great promise for regenerative medicine [2]. The evolution of these applications depends on facilitated and unfettered access to a standardised and well characterised iPSC resource to help avoid dissemination of unauthenticated or substandard cell lines to the research community.

iPSCs are cells derived from somatic cells of the body and reprogrammed by introducing specific transcription factors in order to re-establish pluripotency [1] [3] iPSCs can be differentiated into the three germ layers, the mesoderm, endoderm, and ectoderm, which form the organs during embryonic development. The continued optimisation of protocols now allows producing large quantities of differentiated, human cells in a reliable and reproducible manner. Human iPSCs are established from patients with the promise to capture in cell models specific human disease phenotypes which cannot be revealed in animal models, and to allow studying these in a human context. With the advent of gene editing technologies like the -Clustered Regularly Interspaced Short Palindromic Repeats/associated (Crispr/Cas)-system, specific mutations relevant for a certain disease are being introduced into human iPSCs to again model specific phenotypes and compare with the isogenic parental line. While these efforts will foreseeably improve the consistency with which new cell lines will be developed they will not necessarily foster the standardised and scalable distribution of pre-established or new lines to the wider hiPSC research community.

The rising demand by academia and industry has instigated a number of large scale public and privately funded disease and/or population oriented human iPSC banking initiatives in the US, Japan and UK [4]. However, ‘several issues should be overcome to advance the field quickly. First, it will be critical to network iPSC resources around the world to create an iPSC library of both normal and diseased cells using a common quality standard. Second, a systematic approach to develop an iPSC library in conjunction with a clinical database, tissue bank and genome-wide association study (GWAS) would be most useful. Third, further development of efficient and standardised *in vitro* iPSC differentiation protocols into many more cell types is essential for progress in the field. Forth, continuous effort to recapitulate phenotypes of late-onset diseases *in vitro*, at least partly, would be critical to extend their applications. Lastly, reducing complexity of culture methods will be important to make the system more easily applicable to high throughput screening’ (cited from [5]). Several efforts are ongoing worldwide to address these matters, but still in a highly fragmented way.

In Europe, the **EBiSC** project (https://www.ebisc.org/) funded by the Innovative Medicines Initiative Joint Undertaking (IMI JU) has demonstrated the feasibility and challenges of coordinating existing organisational capacities across Europe to fast track the establishment of a centralised network and facilities to access a standardised resource of established hiPSC lines and data. EBiSC has established a unique European-based iPSC repository and has delivered harmonised and publically accessible Standard Operations Procedures

(SOPs) for tissue procurement, bio-sample tracking, iPSC expansion, cryopreservation, qualification and distribution to the research community. These were implemented to create a quality managed foundational collection of lines and associated data made available for distribution [6].

The critical challenge addressed by this topic is to build on these important infrastructure, capabilities and knowledge to create a fully sustainable European hiPSCs distribution platform with worldwide reach.

Need and opportunity for public-private collaborative research

The complexity of setting up the logistics and infrastructure to secure continued housing, support, and distribution of an iPSC collection in general, and to secure availability of iPSC assets established within public private partnerships including EBiSC plus associated information, needs to be addressed by a public-private-partnership involving a variety of stakeholders as it cannot be accomplished by an individual research group or company and will require a strong collaborative effort to be successful.

Only a collaborative endeavour bringing together academic laboratories and small and medium-sized enterprises (SMEs) with access to and ownership of necessary hiPSC lines, technologies and logistics, and EFPIA partners that closely interact with the hiPSC banking entity, advising and supporting the further expansion of the hiPSC repository, will ensure that therapeutically relevant areas will continue to be addressed and that consistency and quality of preparations meet the needs of drug development campaigns. EFPIA will provide critical feedback on quality and differentiation potentials of iPSC lines and precursor cells provided by the bank facility. Information and data obtained from certain iPSC lines will be added to the banking entity's information management to disseminate knowledge on disease understanding and facilitate development of screening models to be used in drug development.

This engagement of EFPIA will uniquely enable to capitalise on existing capabilities and knowledge to reach the ultimate goal of self-sustainability of the hiPSC banking entity.

Scope

A European iPSC repository that operates on a non-for-profit basis and allows researchers access to a continuously expanding number of well-characterised and fully quality controlled (QC) iPSC lines with clarified access information is mandatory to fuel basic research and development and drug development campaigns. Although previous activities have prepared the ground for such a banking entity, significant aspects listed below remain to be addressed.

The overall objective of the action generated from this topic is therefore to establish a fully self-sustainable European human iPSC banking facility, that has to be operational within the first three months of the action by seamlessly building on and incorporating existing cell lines, knowledge and infrastructure established within former European-wide initiatives (e.g. EBiSC). The bank has to be able from the start to handle and deliver a minimum of approximately 500 quality-controlled, disease-relevant (in particular for neurodegeneration, Alzheimer's disease and other tauopathies, Parkinson's disease, cardiovascular disease, safety, diabetes, and auto-immune and selected monogenic diseases), research-grade iPSC lines, with integrated data and cell services which will be further built on as part of the research and technology work of the action. The ultimate goal is to transform significant pre-existing European banking infrastructures into a sustainable resource for European research and development. The applicant consortium at stage 2 will have to document in the full proposal that this can be achieved efficiently and in the expected timelines as a first go/no go milestone.

Thus the following has to be accomplished:

- transfer of assets established in previous large standardised European collections with linked data and SOPs to the new bank where appropriate technology is in place to handle cells and guarantee seamless continuation of banking and distribution operations;
- secure continued housing, expansion and QC of the existing iPSC collection generated in such previous initiatives;

- ensure a continued and efficient distribution infrastructure with a European and worldwide reach within the first half year after start of the funding period;
- provide long-term storage capacity for up to 10,000 iPSC-vials with a minimum of 3 replicates each under liquid nitrogen gas phase and automated handling. Capability for long-term storage of biosamples;
- banking entity and mirror bank certified to operate according to ISO 9001 standards;
- secure and further optimise established QC-procedures and SOPs by incorporating newly established and accepted methodologies that become available during this undertaking;
- ensure a continued Information Management System to monitor the iPSC line status and keep track of iPSC line data, complement available information related to existing lines (e.g. mutation confirmation and exome sequencing), and incorporate relevant information including clinical records to new entries;
- develop the technology and establish efficient and reproducible protocols for parallelised production of bulk quantities of iPSCs and/or precursor cells in response to drug developers or future costumer demands. Within the project, the cells will be subject to analysis at the participating EFPIA companies in order to establish disease models and screening assays;
- further expand the repository by incorporating additional iPSC lines (patient-derived and gene-edited) that:
    - will be established by the consortium during the lifetime of the action. It is expected that the consortium will support cell line commissioning projects including gene editing technologies, like the Crispr/Cas-system, that are requested by the consortium (public and industry partners) as well as relevant members of the external research community to fuel the repository with iPSC lines relevant for research of benefit to patients and community. Such requests will be reviewed by the consortium board consisting of the EFPIA group and the public partners and approved if the deliverables are of relevance for the scientific community and pharmaceutical industry,
    - will become available in other publicly-funded consortia with a focus on iPSC technology. It is expected that the consortium will actively reach out to other cell line owners or publicly-funded consortia in the process of establishing iPSC lines to discuss and secure integration of new lines into the repository. In addition, reaching out to other biobanking entities to complement offering to the scientific community and/or avoid duplication of work is encouraged,
    - are already available in the scientific community;
- ensure ethical and legal matters are in place for incorporation of iPSC lines into a public accessible bank to allow freedom to operate for research and development purposes;
- establish clinical networks that allow access to well-described patient biosamples for the establishment of iPSC lines and, where the ethical and legal ground is established, allow fast access to samples relevant for academic and industrial research;
- implement all necessary activities to ensure that by the end of the action the repository is fully self-sustainable.

Expected key deliverables

The key overall deliverable of the action is the establishment of a self-sustainable iPSC banking facility that fully leverages significant pre-existing infrastructures and know-how. Key deliverables and goals are:

- establish within the first three months of the action a European standardised and at-scale human iPSC banking facility by successfully transferring existing iPSC lines, knowledge and infrastructure established within relevant pre-existing European wide banking (e.g. EBiSC) initiatives to this collaboration;
- establish and maintain a cell line housing facility with the capacity to handle existing lines and be extendable to incorporate new ones;
- establish and maintain a mirror cell line bank at capacity;
- apply and continuously improve SOPs to achieve highest standards in iPSC technology. QC criteria will be defined for characterisation of newly established, expanded, and differentiated iPSC lines;

- establish and maintain a European and worldwide distribution infrastructure;
- throughout the runtime of the project, the consortium is expected to strive for self-sustainability of the iPSC repository. Therefore, applicants need to formulate in their proposals, deliverables, and milestones related to a business plan that details the operations after the funding period. The repository will have to be fully self-sustainable by the end of the action;
- ensure a continued iPSC-line Laboratory Information Management System;
- establish efficient and reproducible protocols/SOPs to produce bulk quantities of precursor cells that can be differentiated into cells from all three germ layers;
- further expand the repository by incorporating additional iPSC lines:
  - reach out to governmental funding bodies and the scientific community to discuss and secure integration of new iPSC lines into the repository,
  - to support the cell line commissioning projects requested and partially funded by the EFPIA group or the scientific community,
  - establish clinical networks that will facilitate the establishment of iPSC lines from well described patients of relevance to the EFPIA partners and the scientific community,
  - reach out to and network with other biobanking entities to capitalise on synergisms;
- support the iPSC banking entity with regard to ethical and legal aspects to secure freedom to operate and unlimited use of iPSC lines in research and developmental processes.

It is expected that applicants address all the above objectives in the Short proposal (within the available duration and budget) and demonstrate a relevant strategy for achieving them, through partnership with the industry consortium.

Expected impact

iPSC research and banking continues to be fragmented across a broad spectrum of institutions in Europe, and lacks sufficient scale to support the current and anticipated demands of academic and industrial research and development. In Europe, the IMI JU project EBiSC[22] has prepared the ground for establishment of a self-sustaining banking entity by creating a QC'ed iPSC repository of currently several hundred iPSC lines with ethical and legal standards in place. These lines represent important disease areas among them neurodegenerative diseases (Alzheimer's disease, other tauopathies like frontotemporal dementia, and Parkinson's disease), diabetes, neuropathic pain, and cardiovascular diseases that the participating drug developers are actively researching to provide novel treatments to patients.

Availability of iPSC lines derived from patients, as well as of a broad spectrum of lines from healthy donors of different ages, standardised according to how they were made and their *in vitro* behaviour, and the possibility of linking a gene code to cell line phenotype reflective of the disease, will enable the research community to refine original clinical diagnosis into one based on disease stratification and thereby design more precise experiments to discover novel pathogenic pathways, drug targets and new medicines. This is expected to significantly advance research and development activities across Europe by accelerating the progress of understanding certain disease aetiologies, as well as finding potential cures, thereby strengthening European competitiveness.

This European iPSC repository will be uniquely positioned to serve as the central European iPSC repository hub to accelerate and facilitate European research and development activities. Therefore, the consortium will have to continuously monitor the sale of cells produced by the banking entity, and its trend in order to develop in the runtime of the project a plan as to how to transform the repository into a self-sustainable business.

[22] https://www.ebisc.org/

Ultimately this will secure that the public and private investment will establish a resource that beyond the runtime of the project continues to support and fuel European basic research as well as drug development campaigns in pharma companies.

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

Potential synergies with existing consortia

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

More specifically, the applicants have to demonstrate awareness of the most current iPSC landscape across Europe, to be able to reach out to relevant programs to be incorporated or supported in order to ensure that the new banking initiative fully leverages previous significant public and private investments and infrastructures. In Europe, a unique repository of hiPSCells has been created by the IMI JU **EBiSC** project (https://www.ebisc.org/). Also, the IMI JU StemBANCC collection of iPSC lines has become part of the repository during the lifetime of the previous IMI JU EBiSC project. Other examples of IMI/IMI2 JU research collaborations with a strong iPSC focus are **ADAPTED** (https://www.imi-adapted.eu/), **PHAGO** (http://www.phago.eu/), or **IMPRiND** (https://www.imprind.org/). Additional actions related to or employing iPSC technology will be created in response to the topic launched in the IMI2 JU 12th Call for proposals. Coordination with the European Strategy Forum on Research Infrastructures (**ESFRI**, https://ec.europa.eu/research/infrastructures/index_en.cfm?pg=esfri) is to be considered.

Other European wide or national initiatives are:

- the **Human Induced Pluripotent Stem Cell Initiative** (http://www.hipsci.org/);
- the **Human Pluripotent Stem Cell Registry** (https://hpscreg.eu/);
- national initiatives such as **El Banco de Líneas Celulares de Barcelona** (https://www.cmrb.eu/banco-lineas-celulares/que_es.html);
- the **UK Stem Cell Bank** (http://www.nibsc.org/ukstemcellbank);
- the **German Stem Cell Network** (http://www.gscn.org/en/HOME.aspx);
- the **Stem Cell Network NRW** (http://www.stemcells.nrw.de);
- several projects within the funding measures related to the Action Plan 'Individualized Medicine', e.g. 'Innovative stem cell technologies for personalized medicine' (https://gesundheitsforschung-bmbf.de/de/innovative-stammzelltechnologien.php).

Furthermore, it will be mandatory for the applicants to monitor collaborative activities across the European R&D landscape to make the infrastructure available to governmentally-funded scientific projects in the iPSC area.

Industry consortium

The industry consortium is composed of the following EFPIA companies:

- Janssen (lead)
- Bayer
- Eli Lilly

- Lundbeck
- Novo Nordisk
- UCB
- Pfizer
- Takeda
- Fujifilm
- Servier

The industry consortium will contribute the following expertise and assets:

- facilitation of transfer of capabilities and knowledge from EBiSC to reach the ultimate goal of self-sustainability of the iPSC banking entity;
- test of the consistency and quality of iPSC lines as well as preparations of bulk quantities of precursor cell preparations;
- interaction to ensure banking of iPSC lines which will aid in disease understanding and development of screening models to be used in R&D;
- establishment of robust and reliable iPSC disease models and screening assays demonstrating proof of concept for the use of iPSCs for disease and pharmaceutical research;
- support for research activities focusing on:
    - differentiating and analysing iPSC-derived neurons. This will include efforts to shorten the time to achieve electrophysiologically mature neurons with the goal to replace rodent, primary neuron preparations. A focus will be on the analysis of iPSC lines derived from patients suffering from neurodegenerative diseases or gene-edited to carry certain risk genes or mutations that are linked to neurodegeneration,
    - producing iPSC-derived cardiomyocytes and analysing effects of e.g. pro-arrhythmogenic mutations or pharmacological treatments on the electrophysiological characteristics of cells,
    - producing and analysing iPSC-derived pancreatic cells to study the underlying mechanisms of diabetes and beta cell dysfunction,
    - producing iPSC-derived cells from auto-immune and selected monogenic diseases, as well as defined disease phenotypes with known genetic background,
    - they will further support the adaptation of the iPSC technology to automated screening technology by employing precursor cells provided by the consortium.

Indicative duration of the action

The indicative duration of the action is 36 months.

Indicative budget

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

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

The financial contribution from IMI2 JU is a maximum of EUR 4 600 000.

Applicant consortium

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

The applicant consortium, which should include SMEs with relevant expertise and experience in iPSC line derivation and QC, 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. SMEs can be of great benefit to IMI2 JU projects and, inter-alia strengthen the competitiveness and industrial leadership of Europe. Their involvement might offer a complementary perspective to industry and the academia, and help deliver the long-term impact of the project. For these reasons, applicants should consider engaging SMEs throughout the proposal.

Significant experience, knowledge and know-how in logistics and infrastructure to operate a European-wide cell line repository, including a mirror iPSC bank according to ISO 9001 standards are prerequisites. In addition, this may require mobilising, as appropriate, the following expertise on:

- storage and distribution of cells;
- the procurement of biosamples for iPSC generation;
- long-term storage of biosamples to build a clinically relevant source of primary material and allow re-derivation of iPSC lines;
- reprogramming of human-derived cells using state-to-the-art technologies;
- gene-editing approaches to generate isogenic pairs of iPSC cells;
- comprehensive QC of established iPSC lines;
- knowledge in long term storage of biosamples;
- knowledge in reprogramming of somatic cells to generate pluripotent stem cells;
- state-of-the-art gene editing technology (Crispr/Cas);
- handling, expansion and QC of iPSC lines;
- technology and know-how to handle large-scale iPSC cultures as well as the ability to produce bulk quantities of precursor cells or cells with a mature phenotype for distribution;
- database management to monitor status of the cell bank and maintain and amend information available to each cell line;
- knowledge in establishing and maintaining an online portal for purchasing iPSC lines;
- experience in ethical and legal affairs related to the derivation and use of iPSCs;
- business or economics experience to transform the iPSC repository into a self-sustainable business;
- scientific / industrial expertise to guide the expansion of the iPSC repository in therapeutically relevant disease areas;
- general project management (ability to consistently set and achieve milestones on time and within budget; managing varying interests of multiple stakeholders) and professional communication expertise (expertise in communication tools and systems for project management purposes).

It may also require mobilising, as appropriate, the following resources:

- a pre-existing, European-wide, quality-controlled foundational collection of iPS cell lines representing specific disease backgrounds with a focus on neurodegeneration (Alzheimer's disease and related tauopathies, Parkinson's disease), diabetes and cardiovascular diseases and healthy controls including associated data made available for distribution;
- IT capabilities to maintain and support the laboratory infrastructure management system that hosts iPSC-related information and to make the catalogue and the associated data accessible via the internet;
- capacities to allow online ordering and payment of iPSC lines;

- support on legal and ethical matters;
- commercial / industrial application of iPSC-derived assets generated within such a consortium including large-scale production of iPSCs or cell derivatives for medium-/high- throughput screenings;
- access to logistics and infrastructure to operate a cell-line repository including a mirror iPSC bank;
- a fully automated storage system allowing handling of cell lines in the gas phase of liquid nitrogen for long-term storage purposes.

An established distribution pipeline to deliver cell lines to customers and being operational at the outset of the action.

Suggested architecture of the full proposal

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

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

In summary, the work plan should enable activities aiming at:

- managing the existing iPSC collection, including storage, QC, banking, expansion, and distribution of cell lines;
- further expanding the iPSC collection by providing technology to derive and establish iPSC lines, reaching out to the European scientific community and consortia (being operational or in the process of becoming operational) to make use of synergies and support logistics necessary to secure continued access to iPSC-related assets generated within these consortia;
- continuous refinement and optimisation of protocols, QC criteria, and SOPs supporting the operation of the banking activities;
- provide gene editing capabilities to generate iPSCs with specific relevant mutations and creation of reporter cell lines;
- develop the technology and establish efficient and reproducible protocols to produce bulk quantities of iPSCs, precursor cells or cells with a mature phenotype to fuel industrial screening campaigns. Definition of QC criteria to deliver consistent quality of expanded or differentiated iPSCs.

The call topic specifically aims to achieve sustainability as well as further development and maturation of a European-based iPSC repository that includes assets that have been developed by previous public-private iPSC collaborations. One of the key outcomes of this action will be to build on existing assets, and, in the runtime of this project, outline a business plan that will allow the future European iPSC banking entity to continue operations beyond the runtime of the project to support the European research & development activities. The scientific challenges that will be addressed in the action to be generated by this topic will further add technology, differentiation protocols, and iPSC lines, including data attached to individual lines to increase the value of the repository.

The bank has to be self-sustainable by end of the action.

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

Work package 1 – Project management

This work package will focus on:

- grant administration;
- communication (within the consortium and with relevant external collaborators);
- dissemination of scientific results and research data;
- sustainability plan facilitating continuation beyond the duration of the action.

Industry contribution

Co-leadership and the overall coordination of the project.

Expected applicant consortium contribution

All of the above. Preparation of a business plan to run iPSC banking operations in a self-sustainable fashion after funding period to achieve sustainability and continue to serve the European research community with access to iPSC technology.

Work package 2

This work package will focus on:

- continuation, expansion, and further optimisation of banking operations. This includes European and worldwide reach of sales to reach self-sustainability;
- incorporation of iPSC assets developed in previous public-private partnerships;
- refinement of existing SOPs for QC of cell lines;
- facilitate integration of appropriate new iPSC lines generated in other scientific projects (IMI2 JU as well as non-IMI2 JU projects);
- establishing connection to clinical networks, biobanks, and other iPSC banking entities, allowing timely access to patient/donor fibroblasts attached to full donor consent, free distribution for research and development, and freedom to operate.

Industry contribution

Supporting above activities. Supporting iPSC line establishment by advising which cell lines are of interest.

Expected applicant consortium contribution

Banking operations as outlined above.

Work package 3

This work package will focus on:

- establishment of bulk production capabilities / SOPs for generating iPSCs or precursor cells to fuel screening campaigns;
- definition of QC criteria for expanded and differentiated iPSCs.

Industry contribution

Advice and identification of cell lines to be subjected to bulk production.

Expected applicant consortium contribution

- Development of protocols for bulk production of iPSC lines and precursor cell lines for all three germ layers.
- Adaptation of differentiation and maintenance protocols.

Work package 4

This work package will focus on:

- proof of concept experiments across industry consortium partners using cell lines produced in work packages 2 and 3 and focusing on the following areas:
    - neurosciences:
        - explore accelerated maturation and/or aging in iPSC-derived neurons with electrophysiological relevant readouts (multi electrode assays or patch clamp analysis),
        - co-cultivation with astrocytes and / or microglia to explore effect of clinically relevant mutations (Alzheimer's disease, Parkinson's disease) on neuronal function,
        - establish brain organoid cultures suitable for high-content imaging analysis,
        - establish *in vitro* or xenograft models for pathology seeding relating to Alzheimer's disease or Parkinson's disease;
    - diabetes:
        - explore technologies to support the adaptation of established protocols for large-scale production,
        - molecular and functional analysis of pancreatic progenitors as well as mature pancreatic cells,
    - cardiovascular diseases:
        - establish standardised differentiation and maturation protocols for derivation of cardiovascular, iPSC-derived cells (including cardiomyocytes, endothelial cells, smooth muscle cells etc.),
        - establish functional assays and readouts to analyse compound/drug efficacy in iPSC-derived cardiovascular cells; harmonise readouts with FDA-approved activities (e.g. in CiPA),
        - assess ability of iPSC-derived cardiovascular cells for patient stratification (drug efficacy depending on common genetic variation),
        - analyse proteomics/metabolomics in iPSC-derived CV cells;
    - gene editing using e.g. Crispr/Cas system to establish disease-relevant iPSC lines;
    - reprogramming of patient derived somatic cells using state-of-the-art technologies (non- integrating technologies).

Industry contribution

- Support in differentiating and analysing iPSC-derived neurons. This will include efforts to shorten the time to achieve electrophysiologically mature neurons with the goal to replace rodent, primary neuron preparations. A focus will be on the analysis of iPSC lines derived from patients suffering from neurodegenerative diseases or gene-edited to carry certain risk genes or mutations that are linked to neurodegeneration.
- Support in producing iPSC-derived cardiovascular cells and analysing effects of e.g. arrhythmogenic mutations or pharmacological treatments on the (electrophysiological) characteristics of cells.
- Support in differentiating and analysing iPSC-derived pancreatic cells to study the underlying mechanisms of diabetes. This includes molecular as well as functional assays. Focus will be on establishing large-scale cell culture capabilities as well as competences in gene editing in collaboration with the relevant partners.

- The industry group will further support the adaptation of the iPSC technology to automated screening technology by employing precursor cells provided by the consortium.

Expected applicant consortium contribution

Already established and QC'ed hiPSCell lines for all the above disease areas; support of industry consortium activities by producing iPS-cells and / or precursor cells at quantity to allow screening and other R&D activities. Knowledge and capabilities in gene-editing and reprogramming of somatic cells to derive iPSCs.

Reference

[1] Takahashi K, Tanabe K, Ohnuki M, Narita M, Ichisaka T, Tomoda K, Yamanaka S. Induction of pluripotent stem cells from adult human fibroblasts by defined factors. Cell. 2007;131(5):861-72.

[2] Lu X, Zhao T. Clinical therapy using iPSCs: hopes and challenges. Genomics Proteomics Bioinformatics. 2013 Oct;11(5):294-8. doi: 10.1016/j.gpb.2013.09.002. Epub 2013 Sep 21.

[3] Phillips BW and Crook JM. Pluripotent human stem cells: A novel tool in drug discovery. BioDrugs. 2010 Apr 1;24(2):99-108.

[4] McKernan R, Watt FM. What is the point of large-scale collections of human induced pluripotent stem cells? Nat Biotechnol. 2013 Oct;31(10):875-7.

[5] Hankowski KE, Hamazaki T, Umezawa A, Terada N. Induced pluripotent stem cells as a next-generation biomedical interface. Lab Invest. 2011 Jul;91(7):972-7.

[6] De Sousa PA, Stee R, Wachter E, Bruce K, King J, Hoeve M et al. Rapid establishment of the European Bank for induced Pluripotent Stem Cells (EBiSC) - the Hot Start experience. Stem Cell Res. 2017 Apr;20:105-114.

Topic 7: Linking digital assessment of mobility to clinical endpoints to support regulatory acceptance and clinical practice

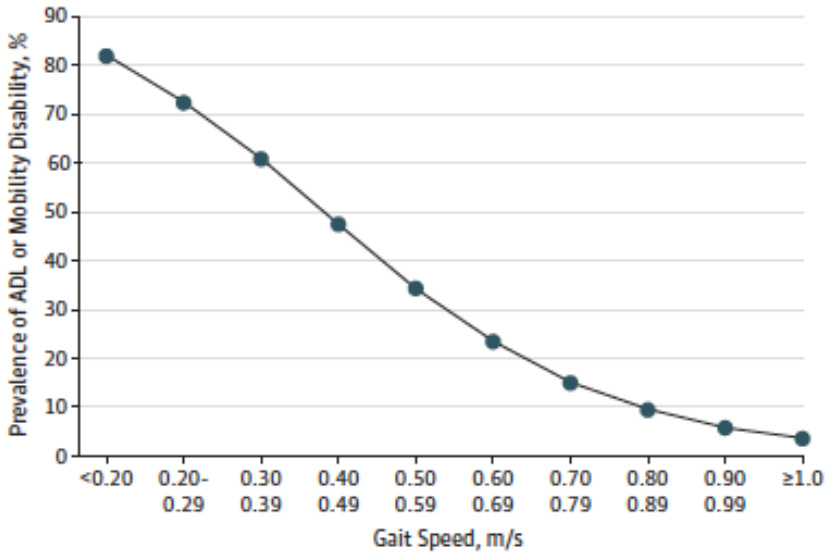
Topic details

Topic code	IMI2-2017-13-07
Action type	Research and Innovation Action (RIA)
Submission and evaluation process	2 stages

Specific challenges to be addressed

Loss of mobility is a growing unmet medical need, driven by chronic illness and frailty in the elderly and by injury in the young (Figure 1). Loss of mobility is a key morbid effect of diseases of various organ systems, including chronic obstructive pulmonary disease (COPD), heart failure, multiple sclerosis, neurodegenerative diseases, etc. New therapeutic approaches target restoration of function and mobility in patients with degenerative diseases, acute injuries, and age-related disabilities, such as muscle anabolic drugs, cartilage regeneration approaches, and other therapies targeting the musculoskeletal system.

Figure. Prevalence of Either Disability for Activities of Daily Living or Mobility Disability by Usual Gait Speed Among Men Aged 80 Years (N=6534)



However, current primary endpoints that measure mobility are either based on patient reported outcome or performance testing, both of which have significant shortcomings. Emerging digital technologies can now measure many aspects of mobility in the 'real world' on a long-term basis. Preliminary results suggest that those technologies have the potential to fundamentally change clinical trials across the development pathway and eventually, medical practice, much the way that Holter monitoring revolutionised the assessment of cardiac arrhythmias decades ago. However, full acceptance and integration of digital mobility assessment into clinical trials and utilisation as primary or secondary endpoint requires rigorous validation and linkage to clinically relevant 'hard' endpoints, such as death, disability, falls, or other complications.

The proposed project will validate digital mobility assessment, focusing on 'real-world walking speed' (RWS) as a primary endpoint for a more sensitive, objective measurement in patients' native environment over longer periods of time and with greater granularity than is currently feasible. RWS is chosen because it requires shorter periods of observation (and lower patient compliance) than 24-hour step counts, fall detection, etc.; and because observed gait speed is already linked to mortality, falls, and hospitalisations in multiple

populations. Emerging data suggest that RWS can be detected using digital inertial sensors, with or without global positioning (GPS) capability, using centre of mass (i.e. belt or skin-worn) devices. Secondary outcomes of additional digital mobility assessment (walking parameters including total time, step counts, gait characteristics, gait cadence, estimated energy expenditure of physical activity, etc.) should be assessed as well. More background information is available in the following list of publications: [1][2][3][4][5][6][7][8][9][10][11][12][13][14][15][16][17][18][19][20][21][22][23]0.

Need and opportunity for public-private collaborative research

Most pharmaceutical companies are grappling with how to apply emerging digital technology to clinical development programmes and post-marketing authorisation assessment of drug efficacy or safety. However, for digital endpoints to truly transform research, regulatory recognition is required. In addition, expertise from pharmaceutical companies and partners with expertise in digital data collection and analysis, use of wearable devices, 'big data' handling and analysis, and data privacy will be required. This expertise is not prevalent among EFPIA partners and will require engagement of companies that are already experienced in the field of continuous monitoring. We believe that physical activity monitoring using inertial sensors is the most advanced technology relevant to pharmaceutical development, and that RWS is the most advanced endpoint that could be validated within a 2-3 year period. By achieving surrogate endpoint qualification, this will harmonise the approach to digital endpoint development, create a powerful regulatory precedent, drive innovation in both pharmaceutical and technology markets, and potentially transform clinical practice relating to frail, elderly, and chronically ill populations. Such an approach can only be done by multiple companies, including small and medium-sized enterprises (SMEs) working with governmental, academic, and patient advocacy groups, to create a harmonised approach.

Scope

The purpose of the action is to measure in three chronically ill or frail populations:

- as a primary outcome, real world walking speed (RWS);
- as secondary outcomes, additional digital mobility assessment (step counts, time walking, gait characteristics, time sitting/standing/walking, cadence, estimated energy expenditure of physical activity, etc.) to be collected and compared (or combined) with RWS to identify outcomes of maximum predictive power[23].

The action will demonstrate that RWS or one of the other gait parameters predicts relevant medical outcomes (falls, injurious falls, hospitalisations, loss of activities of daily living [ADLs], death), and achieve regulatory recognition of RWS as a surrogate endpoint independently of underlying disease diagnosis. To do this, regulatory submission for qualification opinion is anticipated.

The applicant will decide on the three populations to study, and demonstrate that the participants in the applicant consortium have adequate access to such populations for the purposes of this action (e.g. heart failure, multiple sclerosis, Parkinson's disease, COPD, frailty/sarcopenia, post-hip fracture).

The project is envisioned as having two parts:

Part A, a 1-2 year technical validation part that will develop an algorithm for quantifying RWS in the relevant population of slow walkers; and **Part B**, a 3-year validation programme that will demonstrate that the algorithm predicts relevant clinical outcomes (e.g. falls, injurious falls, hospitalisations, disability, and mortality).
The successful applicant consortium will include academic centres and private entities that have expertise in development of digital sensor solutions. The consortium will identify and engage existing longitudinal cohort studies in three relevant populations and support application of digital sensors to the participants with ongoing follow-up for key regulatory endpoints (death, falls, hospitalisations, institutionalisation, loss of ADLs over

[23] http://www.oarsijournal.com/article/S1063-4584(17)30253-4/abstract

several years). Linkage of these novel digital methods and readouts to these clinically relevant outcomes is mandatory for uptake of these methods by the medical community, regulators, and payers.

The specific aims are to develop and apply algorithms that will subsequently become publicly available, so that the validated endpoint consists of the measurement algorithm, the analytic method, and the range of normal or abnormal results that predicts relevant clinical outcomes. This construct should support a variety of wearable hardware and inertial sensor types, and provide design-control characteristics that allow any manufacturer to receive medical device approval by demonstrating comparable performance characteristics to the tested device (i.e. a CE mark and reimbursement approval in the EU or 510(k) process in the USA). For the purposes of the action, however, the successful consortium will only be asked to demonstrate the validity of a single device-algorithm pairing; expansion to subsequent devices will be outside the scope of this action.

For simplification, the following parameters are recommended, although arguments in favour of alternative approaches may be made.

- Devices that capture data from the body centre of mass or lower extremities are preferred to those positioned at the wrist.
- Preference will be given to medical-grade devices over consumer-grade devices, although consumer-grade devices that have adequate documentation of performance characteristics can meet clinical data quality standards, and make raw data available (x, y, z accelerations) in addition to summary outcomes provided by the device firmware, are acceptable.
- The technical specifications of the device – hertz rate of signal acquisition, battery life, presence or absence of feedback to subject – should be described.
- The device must be able to accurately record wear-time to get an estimate of compliance.
- The algorithm to be developed should include step detection, gait speed assessment, and other relevant parameters; any information relating to detection thresholds should be described.
- The method for capturing reference data, i.e. ground truth and other annotations, for Part A (algorithm development) should be stated (e.g. GaitRite, observed 6 minute walk, 400 m walk, etc.). Preference will be given to applications which provide granular and real-world relevant information.
- The development population must be clinically relevant (i.e. gait speed 0.4-1.0 m/s, not only healthy volunteers, although early testing in healthy adults is acceptable). Consideration may be given to remote (internet-based) recruitment and/or follow-up of subjects, with appropriate consent and tracking procedures.
- Once a beta-version of the algorithm-device pair is available, human factor and wearability testing should be performed in a relevant population. Wearability should be tested for at least 7 days, and reliability of measurements when data are collected for fewer days should be assessed to determine the minimal number of days of wear that would constitute adequate collection. In addition, usability testing by patient interview should be conducted.

In addition, important confounding variables should be considered. A key decision is how much gait asymmetry will be acceptable in the study populations, and how much the algorithm can accept without excessive error. In general, the goal of the project is to validate low gait speed and/or inadequate walking as a whole-body function, rather than gait asymmetry due to arthritis, neurological deficits (stroke, etc.) that affect primarily one limb or joint. However, these are not always clear distinctions, and some overlap is expected, especially in elderly populations. In addition, environmental factors limit physical activity to different extents in different geographical locations, depending also on the patient's medical condition (ability to go outside, etc.). Applicants should describe their approach to these confounding variables, including but not limited to:

a. postural stability
b. balance
c. dizziness
d. symmetry of gait
e. medications
f. comorbid conditions

g. weather/external conditions/location.

The regulatory approach, already under discussion with the European Medicines Agency (EMA), will be analogous to multi-indication approval for drugs, where demonstration of efficacy in two or more populations can lead to a broad approval for an indication. Engagement of EMA and the U.S. Food and Drug Administration (FDA) by the successful consortium will be a key aspect of the plan. The aim is to gain approval of mobility assessment as an endpoint, not to certify any particular device. The output of the consortium will be validation of RWS or other endpoints with cut-offs for predicting increased risk of the clinical endpoints for 1) surrogate primary or secondary endpoints for clinical trials carried out under oversight of EMA, FDA, or other competent authorities; 2) recognition by payers and health technology assessment (HTA) bodies of the validity of RWS and application of cut-offs to support pharmacological or other interventions; 3) clinical decision-making outside of clinical trials.

Sustainability of the project beyond the 5-year period should also be considered. Additional work to validate, promulgate, and expand on the use of the algorithm(s) developed during the project period may be considered for separate funding.

Expected key deliverables

The key deliverables for the project include:

Part A

- Development of the appropriate algorithm and one (or more) digital mobility assessment devices to use in the subsequent validation studies. Assessment of algorithm precision and accuracy should be carried out using a reference method (wheel-based speed assessment, video step analysis, GaitRite analysis, shoe insole systems, etc.) in a relevant population of slow walkers (gait speed approximately 0.4-1.0 m/s). The algorithm must be able to function across the relevant range of gait speeds associated with poor clinical outcomes (e.g. 0.4-1.0 m/s). The sensitivity and specificity of the algorithm to detect bouts of purposeful walking should be assessed.
- Human factors and wearability testing in a relevant population.
- Consensus on data collection, database structure, data quality, and analysis algorithms that will be publicly available and can function across multiple devices.
- Ongoing collaboration with and submission of algorithm validation for mobility assessment to health authorities and HTA bodies.

Part B

- Identification of ongoing longitudinal cohort studies in relevant populations, in which the outcome measures are being or can be collected.
- Digital mobility and clinical outcome assessment over 2-3 years in each of three populations (for example, COPD, heart failure, multiple sclerosis, neurodegenerative diseases, sarcopenia/frailty, hip fracture recovery, etc.). The choice of populations is up to the applicant, but applications will be judged in part on the detail and quality of the population cohorts selected. Sufficient detail should be provided about each cohort to demonstrate that there is a stable population, effective follow-up, and adequate data collection. Applicants must be mindful that it is their responsibility to demonstrate in their proposals that clinical sites chosen are able and willing to participate.
- Define the duration and frequency of digital gait assessment needed (e.g. one week every six months?) to successfully predict the endpoints.
- Analysis of the predictive capacity and thresholds for increased risk of clinical outcomes (falls, hospitalisations, loss of ADLs, death) in multiple populations. Definition of what constitutes a meaningful change (e.g. responder definition or minimum clinically relevant difference) in gait parameters in each population studied (e.g. is 0.1 m/s the smallest difference that represents a meaningful change in how the patient feels, functions or survives)?

- Meta-analysis of mobility across populations as a predictor of adverse clinical outcomes. Does RWS or a secondary endpoint predict outcomes equally across all three populations? Are meaningful differences of the same magnitude? What is the minimal device wear time that gives a stable estimate of each predictive parameter?
- Submission of data to health authorities and HTA bodies for consideration as a surrogate endpoint for clinical trials, and for payer recognition of the endpoint for clinical use, respectively.

For guidance regarding timing, it is suggested that years 1-2 (Part A) may consist of algorithm and device selection, algorithm validation, development of clinical protocols and consent forms, coordination with clinical study sites, etc. Years 3-4 may be focused on validating data collection; year 5 on data analysis, and regulatory and HTA submission. Applicants are free to modify this suggestion as they think best. It is recognised that HA and HTA review and feedback will probably continue after the end of the project, and results exploitation will be part of the planning in year 5. As RWS is already in use with pilot data in multiple populations, and several pharmaceutical companies have already initiated discussions with EMA and FDA, the goal of full surrogate endpoint validation should be realistic.

Expected impact

The mission of IMI is to improve health by speeding development of, and patient access to, innovative medicines, particularly in areas of high unmet medical or social need. As the fastest-growing population in Europe is that of people over 80 years of age, and many previously fatal illnesses have been converted into chronic diseases, mobility disability is going to continue to grow in the 21st century. The first step in treating loss of mobility and preventing disability is detecting it effectively, with methods that do not require highly complex, hospital-based solutions. By making mobility assessment feasible, and indeed an integral part of medical care, the consortium could enable development of novel solutions (pharmacological, digital, nutritional, exercise-based) to a major public health problem – the increasing prevalence of mobility disability due to the aging of the population and chronic diseases. The digital assessment of mobility is such a method, and has the potential to revolutionise the care of frail populations and of the development of drugs to treat them.

Successful demonstration that digitally-detected low mobility predicts relevant clinical outcomes will have major impact on drug development and clinical care of the target populations. We anticipate that many additional projects will emerge if the output of the proposed action is successful, for example, demonstration of RWS predictive power in additional populations; further studies required for surrogate endpoint recognition; applications to clinical settings in various national health care system contexts, etc.

Applicants should also indicate how they will strengthen the competitiveness and industrial leadership of Europe by, for example, engaging suitable SMEs.

Potential synergies with existing consortia

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

Applicants should consider any relevant related projects from IMI, FP7, Horizon 2020 and other relevant initiatives outside the EU. For the collaboration with HTA bodies, interaction with EUnetHTA Joint Action 3 (European network for Health Technology Assessment - http://www.eunethta.eu/) should be considered.

Because the project does not focus on a single clinical disease, there is great potential for synergy with existing IMI projects in:

- COPD **(PRO-Active)** (http://www.imi.europa.eu/projects-results/project-factsheets/pro-active)
- multiple sclerosis **RADAR-CNS** (www.radar-cns.org)

- age-related sarcopenia **SPRINTT** (www.mysprintt.eu).

Conversely, there is potential synergy with other IMI projects that focus on digital medicines (e.g. **EMIF** - www.emif.eu , **eTRIKS** - www.etriks.org , **EHR4CR** - www.ehr4cr.eu), especially in regard to learnings about data management, privacy, transfer, and analysis; and capture of clinical outcomes. Finally, consideration should be given to collaborating with non-IMI projects, such as the Clinical Trials Tranformation Initiative (**CTTI**) project 'Developing Novel Endpoints Generated by Mobile Technology for Use in Clinical Trials' (https://www.ctti-clinicaltrials.org/projects/novel-endpoints). Such agreements would enhance the ability of various types of digital data to be captured, analysed, and shared with greater efficiency, and would be an additional boon to the field.

Industry Consortium

The industry consortium is composed of the following EFPIA partners:

- Novartis (lead)
- Amgen
- AstraZeneca
- Bayer
- Grünenthal
- Merck KGa
- Pfizer
- Roche
- Sanofi
- Takeda
- Teva
- Microsoft
- ERT
- ICON

EFPIA participants are already working with actimetry in their own clinical trials, and are working on analysis and measurement algorithms to various extents. This project will utilise this expertise through close collaboration with EFPIA participants. EFPIA participants will also help select a Scientific Advisory Board that will meet regularly throughout the study. EFPIA members may also offer in-kind contributions of expertise and analysis capacity based on their internal research experience with digital devices in general and mobility assessment in particular. Technology companies are expected to bring additional and greater expertise in the data handling and analysis aspects.

Indicative duration of the action

The indicative duration of the action is 60 months.

Future project expansion

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

Specific areas of activity may include additional meta-analyses across the study populations; longer follow-up beyond the initial study period; secondary data analyses for additional endpoints; exploratory analyses of subpopulations, etc. Additional activities for further publication of the results, dissemination of the algorithm, and application to additional digital devices may also be in scope for sustainability.

Indicative budget

The indicative EFPIA in-kind contribution is EUR 24 700 000.

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

The financial contribution from IMI2 JU is a maximum of EUR 25 500 000.

Applicant Consortium

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

The applicant consortium is expected to address all the research objectives and make key contributions to the defined deliverables in synergy with the industry consortium. Relevant technology companies, in particular SMEs, should be part of the successful consortium, along with academic medical centres or other organisations that have access to ongoing longitudinal cohort studies of the patient populations of interest (geriatrics, heart failure, COPD, multiple sclerosis, Parkinson Disease, or other populations with high event rates for mortality, serious morbidity/complications, and falls). Expertise on complex data management and analysis and specifically in validation of technology-related medical tools are also required. It is imperative that at least one technology company with expertise in wearable technologies for activity monitoring be part of all applicant consortia. Experience with medical device registration is also an advantage. It is envisioned that regulatory and HTA bodies will be engaged in an advisory capacity, rather than as consortium members. Patient advocacy groups should be included in the consortium and be in the work packages as appropriate.

Suggested architecture of the full proposal

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

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

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

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

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

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

A plan for aspects related to sustainability, facilitating continuation beyond the duration of the project should also be proposed. For example, if the project is successful, how will dissemination of the results to support use in clinical practice be proposed?

Work package 1 – Project management and oversight

This work package will address the strategy, management, and implementation of the project. Work package (WP) 1 will create regular meetings and interaction between sub-groups and teams, to coordinate and follow up on the work effort. This WP will also be responsible for post-project result sustainability and exploitation planning.

Industry contribution

- Support for project management, including planning, budgeting, follow up and tracking, and consolidation of work package reports to IMI. Project risk management and comprehensive communication and dissemination of its progress and its milestones are important additional elements of EFPIA contribution. In-kind contribution of legal support as feasible for intellectual property (IP) discussions.

Expected applicant consortium contribution:

- Providing detailed follow up and tracking, via regular work package reports, early report of any unexpected organisational or structural issue or delay with respect to the project deployment and intermediate objectives. This WP will also organise a Scientific Advisory Board (SAB) and a Data Monitoring Committee (DMC) (if needed) to review and support the studies and give advice to the project. The WP should also engage with patient support groups and ensure patient input to the development and validation process.
- In addition, this WP will ensure that IP of participants is respected and that dissemination of results is not prevented by IP disputes. Primary legal support will be from the applicant coordinator's institution, with input from the EFPIA lead. The applicants are reminded to familiarise themselves with IMI2 JU IP rules applicable both to pre-existing IP needed for the project, and to IP to be developed during the programme.

Work package 2 – Algorithm development and technical validation

Consortium partners will collaborate to select a digital activity detection device, develop or obtain an algorithm for step detection, purposeful walking detection, and walking speed measurement, and pursue technical validation against a reference method.

Industry contribution

- The industry partners will work closely with the consortium to assist in the steps above, and provide research expertise and in-kind contributions to support data capture, analysis, and interpretation.

Expected applicant consortium contribution

- Should include a strong technology company participant that is capable of: carrying out the technical validation procedures and providing the raw digital data; identify a patient population of slow walkers in whom the initial validation can be carried out; develop the study protocols for initial algorithm development (method development) and subsequent initial method validation. Human factor and wearability/usability testing as described above should be included in the development plan. This will be the bulk of Part A of the project.

Work package 3 – Database development and data management

The consortium will develop and host the clinical and technical database to support the project and provide access to all consortium members.

Industry contribution

- Advice and oversight based on member companies' expertise with database development and function, including privacy assurance and data anonymisation experience. Additional contributions may be supported after discussion between industry and applicant participants.

Expected applicant consortium contribution:

- Server hosting, database development and maintenance; creation of processes for data security, privacy, and transfer; provision of data anonymisation procedures when necessary; definition of data standards that can be used for capture of raw and processed data from a range of inertial sensor types and sensor positioning.

Work package 4 – Validation of RWS vs. clinical outcomes and definition and validation of RWS/mobility clinical endpoints

The consortium will jointly identify at least three (3) clinical populations to study; identify the existing longitudinal cohort studies that are available to the consortium to carry out Part B of the study; and develop the protocol for Part B.

Industry contribution

- Making fully available the member companies' expertise in clinical study initiation and conduct, providing oversight over the study management, the accomplishment of overall objectives. EFPIA members will also support study monitoring and participate in data interpretation.

Expected applicant consortium contribution

- Coordinate with existing longitudinal cohort studies to incorporate the digital device into their procedures; agree on a common set of procedures, endpoints, and analytical approaches; develop the data structures and transfer specifications to support digital data analysis; create the appropriate database structures for Part B; develop endpoint definitions and their measures of meaningful change; lead the analysis of the data and report the results in collaboration with WP 6.

Work package 5 – Regulatory, HTA, and payer consensus over operational definitions

The consortium partners will jointly contribute to the overall evaluation of evidence and results from WP 2 and WP 4. This WP will engage with EMA and FDA, as well as with relevant HTA bodies, to develop the administrative and regulatory pathways for digital mobility analysis in parallel with the development of the data to support submissions. The consortium will engage with EMA on a regular basis. As noted earlier, the scope of these discussions is about the endpoint validation, not specific instrument (device) approval.

Industry contribution

- Planning, hosting and organising workshop(s) with regulators and payers, contributing to discussion of available evidence (including unpublished data), literature analysis, publication support, co-authoring of reviews and white paper(s).

Expected applicant consortium contribution

- Participate and actively contribute to constructive discussion with regulators and payers to promote and achieve consensus over operational definitions. (Co)-author reviews and white paper(s).

Work package 6 – Statistical analysis, evaluation of results, and data availability

The consortium partners will collaboratively review the trial results in order to draw the necessary clinical and regulatory conclusions. This WP will also be responsible for creating the project databases, including those which will become publicly available at the conclusion of the project. The WP will also support regulatory review for a qualification opinion, as required.

Industry contribution

- Planning, hosting and organising workshop(s) with regulators; providing regulatory affairs expertise to the consortium; contributing to results discussion via its experts (including biostatisticians); providing technical support (translations, etc.); (co-) authoring of reviews and white paper(s).

Expected applicant consortium contribution

- Analyse the data and collaborate with EFPIA sponsors on data interpretation and publication. Contribute to constructive discussion with regulators to achieve scientific and regulatory agreement over the interpretation of study results. Co-author primary papers, reviews, and white paper(s). Support consolidation of the scientific consensus necessary to achieve project aims.

Work package 7 – Stakeholder information and results dissemination

The consortium partners will contribute over the 5-year project duration to drive public awareness of the project, including presentation to stakeholders and media as appropriate. In collaboration with WP 6, this WP will develop methods for external researchers to access project results at the end of the project period.

The successful applicant is encouraged to take a leading role early on in the project and engage with the scientific community and make data, standards, and software (including underlying raw measurements, source code, APIs etc.) openly accessible using FAIR (findable, accessable, interoperable, reusable) principles. Since in this case the data can be easily anonymised there should be no privacy concerns to prevent an open innovation approach.
In this way, the project would benefit from the rapid developments in the data science community by encouraging other groups to explore the data and develop alternative analysis approaches; contribute to establishing technical interoperability standards in the field; and educate the data science community about the specific technical and regulatory requirements for digital biomarkers.

Industry contribution

- Logistics and organisational support; contribution of EFPIA experts as appropriate; providing technical support (translations, etc.); this will include a dedicated website and organisation of milestone workshops for stakeholders (and the general public as appropriate).

Expected applicant consortium contribution

- Provide the scientific and medical content for building, consolidating and updating information about digital mobility assessments over the project duration; provide personal and collegial contribution to the dissemination programme implementation; support publication of papers in peer reviewed scientific journals.

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Topic 8: Human tumour microenvironment immunoprofiling

Topic details

Topic code	IMI2-2017-13-08
Action type	Research and Innovation Action (RIA)
Submission and evaluation process	2 stages

Specific challenges to be addressed

Despite the initial clinical success of cancer immunotherapy with the advent of checkpoint inhibitors and other immune modulating agents, most patients still do not experience a deep, durable and satisfactory (e.g. with limited side effects) response. Numerous trials are currently ongoing exploring combinations of checkpoint inhibitors with established therapies to increase the response rate. Experts in the field are, however, discussing whether all these trials follow a sound scientific rationale. An improved knowledge on the molecular and cellular composition of the tumour microenvironment and better understanding of the mechanisms by which the immune system and tumours interact will contribute to more informed decisions on combination therapies and help with developing interventions that would enable better management of the disease and even its cure. Though much has been discovered about the nature of tumour-host interactions, the basic understanding of how the mechanisms and the different types of immune cells involved in the anti-tumour immune response interact with each other and with tumour cells, and how they can be monitored and pharmacologically manipulated to better control disease remains somewhat elusive.

To improve therapy, the understanding of the tumour microenvironment needs to evolve. Firstly, the understanding of **tumour/host interaction on the cellular and molecular level in the absence of therapeutic intervention** needs to improve. Both individual tumours and individual hosts are heterogeneous with respect to the quality and degree of immunity. Understanding the cellular and molecular nature of the tumour microenvironment will (i) help us characterise the ability of a patient's immune system to mount an anti-tumour attack and (ii) provide ideas which pharmacological interventions may support or activate the immune cells to attack the tumour cells.

Secondly and in close alignment with the previous paragraph, one needs to understand **how current therapeutic approaches affect the host/tumour interaction** to **have a baseline** from which to improve the current therapeutic paradigm. Such data could be used to further improve currently available treatments or to develop new potential therapeutic strategies.

A multi-modal approach to assess both the tumour and the host is recommended. Recently developed models and systems allow for large information-rich data sets to be created that can be mined to gain insights for the development of therapeutic interventions. Furthermore, access to informatics and machine-learning tools may lead to the development of clinical and scientific hypotheses that could potentially be validated in the clinic.

This IMI2 JU topic is designed to generate an information set to help evolve clinical hypothesis generation that will drive the development of new therapeutic interventions for cancer and to identify patient sub-populations that may respond to specific interventions, in particular to immunotherapy. **The proposed topic, for the first time, will assemble a consortium to generate a data set sufficient to gain a meaningful view of the tumour micro-environment. The generation of such a data set is the core activity of this IMI2 JU topic**

while the future purposes (improvement of the currently available treatments and development of potential therapeutic strategies) go beyond the frame of this topic.

Need and opportunity for public-private collaborative research

Given the heterogeneity both in patients' immune systems and tumours, large data sets need to be generated to gain meaningful insights into the tumour microenvironment and the tumour-host interaction both at baseline (without treatment) and under therapy, in particular immunotherapy. This requires access to large numbers of patient samples from numerous clinical centres, collaboration of a number of different partners to analyse them for their molecular and cellular composition. Finally, a collaborative effort is needed to store and integrate patient and sample data according to agreed standards to allow for comparability of data and further analyses. Bioinformatics expertise as well as IT and legal support will be needed. Whilst no single organisation has access to all these resources and expertise (e.g. EFPIA partners: clinical biomarker and drug discovery & development expertise; public partners/clinical centres: patient samples, pathology, histology, etc), all share the same desire and need for a large and standardised dataset on the human tumour microenvironment, making this an ideal setting for a public-private partnership.

Scope

The ultimate aim and core activity is **to create a database containing integrated cellular and molecular data from the tumour microenvironment of patients** treated with both targeted and non-targeted therapy, in particular immunotherapy, **as well as key information from patient history and clinical progression**.

- **Core activity (broad profiling):**

  development of a fully integrated data set of defined immune cell subsets (deliverables (1) and (2)) in samples from patients from specific cancer indications treated with radiotherapy, chemotherapy, targeted therapy and, in particular, targeted immune checkpoint therapy and correlation to the oncogenomic profile of the tumour.

- **Supplemental activities:**
  - in-depth profiling of a subset of samples from patients undergoing immunotherapy using **selected** advanced technologies (deliverable (5));
  - development of a sustainable open-access, royalty-free and precompetitive database that houses such a data set, including the required privacy settings (deliverables (7-9));
  - generation of a biomarker validation platform to identify and start to characterise potential predictive biomarkers for single-agent and combinatorial immunotherapy trials (deliverable (10)).

Expected key deliverables

1) **Deliverable 1**

   A data set on presence and spatial distribution of immune cell subtypes (including T cells, NK cells, B-cells, myeloid-derived suppressor cells, macrophages including polarisation markers, neutrophils, dendritic cells, Ki67), using immunohistochemistry (IHC) or immunofluorescence (IF), in surgical specimen (wherever possible) and biopsies with pathologist-validated tumour content, immune infiltrate and invasive front (wherever possible).
   IHC or IF measurements should ideally be centralised at one of the academic consortium partners. In case IHC or IF measurements will be performed at multiple sites, a data package needs to be provided demonstrating that such assays can be run using harmonised analysis platforms, reagents and protocols. In any case, validated antibodies should be used and staining and slide scanning should be performed at the same site.

2) **Deliverable 2**

RNAseq analysis of all samples as profiled under (1) using ≥ 100M reads per sample.

Deliverables (1) and (2) will be referred to as 'broad profiling' which is regarded as the core activity of the consortium and is expected to consume a considerable part of the resources.

3) **Deliverable 3**

Obtaining such data from patients with the following specifications:

a. pre- and post-treatment tumour samples whenever possible (pre-treatment: up to six months, preferably immediately prior to treatment and not older than 1 year; post-treatment: should allow informative analyses, e. g. 6-8 weeks after treatment);

b. for immune checkpoint inhibitor (ICI) treatment, pre-treatment samples are mandatory, post-treatment samples are desirable. In case only peripheral samples are available in post-treatment settings, detection of immune cells needs to be performed using suitable methods;

c. for longitudinal studies; collection of samples during the course of therapy (i.e. 1st, line therapy followed by 2nd line therapy, etc.) would be supported and preferred whenever possible;

d. indications, treatments and envisaged sample numbers:

Indication	
Tumour indication*	**No. of patients envisaged** (please justify deviations from numbers in application)
Lung adenocarcinoma	≥ 600
Head & Neck Cancer	≥ 600
Colorectal Cancer *(with known microsatellite (MS) status)*	≥ 600
ICI failures from different indications	≥ 600
Indication as proposed by academic consortium** (not: melanoma)	≥ 100-600 (flexible; based on the proposal)
All	2500-3000
Treatments	
Type of treatment	**% of patients**
Chemotherapy, radiotherapy, non-ICI targeted therapy	≤ 40% (consortium has to show that large enough sample numbers can be collected for any subgroup to achieve statistical power for broad profiling data set)
ICI therapy (Either post prior therapies or as first line therapy)	≥ 60%
Retrospective versus prospective analysis	

Retrospective (samples max 2ys old, paraffin slides are not sufficient, tumour blocks need to be available)	≤ 30%
Prospective	≥ 70%

*Indications 1-4 are fixed. Lung adenocarcinoma has the highest priority. The consortium should start with this indication and apply any learnings to the other indications.
**This could be a 'classical' tumour indication but could also be a more explorative/subgroup of patients, for example patients who developed cancer under immunosuppressive therapies, e. g. HIV or in a post-transplantation setting.

4) **Deliverable 4**

Established and validated workflow for sample quality control, tracking and storage.

5) **Deliverable 5**

A 'deep profiling' data set for a subset of tumour samples (~50-100 per indication) to address a particular hypothesis, from patients having undergone or undergoing ICI therapy, with the goal of comparing pre- versus post-treatment samples as derived from, for example:

a. single cell RNA seq on sorted immune cell population (important);
b. multi-color flow cytometry, especially of surgical specimen, realised by participating partners that have appropriate capabilities using a standardised panel of markers;
c. multiplex-IF including a panel of functional immune-related markers;
d. selected advanced technologies, e. g. CyTOF;
e. microbiome analysis;
f. ctDNA and ctRNA analysis;
g. proximity ligation assay-based approaches for detection of e. g. receptor-ligand interactions.

A selected and well-reasoned set of these technologies should be employed; a reasonable and limited part of the budget should be allocated to 'deep profiling' (considerably less than 'broad profiling').

6) **Deliverable 6**

For all patients collection and banking of:

a. blood samples including samples for e.g. paxgene blood-RNA or RNA scope as well as plasma;
b. faeces;

matched to immuneprofiled tumours to enable future validation of potential predictive biomarkers in peripheral tissue.

7) **Deliverable 7**

A raw data repository with access for all consortium partners.

8) **Deliverable 8**

Software and bioinformatics packages for full data integration and analysis, for example, gene signatures, gene fusions and latest-generation image processing software for analysis of IHC/IF data.

9) **Deliverable 9**

A sustainable database/IT infrastructure allowing for open-access query of data set and long-term housing of database. The data are initially accessible for consortium partners; following data curation, integration and journal publication, the data will be released into the public domain.

10) **Deliverable 10**

Experimental validation packages and classifier signals for potential predictive biomarkers based on the data collected in the consortium.

Wherever possible, synergies with pre-existing platforms, solutions and databases should be realised.

Expected impact

Immunotherapy, as exemplified by therapeutic antibodies neutralising the immune checkpoint PD1, has been shown to provide sustained survival benefit to patients with melanoma, lung, kidney, and bladder cancers. In general, the response rate in these cancer patients to PD1/PD-L1 blockade is about 20 to 30%. Acquired resistance to immune checkpoint blockade is also likely to be observed in some of these responders. While some biomarkers like PD-L1 expression and IFN-gamma gene signature have been able to predict response to PD-1/PD-L1 targeting therapeutics, the mechanisms of resistance, innate and/or acquired, to immune checkpoint blockade in these cancer patients remains largely unknown.

A comprehensive database, profiling immune cells in the tumour microenvironment (TME) of patients that are responsive to immune checkpoint blockade versus those that are not, is generally lacking at the present time and therefore the creation of such a database is the ultimate aim of this IMI2 JU topic. A searchable database, with integrated tumour genomic information along with matched immune profiles and (immune) therapy outcome, will enable users to identify biological networks involved in, and develop biomarkers to predict response to, immunotherapy. Maximum impact would be achieved by continued integration of clinical outcome data received after the end of the consortium. This IMI2 JU topic is expected to be the basis for future significant impacts but these will go beyond the scope and timeframe of the IMI2 JU topic:

- identification of novel predictive biomarkers and patient selection strategies and thereby improving clinical response rate to current cancer immunotherapy and other therapeutic regimens in oncology; such discoveries and improvements should enhance clinical and healthcare practice;
- understanding mechanism(s) of resistance to current immunotherapy, but also other therapy regimens, to enable identification of new therapeutic targets;
- establishing rational combination immunotherapy strategy (this should strengthen competitiveness and help to address the specific societal challenge of low response rates in cancer patients to current therapies);
- deriving therapy solutions for patients that are insensitive to immune checkpoint blockade (thus generating a positive impact on European cancer patients' health and wellbeing in the long-term);
- understanding molecular effects and potential safety liability of immunotherapy.

Overall, the project is consistent with the IMI2 JU goals of supporting the development of next-generation medicines and treatments for diseases with high unmet medical need as well as treatment biomarkers for diseases clearly linked to clinical relevance.

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.

Industry consortium

The industry consortium is composed of the following EFPIA companies:

- Merck KGaA (lead)
- AbbVie
- Bayer
- Eli Lilly
- GSK
- Janssen/J&J
- Sanofi
- Servier
- Pierre-Fabre

The industry consortium anticipates contributing the following expertise and assets:

- largely financial contribution (most activities centralised at public partners);
- work package co-leadership;
- contribution to database / IT solutions and bioinformatic analyses;
- contribution to biomarker validation studies.

Indicative duration of the action

The indicative duration of the action is 60 months.

Future project expansion

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

As part of a possible future expansion of this IMI2 JU topic, logical next step activities may be performed that go beyond the time and resource constraints here, e.g. (i) additional tumour indications may be explored, (ii) additional deep-profiling activities may be performed, (iii) advanced biomarker testing and validation activities and discovery platforms may be employed, and (iv) further IT and data analytics activities may be warranted.

Indicative budget

The indicative EFPIA contribution is EUR 16 350 000.

This indicative figure includes EUR 6 300 000 as in-kind contribution and EUR 10 050 000 as financial contribution to the beneficiaries receiving JU funding in the selected action.

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

The financial contribution from IMI2 JU is a maximum of EUR 17 830 000.

In relation to the above, applicant should be informed that the financial contribution from the IMI2 JU will be supplemented by an approximate EUR 10 050 000 financial contribution from the participating EFPIA companies, thus resulting in an indicative EUR 27 880 000 total financial contribution.

Therefore, at stage 1 applicants should provide a suggested allocation of the total financial contribution (EUR 27 880 000) in the budget of their short proposal in order to achieve the deliverables, ensuring sufficient funding of core activities (i.e. broad profiling, described in deliverables 1 and 2).

The final allocation of the financial contribution for the project deliverables, to be included in the full proposals, will need to be further discussed in preparation of stage 2 between the applicant consortium selected at stage 1 and the industry partners (full consortium).

Applicant consortium

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

The applicant consortium is expected to address **all the research deliverables** (see 'deliverables'), bearing in mind the core activity of the IMI2 JU topic) 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 size of the applicant consortia should reflect the expertise needed to achieve the proposed objectives within the indicated budget while ensuring the 'manageability' of the consortium as well as efficient and effective team work. Therefore, the number of members of the applicant consortium needs to be thoroughly justified in the proposal and all partners involved should make a significant contribution to the project. **The public partners are expected to carry out the vast majority of the hands-on work,** whereas EFPIA partners contribute in-kind and financially (see above), so that **work can be carried out centrally with clear streamlined processes.** Steering of the individual work packages and content decisions will be done jointly by the public and private partners. To ensure a rapid and efficient start, it is essential that a translational research infrastructure in oncology with demonstrated collaboration across multiple disciplines (e.g. surgeons, trial nurses, medical oncologists, radiologists, pathologists, bioinformaticians, laboratory researchers) is already in place. The consortium is not expected to run dedicated clinical trials.

Specifically, the applicant consortium should be able to demonstrate:

- access to tumour tissue and matched blood samples from untreated and treated patients (as indicated in the table under expected key deliverables), with fixation/storage appropriate for different analysis methods. It is expected that the entire number of patient samples to be profiled in this project will come from the public consortium. Applicants should demonstrate the feasibility of collecting the outlined number of samples (see deliverables). EFPIA companies and private partners may contribute additional individual cohorts of patient samples where possible and appropriate;
- technical expertise to carry out the specified measurements using a harmonised set of platforms, protocols & reagents for all consortium partners;
- established and validated workflow for sample quality control, tracking and storage. If such processes do not exist yet in the manner necessary to centralise essential steps in the consortium as outlined in the deliverables, the ability to set this up should be shown;
- experience (as demonstrated by manuscripts/publications/other study reports) on a core set of 'deep profiling' technologies to be carried out on a subset of samples. Some 'deep profiling' technologies might be established during the course of the project or could be performed by SMEs;
- ability to have a legal frame (informed patient consent forms = IPCF) in place for the full duration of the consortium and beyond that allows:
    - acquisition of samples and experimental & bioinformatics studies outlined in the deliverables,
    - transfer of raw and processed experimental data as well as relevant data from medical history in anonymised fashion into data repository/database and open access for consortium members and later, the greater public,

- maintenance of documentation of IPCFs,
- operation under General Data Protection Regulation (EU) 2016/679 (effective May 2018) for European partners, or according to local regulations in case of data from other partners,
- adherence to any other national laws and regulations;

- experience in handling, analysing and integrating large and complex data sets including housing a database;
- to support standardisation of data, adherence to the FAIR principles (Findable, Accessible, Interoperable and Reusable), as outlined in the standard starter pack developed by **eTRIKS**: https://zenodo.org/record/50825#.Wa5XC7IjHIV;
- ability to technically and legally establish and maintain an open-access database beyond consortium frame;
- a plan for aspects related to sustainability should be proposed, especially ensuring that the database remains accessible and facilitating its population with additional clinical outcome data. This can include a proposal for options transferring the open access database into an existing structure and should include realistic ideas for long-term financial and operational sustainability of the database;
- maximum impact would be achieved if collection of clinical outcome data for at least two years beyond consortium frame and integration of the collected data into the database is possible;
- ability to coordinate a large research initiative and to create a scientific network;
- ability to involve patient advocacy groups in such projects.

The applicant consortium is expected to set up a governance structure that includes the necessary project management skills suitable for the consortium and activities.
This could be ensured by one of the publicly funded partners, who in this case would need to have significant project management and coordination skills as well as the necessary experience in supporting complex – per size and composition – consortia in IMI/EU funded projects.

The resources allocated should be adequate for the complexity and size of the consortium.

Suggested architecture of the full proposal

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

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

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

The public partners are expected to carry out the vast majority of the hands-on work whereas EFPIA partners contribute in-kind and financially (see above), so that work can be carried out centrally with clear streamlined processes. Steering of the individual work packages and content decisions will be done jointly by the public and private partners. In addition to project leadership, industry partners staff efforts will be largely spent on work packages 4-8, with major involvement of industry partners in work package 7. Further details will be worked out between the full consortium, i.e. the industry consortium and the selected applicant consortium, in

preparation of stage 2. In particular, the final allocation of the financial contribution for the project deliverables will be discussed and agreed by the full consortium.

All work packages will be co-led by EFPIA and public partners and are expected to have adequate autonomy. A lean governance structure should be put in place.

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

Work package 1 – Management & steering, coordination, sustainability planning; project management office

Industry contribution:

- project leader;
- coordination across different work packages (including overall scientific and strategic oversight).

Expected applicant consortium contribution:

- project coordinator;
- professional project management expertise (daily operational support with project meetings, reporting and internal communication), e. g. through a project management office;
- see section on applicant consortium.

Work package 2 – Communication, public relations, and involvement of patient advocacy groups

Industry contribution:

- communications and patient advocacy expertise.

Expected applicant consortium contribution:

- carry out communication on project overall;
- involve patient advocacy and other groups of interest, e.g. to support patient consent;
- see section on applicant consortium.

Work package 3 – Legal aspects

Industry contribution:

- legal input to support discussions around informed patient consent form & data privacy;
- enable potential synergies with IMI2 JU DO->IT consortium.

Expected applicant consortium contribution:

- ensure legal frame is compatible with deliverable;
- implementation of a legal frame to allow execution of all the deliverables, e.g. clearance by institutional or pan-consortium ethics committees, availability of IPCFs, data privacy, data repository and access, etc;
- see section on applicant consortium.

Work package 4.1 – Broad profiling (core activity)

Industry contribution:

- input and expertise on selection of profiling technologies, antibodies, and immune cell subtypes to be analysed;
- expertise in selected profiling technologies, image analysis and primary data analysis;
- oversight of broad profiling activities and results.

Expected applicant consortium contribution:

- input and expertise on selection of profiling technologies, antibodies, and immune cell subtypes to be analysed;
- applicants are expected to carry out all broad profiling activities, including sample taking, staining, slide scanning, RNAseq, and analysis;
- see deliverables 1-3 and section on applicant consortium.

NOTE: Profiling costs (consumables, RNA seq etc) for all samples outlined in deliverable 3 are expected to consume a substantial part of the cash budget and resources, which should be outlined in the application.

Work package 4.2 – Deep profiling

Industry contribution:

- input and expertise on selection of deep profiling technologies;
- expertise in selected deep profiling technologies and primary data analysis**.**

Expected applicant consortium contribution:

- input and expertise on selection of deep profiling technologies;
- applicants are expected to carry out all deep profiling activities;
- see deliverable 5 and section on applicant consortium.

NOTE: A selected and well-reasoned set of technologies should be employed; a reasonable and limited part of the budget and resources should be allocated (considerably less than 'broad profiling').

Work package 5 – Patients/indications: oversight sample banking and management, QC and ethics

Industry contribution:

- expertise in sample logistics and quality control;
- expertise on handling ethical questions and obtaining relevant input;
- input into process and oversight of validated workflow for sample quality control, tracking and storage/banking (deliverables 4 and 6);
- oversight of sample logistics, quality control etc.

Expected applicant consortium contribution:

- possess or deliver workflows for sample collection, quality control, tracking, storage, banking and maintenance, also linked to legal frame, and implement and carry them out for the project;
- see especially deliverables 4 and 6 and section on applicant consortium.

Work package 6 – Biomarker validation

Industry contribution:

- experimental and technical expertise, pharmacological tool agents;
- input into idea generation and oversight on biomarker validation (deliverable 10);

- laboratory and computational approaches related to I/O biomarkers.

Expected applicant consortium contribution:

- input into idea generation and execution of biomarker validation (deliverable 10);
- see deliverable (10) and section on applicant consortium;

NOTE: A reasonable and limited part of the budget and resources should be allocated.

Work package 7 – Data integration and bioinformatics

Industry contribution:

- input into and oversight of bioinformatics, data integration and statistics support;
- support / carry out software and bioinformatics packages for data analysis.

Expected applicant consortium contribution:

- input into and implementation of software and bioinformatics packages for full data integration and analysis;
- carry out data analysis;
- see deliverable 8 and section on applicant consortium.

Work package 8 – Database and IT infrastructure

Industry contribution:

- database expertise;
- input on database infrastructure and testing.

Expected applicant consortium contribution:

- implement a raw data repository, upload and maintain data, make data accessible to different consortium members;
- develop and implement a sustainable database/IT infrastructure as outlined in deliverable 9;
- carry out the activities for deliverables 7 and 9;
- see deliverables 7 and 9 and section on applicant consortium.

Topic 9: ConcePTION – Continuum of Evidence from Pregnancy Exposures, Reproductive Toxicology and Breastfeeding to Improve Outcomes Now

Topic details

Topic code	IMI2-2017-13-09
Action type	Research and Innovation Action (RIA)
Submission and evaluation process	2 stages

Specific challenges to be addressed

Information to guide decision making for the safe and effective use of medications during pregnancy and breastfeeding is a large unmet need that hinders optimal care of women of childbearing potential. Pregnant women with serious illness need medicines, to treat conditions in order to prevent irreversible damage to their health and the health of their unborn child. These patients, together with their healthcare professionals (HCPs), are invariably interested in better information on the risks that their disease and/or medication can pose to the foetus as well as to babies during breastfeeding.

Prescribing information leaflets generally lack clear information to inform decision making. Very often pregnancy is listed either as a contraindication, or a warning or advice to use effective contraception to avoid pregnancy and stop medication in case of pregnancy. It is common to have statements such as, *'[drug] should not be used during pregnancy unless clearly necessary'* and *'It is not known whether [drug] or metabolites are present in breast milk; caution should be exercised when administered to a nursing woman*', rather than useful scientific information [1]. In the absence of scientific data to inform decision making, the treating physicians often take a risk avoidance approach and advise women with chronic diseases to avoid becoming pregnant, or to stop or not start treatment during pregnancy and breastfeeding. In some situations, when the treatment is stopped, the disease itself may cause even more damaging effects for both the foetus and the mother than the medication, and this may lead to a higher disease burden, poor quality of life, and more healthcare costs.

After a marketing authorisation has been granted, pregnancy registries may be proposed by the Marketing Authorisation Holder (MAH) or mandated by the Medicines Agencies or National Competent Authorities to better characterise the foetal risk in a real-world setting. Over time it has become evident that product-specific pregnancy registries often have their own shortcomings, as evidenced by the lack of published data from these sources, and according to the Food and Drug Administration (FDA) review based on 59 pregnancy registries, only a minority (12%) informed the label to adequately advise patients and HCPs [2], notwithstanding huge investments in funds and time by the sponsors.

The major reason why most pregnancy registries end up being non-informative is that they do not achieve the targeted number of pregnant women, and commonly lack internal comparator groups to aid data interpretation. Hence, many compound-specific pregnancy registries close several years after initiation, woefully under-enrolled, despite efforts by the sponsors to increase recruitment. Alternative ways of characterising disease and compound-mediated adverse foetal outcomes, like teratology information services cohorts, retrospective database or case control studies, are increasingly used for hypothesis testing, but there are still gaps in our knowledge about the best methods to use. In addition, there is no consistent standard of data quality (data collection and analytical methods) recognised as warranting inclusion in product labels.

The situation is even worse concerning breastfeeding. There is a large information gap for patients and HCPs on the risk to the breastfed child from medication given to the mother. Often, due to a lack of data, and even when some data exists, due to difficulties with the predictability of animal data to humans, women are advised to avoid breastfeeding, despite the proven benefit of breastfeeding. The majority of current drug labels follow this approach which is more based on risk avoidance than on risk/benefit assessment. However, certain compounds, due to their physicochemical properties, are either not excreted in the milk, or are found at

concentrations well below any biologically active concentrations. As there are no broadly accepted ways of generating such data and there is no requirement that such data/calculations are generated, these data are often not available. Although there are many different biological sample banks in the EU, there is no biobank for human breast milk. Such a biobank, when in place, would increase human milk research as well as the assessment of medication concentrations in human milk.

This topic addresses the unmet need for a science and data driven approach to define the standards for generating data on medicines used during pregnancy and breastfeeding. It will result in better and more complete scientific information on drug effects on pregnancy and lactation and this will be used to inform treatment decisions and will increase the quality of care for women.

Need and opportunity for public-private collaborative research

Historically, the two sources of data about medicine use and effects in pregnancy and lactation have been academia and industry. The former focused more on diseases, the latter more on products. Both sources and approaches combined have essentially failed to fill the knowledge gap with relevant, timely and adequate information. Today there are three new and positive elements that can fundamentally change this current unsatisfactory status quo. Firstly, the expectations of the public and regulators about better information connecting risks associated with disease and medication are rising (Pregnancy and Lactation Labelling Rules (PLLR) in the USA, guidelines in EU are expected). Secondly, new data analytics and data sources, such as electronic health records, allow efficient access to and learning from much larger pregnant populations. And thirdly, there is a growing consensus among all stakeholders in healthcare that collaboration is the way forward when facing a challenge, like this one, that is too large or complex for any one player to address.

The magnitude and complexity of the challenges mentioned above are such that they can only be addressed by a strong and dedicated collaboration between stakeholders, such as academic groups, HCP associations, patient organisations, pharmaceutical companies and other commercial entities, regulators and governments. A public-private partnership involving a variety of stakeholders equipped with complementary areas of expertise and working together with a multi-disciplinary integrated approach provides a unique scientific opportunity in finding game-changing solutions to this huge unmet medical and societal need affecting millions of women world-wide every year. It is important to recognise that the private partners are not restricted to large commercial enterprises, such as drug manufacturers, but can include small and medium-sized enterprises (SMEs) that might provide targeted support or innovations, such as in the development of bioanalytical methods and analysis, web design, communication for patients, project management, and other services.

IMI2 JU provides the ideal neutral framework for such a sensitive matter to ensure maximum transparency and buy-in by all stakeholders, and is an established forum where different stakeholders' needs can be put forward. It also provides the framework to share data in a secure environment as well as for interactions with different health authorities, which is essential to guide and advise on recommendations and consensus papers envisaged by the project, as well as gain broad acceptance of methods and criteria for the predictive models generated as part of the proposed project.

Scope

The scope of this topic is to better inform the use of medicines during pregnancy and breastfeeding. To change current practices, the overall objective is to provide improved tools and methods to generate more valuable, reliable and timely information to HCPs and pregnant and lactating women to enhance optimal care.

More specifically the aims are as follows.

- Define more timely and efficient data collection and analytical approaches compared to pregnancy registries to better estimate disease background rates and treatment-related rates of adverse pregnancy and birth outcomes, including long-term outcomes in children. Improved information enables HCPs and pregnant patients to make informed decisions regarding medication use, and enhances care.

- Harmonise data elements collected during routine pharmacovigilance and enhance the collection of spontaneous reports (rate and the quality) of pregnancy cases. The standardised data elements will be also applicable for patients who get pregnant during clinical trials and for use in clinical practice.
- Develop and validate a new animal lactation model in a species that more closely parallels human lactation physiology. Develop a physiologically based pharmacodynamic model for translation between the medication concentration in animal and human breast milk. These data will provide more reliable information for the initial product label than the currently existing prediction based on the presence or absence of medication in human milk mainly using the rat model.
- Establish a non-commercial, Europe-wide breast milk biobank to be built on an already existing biobank setup with existing governmental support and an analytical centre for the analysis of drug concertation in milk. The biobank will be able to host clinical breast milk samples from healthy breastfeeding volunteers as well as patients taking prescription medications.
- Disseminate through various channels educational material for HCPs on the importance of reporting pregnancy cases through the pharmacovigilance system as well as why the follow up is needed. Educational information will be provided to patients on how to read and interpret relevant sections of the label, how to obtain relevant information from HCPs on treatment during pregnancy and breastfeeding, and why clinical research in this field is needed.

Expected key deliverables

The deliverables are as follows.

- **Moving beyond pregnancy registries to enhance our understanding of disease related pregnancy, birth/infant outcomes, medication use and safety in pregnancy**
  1) Comprehensive catalogue of existing data sources and approaches to capturing maternal medication exposure in pregnancy and subsequent pregnancy and birth outcomes, including long-term outcomes in children building on existing catalogues (like the ENCePP pregnancy special interests groups overview, the European Medicines Agency (EMA) funded catalogue and others) and including a quality assessment of data elements included.
  2) Publication of common data elements across data sources, proposing a common data model for consolidating information across multiple sources, regions and countries.
  3) Consensus on key data elements and analytical methods to allow the assessment of medication utilisation and safety in pregnancy to meet regulatory requirements and standards for inclusion in product labelling.
  4) Proposal for a governance structure to enable de-identified data sharing across participating data sources under the common data model (leveraging experience of relevant IMI projects).
  5) Publication of recommendations outlining data collection and analytical standards for conducting drug utilisation studies in pregnant women and conducting demonstration projects for established and newly-marketed products.
  6) Publication of recommendations outlining data collection and analytical standards for conducting medication safety studies in pregnancy using secondary data approaches (e.g. from claims data or similar large non-registry sources). Conducting demonstration projects for established and newly marketed products.
  7) Publication of recommendations on appropriate disease-based comparators (untreated and standard of care treated) with reference to demonstration projects and a range of diseases of varying prevalence using the literature and patient data from clinical trials, and primary data collected through pregnancy registries.
  8) Publication of overall recommendations on the application of different data approaches and analytical methods to study medicine safety in pregnancy, based on the knowledge gained through the project.

9) Publication of aligned recommendations on how to prepare for pregnancy and medication use during pregnancy for HCPs, patients and the general public.

It is expected that the deliverables will be regulatory accepted and be considered for implementation in regulatory practice.

- **Enhance safety data collection in pregnancy and the analysis of case reports**

1) Publication of standardised core data elements (when and what) for pregnancy exposure and follow-up reports, with a specific focus on adverse drug reaction reports, applicable globally across industry and clinical practice.
2) Publication of a standardised method for data analysis for aggregate reviews across individual cases from different sources (e.g. spontaneous and clinical studies).

It is expected that the deliverables will be regulatory accepted and be considered for implementation in regulatory practice.

- **Enhance data generation about lactation during medicine use and standardise approaches to human lactation studies**

1) Publication of a well characterised *in silico* and/or physiology-based pharmacokinetic (PBPK) model.
2) Translatable animal model to human.
3) Developed standards for conducting animal lactation studies.
4) Best practice document for conducting animal lactation studies.
5) Best practice document on how the results can be implemented when studying medication-related risks during lactation, and develop an algorithm when human lactation studies are indicated.
6) Best practice document on standards developed for conducting human lactation studies.
7) Aligned general recommendations on medication use during breastfeeding for HCPs, patients and the general public.

It is expected that the deliverables will be regulatory accepted and be considered for implementation in the regulatory practice.

- **Establish a non-commercial, Europe-wide breast milk biobank building on an already existing biobank setup with existing governmental support and an analytical centre for the analysis of drug concertation in milk**

1) A self-sustaining Europe-wide human milk biobank (building on an existing biobank with existing governmental support) for voluntary donor and study collected samples.
2) Europe-wide human milk sample analytical centre(s) able to comply with quality standards capable of measuring medication concentrations in milk.

- **Dissemination and education for HCPs, pregnant and breastfeeding patients and general public**

1) Partnering to provide online, centralised and verified information on medicines use during pregnancy and breastfeeding as well as risks associated with untreated diseases.
2) Network to deliver and maintain accurate and current information on good scientific and registry practice.
3) Guidelines addressing data privacy, balancing spontaneous comments affecting the benefit-risk profile, use of social media including electronic tools, and ethical questions related to cross-border communication on pregnancy and breastfeeding.
4) Education and training programmes enhancing HCPs', patients' and the general public's ability to understand / comprehend information provided in labels regarding medication use in pregnancy and breastfeeding.

5) Aligned general recommendations for medication use during pregnancy and breastfeeding for HCPs, patients and general public.

Expected impact

It is expected that the funded project will deliver: 1) broadly acceptable methodologies for generating event rates of adverse foetal and birth outcomes, including long-term outcomes in children, as well as rates for selected diseases; 2) promote alternatives to traditional pregnancy registries for timely generation of medication-related adverse foetal and birth outcomes, including long-term outcomes in children, to inform the labels; 3) an enhanced and harmonised way for dealing with pharmacovigilance pregnancy reports; 4) an advanced methodology on how compound milk transfer can be better characterised in animals to inform the initial label with more relevant data, and communication on standards for conducting human lactation studies; and 5) an EU centralised breast milk biobank and an analysis centre(s) to enable research on medication transfer into human milk.

According to United Nations statistics [3], there were around 230 million pregnancies worldwide in 2012. According to the Eurostat data [4] in 2014, 5.1 million children were born in the EU-28 and around 6 million in the US (Centers for Disease Control and Prevention, CDC). The proportion of pregnant women using medicines during pregnancy in developed countries varies in the published literature, the estimates being lowest in northern European countries (44% to 47%), around 50% in the US and highest in France (93%) and Germany (85%, [5]). When only conservatively taking the lowest reported proportion of medication use in pregnancy in Nordic counties of 40%, the population which will benefit from the outcomes of this private-public partnership would be around 2 million pregnant women in the EU alone every year.

The short-term impact of the funded project is that regulatory bodies will be able to review data generated by individual sponsors that use the same broadly acceptable methodologies, hence making review of the individual product datasets easier. The faster and more efficient way of producing data to assess medication-related adverse pregnancy outcomes will enable regulatory bodies to include enhanced information in the label, providing prescribers and patients with much needed information to guide treatment decisions for the benefit of women and children. Better characterisation and prediction of the excretion of medicines in breast milk will deliver more reliable data to inform the initial label, and the breast milk biobank and the analytical centre will allow for future milk research regarding drug transfer to human breast milk as well as milk research in general. The project is expected to deliver scientifically sound and validated information for implementation into the regulatory guidelines, which will lead to better information for HCPs and patients, and generally improve the health of our next generation. If the next generation is healthier, this should reduce the health burden on society and contribute to economic growth. In the absence of the information generated through the project, the diseased pregnant and breastfeeding population will continue to be underserved.
Finally, small and medium-sized enterprises (SMEs) can be of great benefit to IMI2 JU projects and can strengthen the competitiveness and industrial leadership of Europe. Solutions that are co-created with SMEs can provide an economic stimulus that can be enduring. Their involvement in the action might offer a complementary perspective to industry and the academia, and help deliver the long-term impact of the project.

Potential synergies with existing consortia

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

Example of relevant IMI and non-IMI projects include:

- **EUROCAT** (http://www.eurocat-network.eu) has existed for decades and includes most Member States in collecting pregnancy and congenital anomalies data. Collaboration with EUROCAT will eliminate any duplicative work on pregnancy registries, collaboration will be synergistic and will provide outcomes that will be more conclusive, timely and less costly for all stakeholders.

- **EUROMEDICAT** (http://euromedicat.eu/) is a European system for the evaluation of the safety of medication use in pregnancy in relation to the risk of congenital anomalies.
- **IMI EUPATI** project (https://www.eupati.eu/) focuses on education and training to increase the capacity and capability of patients to understand and contribute to medicines research and development and also improve the availability of objective, reliable, patient-friendly information for the public.
- **ISRHML** (International Society for Research in Human Milk and Lactation, https://isrhml.net) is a non-profit organisation dedicated to the promotion of excellence in research and the dissemination of research findings in the field of human milk and breastfeeding.
- **IMI PROTECT** project (http://www.imi-protect.eu). Although the project has ended, its legacy lives on in the knowledge and tools for monitoring the benefits and risks of medicines generated by the project.
- **GAIA** Consortium (http://gaia-consortium.net) aims to improve programmes of immunisation in pregnancy by harmonising maternal, pregnancy, foetal, and neonatal health outcome assessment.
- **European Network of Teratology Information Services (ENTIS)** (https://www.entis-org.eu) has the general objective to coordinate the activities of the different Teratology Information Services (TIS), and to collect and evaluate data in order to contribute to the primary prevention of birth defects and developmental disorders.
- IMI **eTOX** project (http://www.etoxproject.eu). The principles developed by the IMI eTOX project for sharing data, both public and private, through the combination of legal (intellectual property, IP), IT and honest broker concepts would be in principle applicable to the project selected under this topic.
- IMI **eTRANSAFE** project (http://www.etransafe.eu/) aims to improve safety in the drug development process by investigating the predictivity of preclinical data for human clinical effects.
- IMI **EHR4CR** project (http://www.ehr4cr.eu) provides adaptable, reusable and scalable solutions (tools and services) for reusing data from electronic health record systems offering large opportunities for the advancement of medical research, improvement of healthcare, and enhancement of patient safety.
- To help improve access to these patient-level data, the IMI European Medical Information Framework (**EMIF**) (http://www.emif.eu) project develops common technical and governance solutions and improves access and use of health data.
- Future IMI project resulting from the topic European Health Data Network (EHDN) IMI2 – Call 12 http://www.imi.europa.eu/sites/default/files/uploads/documents/IMI2Call12/IMI2_Call12_CallText.pdf.
- The US-based **Mommy's Milk Human Milk Research Biorepository** (https://mommysmilkresearch.org), the first human milk biobank that makes easier for scientists to perform research with standardised, sterile and indexed human breast milk samples.
- **BBMRI-ERIC** (http://www.bbmri-eric.eu/) operates a pan-European distributed research infrastructure of biobanks and biomolecular resources in order to facilitate access to resources.
- **IMEDS** (https://blogs.fda.gov/fdavoice/index.php/2017/01/introducing-imeds-a-public-private-resource-for-evidence-generation/) framework provides governance that allows private sector entities to gain access to the FDA Sentinel System's distributed data, making the scientific methods and tools available for entities outside of the FDA.
- **HBM4EU** (https://www.hbm4eu.eu/) aims to provide better evidence of the actual exposure of citizens to chemicals and the possible health effects to support policy making.
- **WHO milk surveys** (http://www.who.int/foodsafety/areas_work/chemical-risks/pops/en/index1.html) [6]
- **LifeCycle** (https://lifecycle-project.eu/about-lifecycle/project-summary) is conducting innovative research on the role of novel integrated markers of early-life stressors that influence health across the lifecycle using an open and long-term network of European cohorts that started during pregnancy or childhood.

Finally consideration should be given to the work currently ongoing at the European Medicines Agency for potential synergy/complementary in particular:

- **ENCePP** Special Interest Groups in Pregnancy has a key task to regularly review the of data sources for drug safety in pregnancy research (http://www.encepp.eu/structure/structure_specialInterestGroups.shtml).
- **EudraVigilance**, the system for managing and analysing information on suspected adverse reactions to medicines which have been authorised in the European Economic Area (http://www.ema.europa.eu/ema/index.jsp?curl=pages/regulation/general/general_content_000679.jsp)

Industry consortium

The industry consortium is composed of the following EFPIA partners:

- Novartis (lead)
- GSK
- Lilly
- BMS
- UCB
- Takeda
- AbbVie
- Sanofi
- J&J
- Merck KGaA
- Covance
- Teva
- NovoNordisk
- Ellegaard
- Pfizer

The industry consortium will bring extensive expertise in pharmacoepidemiology and pharmacovigilance, experience in collecting additional information on spontaneous pregnancy case reports, prospective data collection, statistical analysis of spontaneous reports, legal and ethics experts, extensive expertise in animal lactation studies, reproductive toxicology, physiologically based modelling and simulation expertise, expertise in bioanalytical methods, assay development, sample collection and handling expertise, sampling protocol development, legal, ethical, financial expertise, expertise in medical communications, patient affairs, drug labelling, experience in monitoring social media, experience of translating highly technical information into usable information for health care providers and patients, as well as experience with interacting with regulatory authorities.

More detailed industry consortium contribution is presented under the section ‘Suggested architecture of the full proposal’ (see below).

Indicative duration of the action

The duration of the action is 60 months.

Future Project Expansion

Potential applicants must be aware that the Innovative Medicines Initiative 2 (IMI2) Joint Undertaking may, if exceptionally needed, publish at a later stage another Call for proposals restricted to the consortium already

selected under this topic, in order to enhance and progress their results and achievements by extending their duration and funding. The consortium will be entitled to open to other beneficiaries as they see fit.

A restricted Call may be launched as part of a future IMI2 JU Annual Work Plan to carry out the correlation/analysis between animal reproductive toxicology data and human adverse pregnancy outcomes safety data. For instance, the standards developed by the IMI2 eTRANSAFE consortium on the correlation of general toxicology studies with adverse effects in humans may be used in the expansion project in case reproductive toxicity correlation would not be covered in the eTRANSAFE project.

Indicative budget

The indicative EFPIA in-kind contribution is EUR 13 500 000.

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

The financial contribution from IMI2 JU is a maximum of EUR 15 300 000.

Applicant consortium

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

- expertise in design and analysis of existing data sets, electronic health records, epidemiological design and analytics;
- teratology and birth defect experts, scientific societies working with malformations;
- experience in legal, ethics and privacy law across regions;
- expertise in gynaecology and neonatology, representatives of patient's advocacy groups and professional medical associations, breastfeeding advocacy groups;
- expertise in animal and human lactation physiology and physiologically based modelling and simulation, capabilities to develop animal lactation models as well as conducting animal lactation validation studies, ability to host a non-commercial breast milk biobank with already existing governmental support and analytical centre, expertise in assay development and adaptation of medication assays to milk;
- financial experts for advising on sustainability;
- experience in use of different communication channels to reach different interest groups and professional associations, ability to communicate and translate complex medical information into lay language, expertise in handling and dissemination of information through internet and social media, expertise in qualitative analysis of social media feedback, web design and website maintenance experience;
- regulatory expertise, experience dealing with regulatory agencies, professional expertise managing complex multi-stakeholder projects, professional project management capability and experience.

Applicants should consider how they will strengthen the competitiveness and industrial leadership of Europe by, for example, engaging suitable SMEs in the consortium. The expected applicant consortium contribution expertise is presented under the section Suggested architecture of the full proposal (see below).

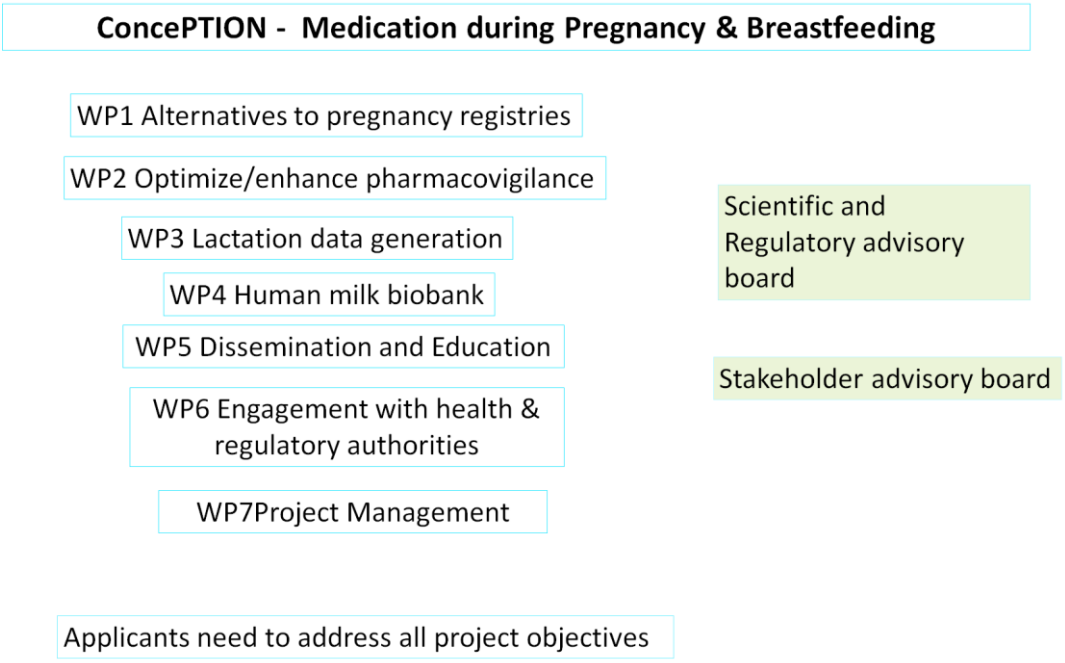
Suggested architecture of the full proposal

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

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

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

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



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

Sustainability

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

It is important to recognise that certain project deliverables are expected to endure beyond the timescale of the project, and particular emphasis should be put on ensuring the sustainability of these deliverables.

It is important that the following deliverables of the project are made sustainable after the completion of the project:

- human breast milk biobank;
- dissemination and education;
- website and social media communication infrastructure and content support.

The list of activities within the work packages below gives more detailed insight into the activities which are proposed in order to achieve the project objectives.

Work package 1 – Moving beyond pregnancy registries to enhance our understanding of disease-related pregnancy outcomes, medication use and safety of use during pregnancy

The goals of this work package will be to:

1. develop a comprehensive catalogue of existing data sources and approaches capturing maternal medication exposure in pregnancy and subsequent pregnancy outcomes building on existing catalogues and including a quality assessment of data elements included;

2. review and publish common data elements across identified data sources, building a proposal for a common data model for consolidating data across multiple data sources, regions and countries by building on existing knowledge;

3. propose and gain consensus on key data elements and analytical approaches to allow assessment of medication utilisation in pregnancy as well as medication safety data to meet regulatory requirements and standards for inclusion in product labelling;

4. propose a governance structure for de-identified data sharing across participating data sources under the proposed common data model;

5. conduct Strengths, Weaknesses, Opportunities, Threats (SWOT) analysis of approaches to collecting and analysing data for medication utilisation and medication safety in pregnant populations: primary data collection (e.g. product specific pregnancy registries) versus alternative approaches (secondary data collection); hybrid approaches and relevant analytical methods for each;

6. based on SWOT analysis, agree standard data collection and analytical methods and publish recommendations for conducting drug utilisation studies in women of childbearing potential;

7. based on SWOT analysis, agree standard data collection and analytical methods and publish recommendations for conducting medication safety studies in pregnancy using secondary data collection approaches and conduct demonstration projects (case studies) for established and newly marketed products;

8. develop and publish recommendations on appropriate disease-based comparators (untreated and standard of care treated) with reference to demonstration projects and a range of diseases of varying prevalence (e.g. examples for frequent (e.g. hyperemesis); common (e.g. depression); and rare (e.g. breast cancer or lupus));

9. publish recommendations on application of several types of data collection and analytical approaches to study medicine safety in pregnancy based on the knowledge gained through the project;

10. prepare aligned recommendations on how to prepare for pregnancy and medication use during pregnancy for HCPs, patients and general public.

Industry contribution

Expertise in pharmacoepidemiology; drug regulatory experience; legal and ethics expertise; experience conducting databases/registry studies. The industry consortium will share placebo clinical trials pregnancy cases and non-treated/standard-of-care-treated patients data from pregnancy registries (as far as available); experience and challenges as well as roadblocks encountered during primary data collection and use of alternative approaches as well as sharing of experience of what worked well.

Expected applicant consortium contribution

Experience in leveraging alternative data sources; experts in analysis of large data sets like electronic health records; expertise in epidemiological design and analytics, teratology experts; statisticians; data modelling; legal, ethics and privacy law experience; expertise in gynaecology and neonatology; patients' advocacy groups; representatives of professional medical associations; regulatory experience.

Work package 2 – Enhance safety data collection in pregnancy and the analysis of case reports

The goals of this work package will be to:

1. conduct cross-company inventory on handling pharmacovigilance (PV) pregnancy exposure and follow up case reports;

2. develop and standardise core data elements (when and what) for pregnancy and infant follow-up, with specific focus on adverse drug reaction reports. This core set should apply across industry and clinical practice and be applicable globally;

3. develop standardised method for data analysis for aggregate reviews across individual cases from different sources (e.g. spontaneous reports and clinical studies);

4. publish standards for handling PV pregnancy case reports in peer review journal(s);

5. prepare aligned information on importance of reporting pregnancy cases though PV system for HCPs in order to stimulate data reporting and create a safe environment for reporting pregnancy cases with compounds without appropriate safety information in labels.

Industry contribution

Extensive expertise in pharmacoepidemiology and pharmacovigilance; experience in collecting additional information on spontaneous pregnancy case reports; prospective follow up data collection; statistical analysis of spontaneous reports; legal, and ethics experts. The industry consortium will also share pharmacovigilance pregnancy data under the Honest Broker concept to better inform the feasibility of the outcome.

Expected applicant consortium contribution

Expertise in design and analysis of existing data sets; teratology and birth defect experts; legal, ethics and privacy law experience; expertise in gynaecology and neonatology; representatives of patient's advocacy groups and professional medical associations.

Work package 3 – Enhance data generation about lactation during medicine use and standardise approaches to human lactation studies

The goals of this work package will be to:

1. review the literature and evaluate the existing animal lactation models for comparison to human physiology and milk composition and/or develop animal lactation model (included but not limited the learnings from the FDA lactation workshop 2016);

2. conduct experiments to validate the selected or new animal lactation model – respecting the Reduce, Refine, Replace (3Rs) principle;

3. develop a well-characterised in silico and/or PBPK model(s) based on physicochemical properties of drugs and preclinical data to better predict human milk transfer of drugs and to derive concentrations

of drugs in milk, permitting a more accurate prediction of Relative Infant Dose (RID); where justified, also using available human lactation data;

4. validate that the developed model(s) can predict the known human lactation data;

5. define factors that should be considered when calculating neonatal exposure e.g. gastro-intestinal maturation;

6. develop and publish standards and best practices in peer reviewed journals;

7. develop a guidance document when generating human data might still be justified;

8. propose consensus on minimal amount of any breastfeeding data to meet regulatory requirements for inclusion in the label;

9. publish the guidance document in peer reviewed journal(s) on best practice for conducting human lactation studies;

10. prepare aligned recommendations on medication use during breastfeeding for HCPs, patients and general public.

Industry contribution

Expertise in animal lactation studies; general and reproductive toxicology; physiologically based modelling and simulation expertise; expertise in bioanalytical methods; capabilities to develop animal lactation models and conduct animal lactation studies. The industry will also share relevant preclinical and/or clinical lactation data under the Honest broker concept.

Expected applicant consortium contribution

Expertise in animal and human lactation physiology and physiologically based modelling and simulation; capabilities of conducting animal lactation studies and/or developing animal lactation models; expertise in bioanalytical methods; expertise in gynaecology and neonatology; patients advocacy groups; representatives of professional medical associations; breastfeeding advocacy groups and experts in legal, ethics and privacy laws.

Work package 4 – Establish a non-commercial, Europe-wide breast milk biobank building on an already existing biobank setup with existing governmental support and an analytical centre for analysis of drug concertation in milk

The goals of this work package will be to:

1. investigate the legal basis of establishing a Europe-wide human milk biobank from healthy breastfeeding women and women taking medicines;

2. utilise and expand on existing tissue biobank structure/collaboration;

3. identify the population and stakeholders for breast milk collection;

4. develop human milk sample collection and handling methodology guidance (sampling, storage shipment, health data needed from breastfeeding women) and model informed consent form (ICF);

5. suggest a biobank Scientific Board structure to review and approve requests for milk samples for research purposes;

6. develop analytical methodology for human breast milk adaptable for drug product analysis;

7. propose the potential financing structure to ensure sustainability, in addition to the existing governmental support;

8. generate charters for collaboration between industry and academia based on the Good Pharmacovigilance Practice (GVP) Module 8 and Council for International Organizations of Medical Sciences (CIOMS).

Industry contribution

Expertise in bioanalytical methods and assay development; analytical capabilities, sample collection handling and transportation expertise; biological material sampling protocol development; legal, ethical, financial expertise.

Expected applicant consortium contribution

Ability to host a non-commercial human milk biobank, building on existing biobank structure with already existing and sustainable governmental support; milk samples analytical capabilities preferably in the same country, able to set up and analyse medications in human milk and capable of complying with all the necessary analytical quality standards. Expertise in assay development and adaptation of medication assays to milk; experts in regulatory environment related to collection and transport of biological material; experts in ethics; experts for advising on sustainable financial support.

Work Package 5 – Dissemination and education for HCPs, pregnant and breastfeeding patients and general public

The goals of this work package will be:

1. inventory of possible communication means to HCPs and patients using different professional and patient associations and selection of the most appropriate ones for the project purpose;

2. inventory of existing social media communication channels, including electronic tools to HCPs, pregnant and breastfeeding women and general public;

3. analysis of information searched and feedback on the quantity, utility and clarity by HCPs, pregnant lactating women, breastfeeding women and general public;

4. partnering to provide online information packages on points to consider when preparing for pregnancy and medication use during pregnancy and breastfeeding to HCPs, patients and general public, including generation of communication guidelines and customising information packages for different target audiences;

5. engage HCPs, pregnant and breastfeeding women and general public to set expectations and stimulate pregnancy reporting through PV system and participation in research;

6. communication tools for internal and external communication.

Industry contribution

Expertise in medical communications, patient affairs, drug labelling; experience in monitoring social media; experience of translating highly technical information into usable information for HCPs and patients.

Expected applicant consortium contribution

Experience in use of different communication channels to reach different interest groups and professional associations; ability to communicate and translate complex medical information into lay language; expertise in handling and dissemination of information through social media; expertise in training and continuous medical education; expertise in the area of legal and ethical questions across regions; expertise in psychology and

sociocultural aspects; expertise in qualitative and quantitative analysis of social media feedback and machine learning; hosting and webmaster capacities; patient organisations; regulatory expertise; scientific societies working with malformations; and experts for advising on sustainable financial support.

Work Package 6 – Engagement with health and regulatory authorities

The goals of this work package will be:

1. interact with work package leaders on the need for health authorities (HA) input;
2. assist work package leaders in using correct regulatory language;
3. organise HA interaction webinars, teleconferences and/or meetings;
4. share the regulatory interaction knowledge gained through the process with other work packages;
5. regulatory support to milk biobank establishment.

Industry contribution

Expertise in drug labelling and interaction with the regulatory authorities as well as experience in use of real world evidence generated data.

Expected applicant consortium contribution

Experience in regulatory communication; experience in using real world data for scientific purposes as well as labelling expertise.

Work package 7 – Project management

The goals of this work package will be:

1. participate in joint governance structure;
2. implementation and management of the project, setting-up regular meetings and interaction between sub-groups and teams, coordination of the work efforts, preparing meeting minutes;
3. manage collaboration with external stakeholders and synergies with other related projects;
4. communication and information dissemination within the project;
5. coordinate activities across all work packages, track deliverables, ensure deliverables are achieved according to plan, on time and budget;
6. ensure meetings and interactions between work packages and consortium governance bodies to coordinate and follow-up on work effort.

Industry contribution

Support in work package project management within the company leading this work package.

Expected applicant consortium contribution

The applicant consortium should bring proven record of professional project management capabilities; expertise and experience in managing complex and long lasting projects, such as this one.

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Topic 10 : Improving the preclinical prediction of adverse effects of pharmaceuticals on the nervous system

Topic details

Topic code	IMI2-2017-13-10
Action type	Research and Innovation Action (RIA)
Submission and evaluation process	2 stages

Specific challenges to be addressed

Neurotoxicity (used in the context of this document as “any adverse effect on the central nervous system (CNS) or peripheral nervous system (PNS)”) is poorly predicted by preclinical studies performed on pharmaceuticals during research and development (R&D) process. As a consequence, adverse effects on nervous system are not uncommon during clinical development and post-marketing. This lack of predictability might have two types of consequences:

- for human volunteers/patients, this can lead to a risk of adverse effects during clinical trials or even after marketing;
- for the pharmaceutical industry, this can lead to substantial neurotoxicity-related attrition rates, generally at late stages (clinical phase 2 or 3); according to sources, the figures for this type of attrition are variable, but typically in the range of 5-25%.

Therefore, a better preclinical prediction of adverse effects on nervous system would benefit to human volunteers/patients (by safer drugs) and pharmaceutical industry (by increased productivity).

There are various reasons for poor prediction/detection of adverse effects on the nervous system at preclinical stages. The challenges relate to the following considerations:

- the brain is the most complex organ in the body, comprising numerous cell types and functions;
- full knowledge is lacking about the chain of events (molecular, subcellular, cellular, tissue, organ-level) and their timing leading to neurotoxicity;
- no robust *in silico* tool is available to establish (quantitative) structure-toxicity relationship;
- no *in vitro* cellular/tissue system is widely accepted/validated for screening;
- there is a lack of predictive *in silico* simulation or *in vitro* test system to predict blood-brain-barrier penetration or exposure of target tissues;
- traditional neurotoxicity testing in animal models is generally limited to symptoms (with lack of specificity), electroencephalography (EEG) (with inconsistent interpretation) and histopathological investigations (with lack of sensitivity) that are late endpoints, detecting rather severe effects;
- sensitivity and translatability to the human condition of each animal species are not clearly established;
- no soluble biomarkers of neurotoxicity are formally validated nor identified yet.

Under the wide umbrella of “neurotoxicity”, at least three types of effects are even more challenging in terms of preclinical prediction and translation to human situation:

- seizures/convulsions, thus further epileptogenic events/epilepsy;
- psychological/psychiatric changes: memory impairment, mood disorders, suicidality;

- peripheral sensory neuropathies (this may include optic/auditory nerve).

Recent scientific and technical developments in neurosciences have been made that raise hope for the future, especially in the field of *in vitro* [1] and *in vivo* [2] models, translational biomarkers [3]and risk assessment [4] e.g. : *in silico* modelling of the blood-brain-barrier, use of (embryonic or human induced pluripotent) stem cells, single-cell analysis, 3D models and organs-on-chips, measurement of micro RNAs or post-transcriptional (e.g. RNA editing) biomarkers.

Consequently, there is a clear need for a project to deliver on: (i) increased knowledge on mechanisms of neurotoxicity (e.g. establish adverse outcome pathway for each type of neurotoxicity); (ii) better understanding of factors that favour neurotoxicity (pharmacological targets and pathways, physico-chemical properties, pharmacokinetics); (iii) implementing new-found knowledge to improve the current preclinical toolbox, through a combination of high throughput, predictive *in silico*, *in vitro* and *in vivo* models, including safety biomarkers, where appropriate (iiii) combine these tools in an integrated risk assessment approach for better decision-points throughout R&D process, and better protection of human volunteers and patients.

Need and opportunity for public-private collaborative research

Research for improved predictive preclinical tools necessitates (i) expansion of knowledge regarding physiopathology of neurotoxicity: individual genetic/epigenetic susceptibility, role of blood-brain-barrier (under normal and pathological situations), non-neuronal and neuronal interplay, protection factors, receptors and neurotransmitters involved, novel safety biomarkers, functional changes as precursor of lesions, thresholds for effects (ii) establishing, testing and validating new/improved *in silico*, *in vitro* and *in vivo* models.

It is clear that such a wide range of complex questions can only be addressed via a public-private multi-stakeholder consortium, bringing their diverse expertise in the following fields:

- *in silico* modelling;
- cellular culture (especially stem cells and organs-on-chips);
- 'omics, systems biology/toxicology;
- imaging;
- single-cell analysis;
- electrophysiology;
- animal models (especially behavioural investigations);
- predictive biomarkers.

These areas of expertise could be addressed by the following type of public-private stakeholders:

- research organizations and universities would better contribute in the field of fundamental research, biomarkers identification, data management (especially when data in the precompetitive field will be shared) and project management/logistical/administrative support;
- small- and medium-sized enterprises (SMEs) would better contribute in the field of *in silico* and *in vitro* tools;
- pharmaceutical industry would better contribute in the field of *in vivo* studies, drug testing, historical data, reference and test compound supply;
- patient associations could join as partners, especially in the field of therapeutics indications where adverse effects on nervous system could be viewed as more frequent (psychiatry, oncology, neurology, immunology) as well as providing access to disease-specific donor material for *in-vitro* (primarily induced pluripotent stem cells ((iPSC)-related) work.

Lastly, a joint public-private project engaging key stakeholders' expertise could provide clinicians and regulatory bodies with robust data for possible evolutions in the regulatory field. As appropriate, these potential partners will be asked to contribute, e.g. through participation to the advisory board.

Scope

The objective of the project is to improve the preclinical predictivity of adverse effects of pharmaceuticals on the central and peripheral nervous systems through increasing our knowledge on mechanisms of neurotoxicity and improving the experimental toolbox. The results would be an integrated prediction/evaluation approach that would include a combination of *in silico*, *in vitro* and *in vivo* models, including safety biomarkers (for peripheral neuropathies). This toolbox would increase the preclinical prediction of adverse effects of drugs throughout all aspects: identification of hazards, characterisation of mechanisms of toxicity, prediction of clinical consequences and possible follow-up in trials with safety biomarkers, and integrated risk-assessment approach for proper decision-making process.

The adverse effects in the following areas of test articles should be considered by the applicants.

- Any pharmaceuticals under research and development stages. Not only small molecules are in the scope of the present topic, since biotherapeutics can lead to adverse effects on nervous system, directly or indirectly:
    - in a recent search performed by Abbvie on Food and Drug Administration (FDA)/ European Medicines Agency (EMA) labels in 2015, about 40% of biological products (vaccines, recombinant proteins, monoclonal antibodies) had mention of two or more neuropsychiatric adverse events in approval documentation/label. In the field of oncology, antibody drug conjugates can also lead to similar safety risks than small molecules.
- Drugs that pass blood-brain-barrier (BBB) but also drugs that do not overtly pass the BBB, since (i) passage can be very low but still have consequences, especially if accumulation or microglia-based responses occurs in the brain (ii) passage can be increased under various pathological conditions (infection, inflammation, neurodegenerative diseases).
- Whether the indication is CNS or PNS or not: off-target pharmacology can often be responsible for adverse effects on nervous effect independently of the desired on-target action, as shown in a recent publication: out of 70 targets that have established linked with adverse effects, 50 (71%) relate to nervous system [5]. As an example, modulation of inflammation can lead to mood disorders, as illustrated by interferon effects.
- Biomarkers of peripheral neuropathies.

Should not be considered by the applicants:

- vaccines, because of specific development plans and regulatory requirements;
- recreational drugs;
- drug abuse liability assessment (DALA), since it is already addressed by international guidelines;
- biomarkers of central neurotoxicity, which might be covered in another IMI2 JU project and in an Health and Environmental Sciences Institute (ILSI-HESI) initiative on translational biomarkers of neurotoxicity (NeuTox).

Expected key deliverables

With the aim of improving the predictivity of the preclinical toolbox for assessment of neurotoxicity, the following deliverables are expected.

- **Deliverable 1:** new/improved *in silico* tools that allow establishing (quantitative) structure-activity relationship ((Q)SAR), "activity" meaning here neurotoxic effects.

These tools would permit identifying “neurotoxicophores” and, thus, help companies to build chemical structures devoid of neurotoxic liabilities, as early stages of research (selection of best (pre-)candidates or chemical series).

In silico models of cell networks will also be considered, to allow studying the effects of a target activation on the total network of a cell leading to an increased understanding and prediction of the regulation of other targets or pathways that might be involved in the adverse effects.

- **Deliverable 2:** better understanding, modelling and simulation of the blood-brain barrier passage (e.g. using human induced pluripotent stem (hiPS)-cell based models) or exposure of target organs (brain, nerves), including for biologics and novel drugs used for focal disease interception.
- **Deliverable 3a:** at least one new/improved *in vitro* tool for screening (pre-)candidate drugs for each type of toxicity tackled in this topic, especially using stem cell systems and organs-on-chips.
- **Deliverable 3b:** an improved blood-brain barrier model (e.g. using hiPS combined with microelectrode assay applied to neurons from the same clone, in order to provide correlation between permeation and neurotoxicity).
- **Deliverable 4:** at least one tool for elucidating mechanism of toxicity (target, pathway), especially using stem cell systems and organs-on-chips.
- **Deliverable 5:** new improved *in vivo* animal models, with more specific investigational endpoints, allowing focused, non-invasive detection and longitudinal follow-up of the central and peripheral nervous toxicities during drug development.

  Ultimately, this might help change regulatory requirement for entry into phase 1 (safety pharmacology assessment of central nervous system, as described in International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (ICH)-Safety guideline)
- **Deliverable 6:** better characterisation of the most relevant animal species for each type of toxicity.
- **Deliverable 7:** Identification and validation of safety biomarkers predictive of peripheral nervous system toxicity, translatable from pre-clinical testing (*in vitro* and animal) to humans. Non-invasive biomarkers that do not necessitate cerebrospinal fluid sampling will be preferred (e.g. from saliva).
- **Deliverable 8:** integration of the deliverables in a pharmacokinetic/pharmacodynamic/toxicodynamic (PK/PD/TD) platform with appropriate quantitative and qualitative decision points for risk assessment.
- **Deliverable 9:** Improved toolbox, especially for early, non-animal testing which would fulfil the 3Rs objective (reduction/refinement/replacement). In particular, automation strategies for high-throughput testing will be considered.

Expected impact

At the level of R&D, regulatory, clinical and healthcare practice the impact would be (i) safer drugs for human volunteers/patients (ii) shortened development timelines, through reduced attrition, reduced testing, and shortened development plans:

- improved subjects/patients safety during clinical trials and after marketing authorisation;
- reduced attrition, especially at late stages of R&D (during clinical trials), for safety reasons related to neurotoxic effects;
- reduced post-marketing events necessitating labelling changes;
- reduced post-marketing events resulting in drug withdrawal;
- greater R&D productivity/shorter timelines;
- lower development costs.

In terms of ethics/animal welfare/3Rs, innovation and integration of new knowledge the impact would be:

- replacement: whenever possible animal models would be replaced by *in silico/in vitro* models, provided they have at least the same level of prediction;
- refinement and reduction: relevant biomarkers or any other appropriate endpoints would enrich current *in vivo* animal experiment and help (i) earlier detection and longitudinal follow-up of toxicities before inappropriate animal suffering (ii) decision-making process.

In terms of improving European citizens' health and wellbeing (volunteers and patients), the impact would be:

- lower risk of neurotoxic events during clinical trials, whatever the clinical indication (relating to nervous system or not);
- improved monitoring and risk minimisation procedures during clinical trials;
- drugs with a better risk/benefit ratio.

In terms of industrial competitiveness the applicants should indicate how they will strengthen the competitiveness and industrial leadership of Europe by, for example, engaging suitable SMEs.

Potential synergies with existing consortia

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

The following completed, ongoing or forthcoming initiatives (the list is not exhaustive) have been identified and could be considered by the applicants.

- **FP7-HEALTH project PREDICT-IV** (http://cordis.europa.eu/result/rcn/148238_en.html)

  The objective was profiling the toxicity of new drugs: a non-animal-based approach integrating toxicodynamics and biokinetics. Two neuronal primary models were analysed and the work package on convulsions/seizures could be relevant.

- **FP7-HEALTH project NEUROBID** (neuroscience on barrier in development) (http://cordis.europa.eu/result/rcn/57029_en.html)

  One axis of research is to understand the involvement of normal and disturbed BBB function in normal and abnormal brain development therefore the entire project could be relevant.

- **FP7-HEALTH project ERA-NET NEURON** (http://www.neuron-eranet.eu/)

  The project supports basic, clinical and translational research in the diverse fields of disease-related neuroscience, in order to pave the way for new or improved routes for diagnosis and therapy and therefore could be of relevance.

- **HESI Committee on Translational Biomarkers of Neurotoxicity** (NeuTox) http://hesiglobal.org/committee-on-translational-biomarkers-of-neurotoxicity/

  The objective is to identify biomarkers for improving the prediction of neurotoxicity therefore the work packages 1 (*in vitro* prediction of electrical abnormalities) and 2 (peripheral neuropathies) could be relevant.

- **NC3Rs CrackIt challenge 17 Neuratect** (https://www.crackit.org.uk/challenge-17-neuratect)

  The objective is to generate physiologically relevant human stem cell-based model(s) to identify neurotoxicity and seizure liability (neuronal viability/functional impairment) *in vitro* and the work package on convulsions/seizures could be relevant.

- **IQ consortium on Preclinical Suicidality** (https://iqconsortium.org/initiatives/working-groups/preclinical-suicidality/):

The goal is to provide an expert assessment of the science of preclinical evaluation of treatment-emergent suicidality therefore the work package on psychological changes could be relevant.

- **IQ consortium on MicroPhysiological Systems** (co-initiative with National Institute of Health (NIH)) https://iqconsortium.org/initiatives/working-groups/microphysiological-systems-iq-nih-collaboration/

  The work packages on convulsions/seizures and peripheral neuropathies could be relevant.

Please note that during the project implementation phase the applicants should also consider other potential knowledge generated by the forthcoming projects under IMI2 JU in the area of blood brain barrier, biomarkers of central nervous system toxicology, integrative knowledge management approaches, as well as the ongoing IMI/IMI2 JU initiatives:

- **TransQST** – for the use of quantitative systems toxicology(http://www.imi.europa.eu/projects-results/project-factsheets/transqst);
- **EBiSC** (European Bank for induced pluripotent Stem Cells) (http://www.imi.europa.eu/projects-results/project-factsheets/ebisc).

Industry consortium

The industry consortium is composed of the following EFPIA partners:

- Sanofi (lead)
- Novartis
- MSD
- AstraZeneca
- Fujifilm (CDI)
- Pfizer
- UCB

The industrial participants will contribute through their expertise, data and resources, and materials especially (i) direct full-time employees (FTE), (ii) data and data valorisation (iii) financial contribution (iv) material/reagent/consumable contribution.

Expected contribution from industry consortium:

- perform retrospective search into preclinical and pharmacovigilance databases to assess the incidence and nature of effects, and evaluate the predictability of current preclinical toolbox;
- provide necessary number and diversity of drugs for validation of models;
- provide retrospective data on reference or proprietary drugs that have showed neurotoxicity issues, preclinically or clinically;
- run prospective assays/studies with drugs under development;
- data and samples management:
  - expertise in samples and data management (including e.g. automated analysis of EEG),
  - database information and assessment,
  - biostatistics/programming,
  - provide data and samples from pre-clinical and clinical fields,
  - it is worth noting that competitive data would be shared to processes that will ensure protection of confidentiality/anonymity;
- coordination and communication:

- project management support with project design and day-to-day operation,
- legal expertise scientific background to support regular review of deliverables regarding quality and operational ability.

Applicants should also note the detailed description of the industry contribution under “Suggested architecture of the full proposal”.

Indicative duration of the action

The indicative duration of the action is 36 months.

Indicative budget

The indicative EFPIA in-kind contribution is EUR 4 331 000.

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

The financial contribution from IMI2 JU is a maximum of EUR 5 331 000.

Applicant consortium

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

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

- systems toxicology/biology for the identification of mechanism of peripheral and central neurotoxicities;
- conception of *in silico* tools for the identification of neurotoxicophores and (quantitative) structure-toxicity relationship;
- building of dedicated modelling and simulation models of blood-brain-barrier passage supported by appropriate tools and databases;
- *in vitro* screening of neurotoxicity using human stem cell-derived systems;
- organ-on-chip: brain, nerve;
- animal neurotoxicity and neurobehavioral testing (including EEG, connection between cardiovascular function and convulsions…);
- safety biomarkers identification and bioanalysis; process for qualification;
- data management, data mining, biostatistics; integration of tools, applications and data in a single platform;
- project management.

Expected contribution from applicant consortium

The academic partners, research organisations and universities could potentially bring:

- scientific input to better understand parameters that lower the seizure threshold, and the transformation of seizure into convulsions;

- identify pharmacological targets and biological pathways involved in the neurotoxic effects (on-target and off-target);
- identify physicochemical parameters or any other feature that correlate (and allow prediction) of blood-brain-barrier passage; it was found that only 40% of the blood-brain barrier permeation kinetics was explainable by physicochemical parameters. Other parameters such as protein binding, lysosomal storage in CNS cells etc. contribute to the clinical relevance and free fraction of the compound, and thus, should be considered;
- propose biomarkers of peripheral neuropathies.

The contribution from SMEs can be of great benefit to IMI2 JU projects and, *inter alia* strengthen the competitiveness and industrial leadership of Europe. Their involvement might offer a complementary perspective to industry and the academia, and help deliver the long-term impact of the project. For these reasons, applicants should consider engaging SMEs throughout the proposal, if relevant. Under this topic, the contribution of SMEs could be beneficial for the following activities:

- propose innovative assays/techniques for detection of neurotoxic effects: stem cells, organs-on-chip, subcellular systems (synaptosomes, mitochondria), micro-electrode array (MEA) technology, blood-brain barrier assay (optionally: combined with MEA, in order to correlate brain passage and neurotoxicity), continuous video monitoring in rodents and non-rodents, live-brain imaging of neuronal activity;
- run prospective assays/studies with reference drugs;
- data and samples management:
  - data management: data access and data cleaning expertise,
  - biostatistics/programming: data analysis and programming expertise;
- coordination and communication:
  - 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.
  - ensuring the communication and dissemination with and/or media expertise and in developing tools.

The patient organisations and clinicians could potentially:

- identify indications, pathologies, treatments for which neurotoxicity is a more critical issue.

The regulatory bodies could:

- give feedback on tools, strategies, biomarkers that are proposed and their possible implementation in official guidelines (e.g. through qualification advice for biomarkers).

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 contributions and expertise provided below.

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

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

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

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

Work package 1 – Convulsions and seizures

The goal of the work package "Novel methods and assays to predict seizures, convulsions and epileptogenesis" is to better detect pro-convulsant and convulsant compounds, using a combination of in silico (modelling, QSAR), *in vitro* and *in vivo* methods, including:

- ***in silico* models**

To develop and evaluate suitable *in silico* models to detect the potential for convulsions/seizures in drug development candidates. Such models may include systems biology/toxicology tools based on analysis of targets and pathways involved in such changes, as well as (Q)SAR systems that could help identifying toxicophores, based on physicochemical properties or peculiar exposure patterns in brain structures.

- ***in vitro* / *ex vivo* models**

To build on existing models and define their context of use for early *in vitro / ex vivo* detection of pro-convulsant/convulsant compounds. The aims of this work package are (1) to improve the performance of *in vitro* models, while moving away from and minimising the use of animal models with alternatives such as human iPSC-based neuronal tissue cells, and (2) to define the context of use for various models; 3D models (spheroids, hydrogel models, hollow-fiber models, models based on BioVascs) employing multiple cell types may be more physiological relevant, but this comes at a cost with material, time, resources, etc. Models will be specifically challenged to define their relative utility over each other and to provide guidance on when they should be employed. Effort will be directed toward creating robust, reproducible, and translatable models with clear benefits in these areas over existing current, commonplace models. Efforts can include 2D and 3D models using multiple relevant cell types, i.e. gamma-aminobutyric acid (GABA)ergic and glutamatergic neurons, astrocytes, microglia, etc. Blood-brain barrier models using hiPS cells from epileptic patients should also be considered, in order to increase the relevance to the human-disease situation.

  - Applicant consortium: will contribute expertise in *in vitro* neuronal network (2D and 3D), electrophysiology, and systems analytical skills and expertise, which may contribute to the development of seizurogenic and pro-convulsant assays for detecting CNS-based electrical perturbations. Collaborators will develop appropriate assays and then evaluate their performance using a variety of drugs with known pre-clinical and clinical effects to assess sensitivity, specificity, and utility of the *in vitro* assay(s).

  - Industry consortium: will contribute expertise in *in vitro* assay development, cellular material, and retrospective data on reference or proprietary drugs that have shown convulsant / electrical neurotoxicities in preclinical and clinical settings.

- ***in vivo* models**

The aims of this work package are to improve the performance and the specificity of *in vivo* models, especially through the refinement of endpoints in safety pharmacology and toxicology studies.

  - Applicant consortium: will contribute expertise in animal models of seizure and/or EEG signal processing which may contribute to the development of relevant tools for detecting convulsions/seizures (e.g. automated home cage detection of convulsive behaviours in rodents using continuous video monitoring, EEG signal processing, live-brain imaging of neuronal activity, etc.). This could be extended to non-rodents. Collaborators will develop appropriate tools/assays/endpoints and then evaluate their fit-for-purpose performance using a variety of drugs to assess sensitivity and specificity. "Non-classical" animal species could be considered (e.g. zebrafish).

  - Industry consortium: will contribute expertise in the conduct and analyses of *in vivo* animal studies, and retrospective data on reference or proprietary drugs that have shown seizurogenic/convulsant

issues, both preclinically and clinically. Classical animal species for toxicology (rodent/non-rodent) will be considered as part of safety pharmacology/toxicology study packages as well as biological samples and/or raw data to partners for analysis.

Work package 2 – Psychological/psychiatric changes

The goal of this work package is to establish *in silico* (modelling, QSAR) and *in vitro* techniques and animal *in vivo* models for a better detection/prediction of psychological/psychiatric changes that may occur in clinical trials, including memory and cognition disorders, mood disorders (including suicide ideation and behaviour).

- ***In silico* and *in vitro* models**

To develop and evaluate suitable *in silico* models and *in vitro* assays to detect the potential for psychological/psychiatric changes in drug development candidates. *In silico* approaches may include systems biology/toxicology tools to identify targets and pathways that are involved in psychiatric/psychological changes. *In vitro* assays may include iPSC-derived neurons to identify early molecular signals that may predict development of such adverse effects. Blood-brain barrier models using hiPS cells from psychiatric (e.g. schizophrenic) patients should also be considered, in order to increase the relevance to the human-disease situation.

- Applicant consortium: will contribute expertise in *in silico* neurotoxicity expertise or *in vitro* neuronal cell assay development expertise which may contribute to the development of relevant tools for detecting psychological/psychiatric disorders. Collaborators will develop appropriate tools/assays and then evaluate their performance using a variety of drug to assess sensitivity and specificity.

- Industry consortium: will contribute expertise in *in vitro* assay development, and retrospective data on reference or proprietary drugs that have shown psychological/psychiatric issues, both preclinically and clinically.

- ***In vivo* models**

To develop and evaluate preclinical models that model features and traits of memory, cognition or mood disorders (including suicidal ideation and behaviour). Perform proof of concept in nonclinical models with known drugs. Evaluate their ability to translate across nonclinical species with potential to predict psychological/psychiatric changes in humans.

- Applicant consortium: will contribute expertise in animal models of memory, cognition and mood (i.e. rat, dog, and non-human primates). Studies or endpoints will need to be established, if not commercially available, and have some level of fit for purpose validation conducted.

- Industry consortium: will contribute expertise in animal studies, especially neurobehavioral endpoints, in rats, dogs and non-human primates.

Work package 3 – Peripheral neuropathies

The goal of this work package is establish *in vitro* methods to detect peripheral neuropathy risk in drug development candidates, and to identify and evaluate safety biomarkers to monitor peripheral neuropathy *in vivo* for nonclinical use and translation to the clinical.

- ***In vitro* models**

To develop and evaluate suitable *in vitro* assays to detect the potential for peripheral neuropathy in drug development candidates. Such models may include iPSC-derived sensory neurons with peripheral neuron character that can be used to screen drugs and detect toxicity or identify early molecular signals that may predict development of peripheral neuropathy.

- Applicant consortium: will contribute expertise in *in vitro* neuronal cell assay development expertise which may contribute to the development of relevant assays for detecting peripheral neuropathies.

Collaborators will develop appropriate assays and then evaluate their performance using a variety of drug to assess sensitivity and specificity of the *in vitro* assay.

- Industry consortium: will contribute expertise in *in vitro* assay development, and retrospective data on reference or proprietary drugs that have shown peripheral neurotoxicity issues, both preclinically or clinically.

- ***In vivo* models and safety biomarkers**

Candidate biomarkers should have some level of evaluation in preclinical models that demonstrates their association with peripheral neuronal cell degeneration/necrosis. Depending on the nature of that evaluation, promising biomarkers may need additional proof of concept in nonclinical models with known induced peripheral neuronal injury. In addition, candidate biomarkers should be selected for their ability to translate across preclinical species with potential to monitor peripheral neuropathy in humans. Lastly, preparatory work for qualification advice will be sought through interaction with regulatory bodies.

- Applicant consortium: will contribute expertise in (preferably non-invasive) biomarker candidate evaluation, or experience with particular biomarkers for peripheral neuropathy which may contribute to the assessment of sample sets. Biomarker candidates will be evaluated in rat, dog, and non-human primates. Assays will need to be established, if not commercially available, and have some level of fit-for-purpose validation conducted. In addition to the assessment of sensitivity, specificity will also be determined for biomarker candidates.

- Industry consortium: will contribute expertise in assay development and analytical fit-for-purpose validation for clinical and/or non-clinical use. Industry participants will also provide samples (e.g. plasma, serum, cerebral spinal fluid) from rat, dog, and non-human primate studies with toxicants known to induce peripheral neuropathy. These study samples will be anchored with histopathological assessment, and should include nerve morphometry on semi-thin sections, neuro muscular junction (NMJ) imaging on whole mount and lumbrical muscle sections, functional endpoints (e.g. nerve conduction), as well as surrogate markers of small fiber damage such as intra-epidermal fiber density (IEFD) and conreal nerve fiber density (CNFD).

Work package 4 – Data and samples management

The goal of this work package is to ensure and develop appropriate processes for data and samples management with respect to guidelines and laws, including:

- identification and standardisation of diverse data sources: preclinical and clinical data coming from industry and public;
- develop plans for data (Data Management Plan, Data Sharing Plan) as well as for samples (Samples Management Plan and Samples sharing plan);
- integration of data into an appropriate support (ideally and integrated platform connected to database with appropriate granularity, so that it is usable by experts from various fields: biologists, toxicologists, chemists, modellers…).

Work package 5 – Consortium coordination and communication

The goal of this work package is the overall project coordination and communication, including:

- define work expectations of different work streams, deliverables, dates and activities and review progress regarding adherence to budget, timelines and quality;
- ensure legal and contractual management;
- ensure the set-up of joint governance structure;
- ensure appropriate communication/dissemination within the consortium and with the external scientific community and the public;

- ensure interaction with regulatory bodies, as necessary (e.g. for qualification process/advice of biomarkers);
- develop and manage communication via web portal and other social media tools with a repository of key document;
- quality assessment of documents;
- ensure that key cross-functional partners are engaged;
- define project interdependencies, stakeholders and risks;
- ensure ethics management.

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Topic 11 : Translational Safety Biomarker Pipeline (TransBioLine): Enabling development and implementation of novel safety biomarkers in clinical trials and diagnosis of disease

Topic details

Topic code	IMI2-2017-13-11
Action type	Research and Innovation Action (RIA)
Submission and evaluation process	2 stages

Specific challenges to be addressed

Early and reliable detection and monitoring of adverse events is essential for improving of patient safety, reducing late attrition of drug candidates, and enhancing understanding of toxic mechanisms. In particular, biomarkers that provide insights into mechanisms of tissue injury have the potential to revolutionise drug development as well as diagnosis of diseases. Therefore, the development of innovative, non-invasive biomarkers of tissue injury is of great interest to drug developers, regulators and the broader scientific community. Recent progress in biomarker development including the previous **SAFE-T** (http://www.imi-safe-t.eu/) that identified several promising biomarker approaches as well as the latest scientific advances in analysis of circulating microRNA provide excellent opportunities for biomarker research. Furthermore, the recent progress in regulatory science of biomarker qualification achieved by the Critical Path Institute and the Foundation for the National Institutes of Health (FNIH) provides a blueprint for conduct of formal qualification of emerging biomarkers via an innovative translational paradigm that relies on tissue injury caused by diseases and only limited clinical and non-clinical studies for assessment of biomarker performance. This approach optimises resource use and accelerates biomarker development.

Need and opportunity for public-private collaborative research

New biomarker approaches are needed to enable development of new therapeutic modalities and improve diagnosis of diseases. The development and qualification of biomarkers is a costly and time-consuming process. It requires developing new innovative scientific approaches and analytical technologies as well access to appropriate human populations for biomarker qualification and assay validation, and other large-scale cross-institutional efforts. Therefore only large international scientific collaborative projects that include industry, academic researchers and regulators can be successful. For instance, the previous IMI project SAFE-T in the EU and the Critical Path Institute's Predictive Safety Testing Consortium (PSTC) yielded several promising biomarker candidates that are under review by the regulatory agencies in Europe and USA. The PSTC approach that relies on human disease as approximation of chemical injury for evaluation of biomarker performance significantly reduced need for conduct of costly clinical trials. Furthermore, recent progress in circulating microRNA analysis and next generation sequencing has opened new avenues for development of mechanistic biomarkers and precision medicine. However, more research and robust datasets are necessary to qualify new biomarker approaches by regulatory agencies and to enable their implementation in clinical trials and diagnosis of disease. The proposed TransBioLine topic with funding from the Innovative Medicine Initiative 2 Joint Undertaking (IMI2) provides a unique platform for leading experts from industry, academia and regulators to design and execute the research needed for development and

implementation of novel safety biomarkers in clinical trials and clinical practice. Furthermore, the topic provides an opportunity for partnering with Small- and Medium-sized Enterprises (SMEs), including diagnostic companies to enable the development of robust assays that are compliant with regulatory requirements for use in clinical laboratories thereby decreasing the time needed for transferring biomarker discoveries from bench to bedside.

Scope

The TransBioLine project will focus on development of biomarkers of injury for liver, kidney, pancreas, vasculature, central nervous system (CNS) and the development of non-invasive liquid biopsies. The project will have four strategic goals:

1. **Develop data sets enabling the implementation of emerging safety biomarkers in clinical trials and/or diagnosis of disease:**

   The consortium will be expected to develop robust learning and confirmatory datasets that will support appropriate "contexts of use" for the emerging biomarkers. The resulting datasets will form the foundation for formal biomarker qualification by the European Medicine Agency (EMA), Food and Drug Administration (FDA) and Pharmaceutical and Medical Devices Agency (PMDA).

2. **Develop non-invasive mechanistic biomarkers of tissue damage called "liquid biopsy" that will have a potential to revolutionise drug development and diagnosis of disease:**

   The consortium will be expected to exploit the circulating cell free serum microRNAs for development of non-invasive tissue- and mechanism- specific diagnostic signatures/biomarkers. This effort will exploit state of the art technologies such as next generation sequencing in conjunction with systems biology approaches to gain insights into mechanisms of toxicity and disease, and risk assessment.

3. **Develop standardised assays and technologies for detection of biomarkers and data interpretation:**

   For biomarkers pursued by the TransBioLine project, the consortium is expected to develop robust assays compliant with regulatory requirements for implementation in clinical laboratories for clinical trials and clinical practice including appropriate level of validation as well bioinformatics, sample and data management tools. This will provide opportunities for partnership with diagnostic companies and SMEs.

4. **Achieve regulatory acceptance for biomarkers:**

   The consortium is expected to submit regulatory documentation that supports formal biomarker qualification with EMA, FDA and PMDA, and manage biomarker qualification process. Furthermore, the consortium will establish and maintain collaborative relationship with regulatory agencies (EMA, FDA, PMDA) organise workshops and meetings.

Research approach: The biomarker development for each target organ will concentrate on a specific context of use with limited number of already identified emerging biomarker candidates. The main focus of each individual target organ work package will be on the development of learning and confirmatory datasets that are essential for supporting regulatory qualification and implementation of emerging biomarkers in clinical trials and diagnosis of disease. To enable application of biomarkers developed under TransBioLine project to routine clinical laboratories, assay development, statistics and an expertise in regulatory science will be essential for achieving regulatory acceptance by EMA, FDA and PMDA. It is expected that these functions will be fully integrated with target organ work packages (WPs) to achieve maximum flexibility and impact. The appropriate resources for these activities in addition to project management will be allocated from individual target organ WPs budgets.
Since disease approximates chemical injury, TransBioLine project will rely mainly on samples from subjects with tissue injury caused by appropriately selected diseases. Only targeted clinical and non-clinical studies with drug/chemical induced organ injury will be used as supportive evidence for assessment of biomarker performance. The clinical sample set for analysis of biomarker performance will predominantly consist of

remaining samples from clinical studies and remaining samples from subjects with appropriate disease phenotypes collected during medically indicated examinations. This approach limits effects of storage on biomarker stability, optimises resource use and accelerates biomarker development. It requires close collaboration with clinics and clinical researchers, especially to enable accurate diagnosis and anchoring endpoint evaluations, adherence to inclusion/exclusion criteria, ensuring correct patient consent, and correct sample collection. The state of the art next generation sequencing and system biology with a proven track record in identifying miR signatures in human subjects and normalization approach to enable consistent quantification will be necessary for development of miR-based liquid biopsies. A partnership with SMEs and diagnostic companies will be required for development of robust assays that will enable application of the studied biomarkers in routine clinical laboratories. Since the qualification of biomarkers by regulatory agencies is essential for implementation of biomarkers in clinical trials and diagnosis of disease, strong expertise in regulatory science and established relations with Health Authorities by the applicant consortium will be required. To achieve the TransBioLine goals appropriate sample and data management systems, statistical and bioinformatics tools and strategy will need to be integrated throughout TransBioLine WPs.

Expected key deliverables

The TransBioLine primary objective is the development of datasets enabling formal biomarker qualification and biomarker implementation in clinical trials and/or diagnosis of disease. The key deliverables will consist of:

- Biomarker qualification submissions to EMA, FDA and PMDA for specific high priority context of uses defined by TransBioLine for liver, kidney, vascular, pancreas and Central Nervous system (CNS);
- Datasets that will enable the acceptance of emerging safety biomarkers by regulatory agencies for specific drug development programs under individual Investigational New Drug (INDs) even before the biomarkers are qualified as drug development tools;
- A new paradigm-changing non-invasive biomarker approach for interrogating mechanisms of toxicity and disease via miR-based “liquid biopsies”. This will include (a) detailed characterization of cell free serum miR-nome in healthy subjects and in subjects with diseases and (b) system biology platform applicable for addressing safety in clinical trials that will enable investigators to de-convolute observed miRs signatures to biological pathways in specific tissues;
- Robust biomarker assays compliant with regulatory requirements defined as “Research Use Only” (RUO), “Laboratory Developed Tests” (LDT) and/or “In Vitro Diagnostics” (IVD) as appropriate. The long term goal is to have assays broadly available in clinical laboratories world-wide;
- To facilitate the biomarker qualification by regulatory agencies, the TransBioLine will organise an annual biomarker qualification workshop with EMA, FDA and PMDA. It is expected that the workshop will have a significant impact on harmonization of biomarker qualification across regions, maintain organisational timelines, and facilitate global collaboration and global reach;
- To promote application of new biomarkers in clinical practice, publications in high quality peer-reviewed journals as well as presentations at various national and international meetings is expected.

Expected impact

The biomarkers developed during TransBioLine are expected to accelerate drug development by providing innovative drug development tools and also significantly improve diagnosis of disease by enabling non-invasive interrogation of disease mechanisms. The availability of qualified biomarkers as drug development tools will have a broad positive impact on patient safety in clinical trials as well. The TransBioLine will open new markets by introducing new commercially available diagnostic products and services by diagnostic companies and SMEs. This will strengthen the competiveness and industrial leadership of Europe. TransBioLine will enable the development of new innovative biomarker approaches derived from genomics

applicable as non-invasive “liquid biopsies” providing tools for precision diagnosis of mechanisms of toxicity or disease at the molecular level. Although the formal qualification of biomarkers as drug development tools by regulatory agencies is the ultimate deliverable, the biomarker data produced by TransBioLine will enable the acceptance of biomarkers by regulatory agencies under individual INDs even before the biomarkers are fully qualified.

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

Potential synergies with existing Consortia

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

Biomarker development and biomarker qualification by regulatory agencies is a recognised unmet medical need. In fact, IMI JU funded its first translational biomarker project **SAFE-T** (http://www.imi-safe-t.eu/) that yielded several biomarker candidates. Among current and future IMI consortia, **TransQST** (http://transqst.org) and TransBioLine WP liquid biopsies have an excellent opportunity to bridge in non-clinical and clinical systems toxicological approaches and realise synergies in the development of systems toxicology tools. Furthermore, several international organizations and consortia in the EU and US are actively working in this space. Most notable are the Predictive Safety Testing Consortium of Critical Path Institute in Tucson, AZ, and Biomarker Consortium of FNIH in Washington, DC, that have made significant progress in biomarker qualification for selected liver and kidney biomarkers and are collaborating with the FDA on developing a regulatory framework for biomarker qualification and more recently, biomarker assay validation. In addition, several technical committees at the Health and Environmental Science Institute in Washington, DC, are working on evaluating analytical technologies and developing best practices. Recently, Japan’s NIHS initiated a large collaborative project in liver biomarkers. Therefore, developing collaborative partnerships with these organizations when applicable throughout duration of TransBioLine project will be important. In contrast to the previous and current biomarker development efforts, the proposed TransBioLine will focus on enabling implementation of emerging biomarkers in clinical trials via qualification by EMA, FDA and PMDA and integrating the progress in regulatory science with the development of unique state-of-the-art mechanism-based biomarkers and clinical assays.

Industry consortium

The industry consortium is composed of the following EFPIA companies:

- Pfizer (lead)
- Novartis
- Sanofi
- J&J
- MSD
- Roche (Genentech)
- Eli Lily

The industry consortium will provide expertise and assets in developing large data sets derived from subjects in clinical trials, access to healthy volunteer populations, and data generation for full characterization of

biomarker performance. The use of samples from prospective clinical trials run by the member companies will bring significant savings to the project notwithstanding limiting the need for unnecessary clinical investigations. Because of the global nature of clinical studies run by the industry consortium, the TransBioLine project will be able to evaluate performance of biomarkers in a variety of populations. Furthermore, the member companies will contribute targeted non-clinical studies, targeted clinical studies, and clinical and non-clinical datasets. Additionally, the industry consortium will contribute expertise in assay validation and a regulatory perspective, expertise in conduct of clinical investigations, experience with biomarker use in preclinical and clinical studies, study data that will support development of novel imaging agents, and managing processes and samples among various laboratories participating in the project. The expected industry consortium contributions will also include biomarker assays when applicable, and expertise and scientific leadership.

Indicative duration of the action

The indicative duration of the action is 60 months.

Indicative budget

The indicative EFPIA in-kind contribution is EUR 14 000 000.

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

The financial contribution from IMI2 JU is a maximum of EUR 14 000 000.

Applicant consortium

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

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

- Expertise with a demonstrated track record via publications in peer-reviewed journals in pertinent biomarker assay technologies needed to conduct TransBioLine research;
- Demonstrated analytical capabilities such as immunoassays, Liquid Chromatography-Mass Spectrometry (LC-MS), next generation sequencing etc;
- Expertise and capabilities in sample management systems, patient compliance statements, data management including database systems that comply with managing clinical data, state-of-the-art statistical and bioinformatics tools including tools for next generation sequencing data;
- For the liquid biopsy approach, extensive expertise and proven track record in peer-reviewed literature in analysis and normalisation of circulating miRs in human subjects using next generation sequencing and state-of-the-art bioinformatics with demonstrated expertise in generating signatures of circulating miRs for specific disease phenotypes and/or toxicities in human subjects;
- To achieve regulatory acceptance of biomarkers by regulatory agencies, extensive expertise in regulatory science with a proven track record in biomarker qualifications including preparation of regulatory submissions to regulatory agencies (EMA and/or FDA), and interactions with regulatory agencies world-wide;
- Ability to prospectively enrol the remaining samples from subjects with disease phenotypes defined by individual WPs to assess the biomarker performance pertinent to the TransBioLine research;
- Capability to identify, retain and manage remaining serum, Cerebrospinal fluid (CSF) and urine samples from healthy subjects and subjects with relevant disease phenotypes, including a broad range of aetiologies and/or treated with a variety of therapeutic modalities as specified by individual WPs;

- Capability to obtain appropriate patient consent forms, access detailed medical records data for all subjects/samples, and adjudicate the data;
- Ability to potentially recruit subjects treated with appropriate drugs for conduct of limited prospective studies;
- Proven expertise in efficiently managing and maintaining time lines for large, multi-institutional scientific projects and proven expertise in project management.

In addition to academic groups, relevant Small- and Medium-sized Enterprises (SMEs) with relevant proved expertise are encouraged to participate in the applicant consortium. SMEs can be of great benefit to IMI projects and, inter-alia strengthen the competitiveness and industrial leadership of Europe. Their involvement might offer a complementary perspective to industry and the academia, and strengthen the long-term impact of the project. For these reasons, applicants should consider engaging SMEs throughout the proposal. Under this topic, the contribution of SMEs would be considered especially beneficial in areas that include bioanalytical expertise for diagnostic assay development, bioinformatic analysis, data mining, and data and sample management.

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

Suggested architecture of the full proposal

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

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

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

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

Work package 1 – Biomarkers of Kidney injury

Context of Use:

A panel of qualified urinary kidney safety biomarkers may be used together with sCr and BUN in subjects with normal kidney function or in patients with some pre-existing kidney disease (and not just normal healthy volunteers**)** as a more sensitive and/or earlier biomarker to monitor for both glomerular as well as renal tubular safety in clinical trials. These biomarkers will be used when such injury has been demonstrated to be monitorable by the biomarkers in animal studies of similar duration with the same test agent. Applying the biomarkers in initial single and multiple ascending dose clinical studies, or in continuous dosing clinical studies

could enable or restrict initial dose level selection and planned dose escalations, or drive decisions to interrupt or continue dosing.

Specific Goals:

1. **Progressive Qualification of Translational Tubular Injury Biomarkers in Patients with Mild Pre-existing Kidney Dysfunction:**

   Given that diabetes and hypertension are the two known top causes of chronic kidney disease (CKD) most worthy of being considered for advancing confidence in the use of tubular injury biomarkers in patients (and not just normal healthy volunteers (NHVs)), cohorts of such hypertensive and diabetic patients could be targeted for testing, such that comparable thresholds and significant fold-change from baseline performance results are seen as comparative data to reference against data on translational kidney safety biomarkers that have already been collected for NHVs and patients with normal renal function [1]. There is also anticipated value in comparing these tubular injury urine protein biomarkers that are currently being clinically qualified by IMI and FNIH/PSTC with the FDA and EMA. A goal is to complete and expand the context of use for protein urine biomarkers undergoing qualification presently and also to open the door for potentially exploring additional promising new biomarkers that may appear in blood and to derive an optimal panel for detection of drug-induced tubular injury in humans and that may not therefore also require urine collections.

   Expected Applicant consortium contribution:

   This is an example of contributions that will be required to support the proposed project. Since cisplatin has been used to benchmark thresholds and biomarker performance results in subjects with normal renal function (IMI-SAFE-T, FNIH Kidney Team) the proposal is made to assess cisplatin next in patients with hypertension and diabetes. Lung cancer patients often have a long history of smoking preceded by chronic obstructive pulmonary disease requiring corticosteroid treatment. Such patients frequently have concomitant hypertension and/or steroid induced diabetes. Lung cancer patients presenting with CKD1 or CKD2, who are eligible for cisplatin therapy could provide urine and plasma samples following treatment with cisplatin. Assessment of biomarker baseline values, variability, and responses associated with standard of care cisplatin treatment would be compared to the data generated from similarly treated subjects with normal renal function that have already been assessed [1]. Primary hypotheses should focus on statistical power for subgroups of patients based upon hypertension and diabetes and that secondary hypotheses could include investigation as to whether higher BMI (> 30 kg/1.73 m^2) and eGFR < 60 ml/min may pose challenges to interpretation of biomarker responsiveness and utility.

   Industry contribution:

   (a) Pre-diabetic/diabetic, (b) hypertensive, (c) obese, (d) metabolic syndrome patients familiar to clinical research units already well benchmarked for their CKD1/ 2 status would be a valuable source for benchmarking baseline variability for this kidney safety biomarker research, (e) Additionally, monitoring of these injury biomarkers following initiation of therapy with new oral hypoglycemic Sodium Glucose Co-Transporter (SGLT2) inhibitors [2], which appear to be potential intervention agents against CKD progression, is also proposed for consideration to generate data to investigate a hypothesised baseline-elevated set of biomarkers, and post-intervention return of these biomarkers toward normal to support expanding the evidence for such biomarkers for qualification in a weight-of-evidence strategy.

2. **Advancing the Qualification of Translational Glomerular Injury Biomarkers:**

   There is also value in advancing the qualification of novel early biomarkers of drug-induced glomerular injury to support drug development. Translational urinary protein biomarkers of drug induced glomerular injury have shown promising results (e.g., albumin, cystatin C, clusterin) in rodent studies [3][4], and it is hypothesised that small RNAs that may be measured in blood for the liquid biopsy project to strengthen the urinary protein biomarker data.

   Expected Applicant consortium contribution:

Several types of studies are suggested for consideration within a proposal from academia to generate the appropriate clinical samples to support drug-induced glomerular injury biomarker qualification [5]. At least two of the following studies or other more appropriate suggestions are welcomed: (a) Renal adverse effects following mechanistic target of rapamycin (mTOR) inhibitor therapy of breast cancer are often preceded by hyperlipidemia, and may present with asymptomatic proteinuria increase to full nephrotic syndrome (15%), elevated serum creatinine (44%), or acute renal failure. (b) Renal adverse effects following anti-VEGF therapies may present as hypertension, asymptomatic proteinuria (23%), and, rarely, nephrotic syndrome or acute renal failure, suggesting a rich source of patient urine samples for detecting biomarkers of the earliest signals of glomerular change. (c) Elevation of serum creatinine is not uncommon in patients with hypercalcemia of malignancy or osteolytic bone metastases (breast cancer, multiple myeloma) receiving I.V. bisphosphonate therapy [6]. (d) Pre-eclampsia manifesting as proteinuria and hypertension can be observed in 5-10% of pregnancies. Such patients considered as high risk for such, would be expected to be readily detected by standard of care pre-natal blood pressure monitoring and urinalyses.

Industry contribution:

Industry member conduct of Non-human primate studies using the same agents as for those selected clinical glomerular injury studies, and using the same biomarker assays as for the human biomarkers to generate translational biomarker performance data supported by histopathologic analyses, would be highly supportive of a favorable regulatory qualification decision and to inform the optimised scheduling of clinical sampling.

Work package 2 – Biomarkers of liver injury

Context of Use:

1. **Risk of progression:**

Biomarker X or a panel of liver safety biomarkers anticipate a risk of progression from hepatocellular injury to severe Drug-Induced Liver Injury (DILI) in patients in whom an initial DILI diagnosis has been established based on elevations of the standard marker Alanine transaminase (ALT) alone or in combination with Total Bilirubin (TBIL). Applying the biomarkers to compounds with an identified hepatotoxic risk may allow prospective monitoring and identification of a DILI signal. Biomarker levels will be correlated with subsequent clinical outcome to allow prognostic assessment of patients with idiosyncratic DILI. This may drive decisions to interrupt or continue dosing or to implement intensified monitoring according to risk stratification (progression – recovery – adaptation).

Specific goal: As evidenced by the EMA and FDA Letters of Support [7], biomarkers suitable for this context of use include macrophage colony stimulating factor receptor 1 (MCSFR1), total and hyperacetylated high mobility group box 1 (HMGB1), osteopontin, and total and caspase cleaved keratin 18 (K18 and ccK18).

2. **Mechanism of DILI:**

Biomarker X may be incorporated into clinical trials to assess the mechanism of hepatotoxicity induced by (i) compounds, which cause DILI in patients, and (ii) compounds that have shown hepatotoxicity in preclinical species or in in vitro investigations. The focus will be placed on any of the following mechanisms of intrinsic DILI: (a) mitochondrial toxicity, (b) reactive metabolite generation/ oxidative and endoplasmic reticulum (ER) stress, (c) inhibition of transporters such as the bile salt export pump (BSEP). For inhibition of BSEP, serum bile acid profiles should be measured and correlated with parameters such as drug dosage, clinical outcome, pattern of DILI and preclinical findings.

3. **Causality assessment:**

Biomarker X or an *in vitro* assay will assess causality of a suspected DILI causing drug in patients in whom a diagnosis of DILI has been established. There is no test available which allows causality assignment of a suspect drug to the onset of DILI in patients.

Specific goal:

To carry out a proof-of-concept study with a test system that assesses the causality of a suspected drug in the context of acute DILI. In patients in whom a diagnosis of DILI has been established based on elevations of the standard markers ALT, AST, ALP and bilirubin, potentially hepatotoxic medications administered to the patient should be assessed individually in a personalised medicine approach in material derived from the patient. With this *in vitro* assay, causality of DILI with a suspected drug can be confirmed; conversely, a drug that is falsely suspected to cause or contribute to DILI, can be de-risked if the result is negative.

Expected Applicant consortium contribution:

- Applicant consortium will provide samples from patients with acute severe DILI identified in clinical routine, and – if available – disease controls (e.g. non-alcoholic steatohepatitis (NASH), fibrosis, autoimmune hepatitis). In addition, the academic consortium will prospectively enrol samples from subjects with disease phenotypes that resemble chemical injury for evaluation of biomarker performance. Academic involvement includes protocol design and writing and close collaboration with the work package lead. This will allow the generation of a sufficiently large clinical sample set;
- Academic labs and/or SMEs should provide biomarker assays according to the context of use statements above. Assay providers should aim to achieve GLP/GCP standard validation during the course of the consortium. Academic partners are expected to have a track record in DILI research, and extensive experience with DILI samples is mandatory for any biomarker or assay provider.

Industry contribution:

Clinical samples from patients who developed hepatotoxicity in phase I-III, clinical samples from placebo-treated patients and – if available – disease controls (ongoing trials for liver disease, e.g. NASH, fibrosis, autoimmune hepatitis); additional clinical or preclinical data (including biomarker data) for compounds for which biomarker measurements are performed in human samples, FTE support (e.g. for work package leads, statistical support, medical writing and data management support).

Work package 3 – Biomarkers of pancreas injury

Context of use:

A panel of serological pancreas safety biomarkers may be used together with enzymatic Amylase and Lipase in normal healthy volunteers in early phase clinical trials as a more sensitive and specific biomarker to monitor pancreas acinar cell degeneration/necrosis. These biomarkers will be used when such injury has been demonstrated to be monitorable in animal studies of similar duration with the same test agent.

Specific goals:

1. **Delivery of robust validated assays suitable for use in human plasma or serum:**

   Prioritised pancreatic safety biomarkers shall consist of candidate proteins showing at least preliminary evidence of an association with acinar damage and pancreas-specific microRNAs (e.g. 216a-5p/216b-5p) [8][9]. It will be critical that reliable and sustainable assays are available to support clinical testing. Non-clinical versions of these assays are also desired.

   Expected Applicant consortium contribution:

   Academic collaborators with assay development expertise may contribute to the development and/or validation of relevant assays. Specific expertise with miRNA quantification is desired to help address important platform-related issues (e.g. qPCR) and supply suitable clinical assays.

   Industry contribution:

   Industry members will be expected to contribute platform expertise in assay development and analytical fit-for-purpose validation for clinical and/or non-clinical use. Industry participants will also provide

important experience that will guide the transfer of assays to reliable commercial vendors or contract research organisations including SMEs to provide sample analysis to the consortium.

2. **Biomarker baseline determination:**

Characterization of biomarker variability, and effects of potential confounding variables (e.g. gender, age, body mass, etc.) present in populations representative of volunteers in early phase clinical trials. In order to confidently interpret significant changes in the biomarkers, relevant reference ranges in cohorts representative of these volunteers must be generated.

Expected Applicant consortium contribution:

Academic collaborators with access to unique cohorts of volunteers (e.g. various ethnicity, gender, age) may contribute to the assessment of sample sets, as well as and analytical support for the generation of these baseline assessments.

Industry contribution:

It is envisioned that industry members will provide a majority of the samples required from normal healthy volunteers with relevant metadata for sample analysis.

3. **Provide proof of concept that the biomarkers can detect pancreatic acinar cell degeneration/necrosis:**

Provide determination of biomarker variability in diseases known to be associated with such injury (e.g. pancreatitis, pancreas transplant, pancreatic cancer, alcoholism). Establishing a greater understanding of candidate biomarkers with respect to disease onset, progression, or resolution is an important component of the work package that would support extending the context of use to later phase clinical trials.

Expected Applicant consortium contribution:

Disease samples from medical centers/institutions. In cases of patients presenting diseases such as pancreatitis, longitudinal sampling and the recording of disease outcomes are essential. In addition, it is expected that standard of care tests (e.g. amylase, lipase, c-reactive protein (CRP)) will be collected. Academic partners are encouraged to investigate the candidate markers using clinical samples to probe the influence of co-morbidities and factors that affect biomarker clearance from circulation.

Industry contribution:

Analytical and experimental support using non-clinical species to support reverse translation of qualified clinical markers of pancreatic acinar injury.

Work package 4 – Biomarkers of vascular injury

Context of Use:

The panel of vascular injury safety biomarkers used in conjunction with the totality of preclinical and clinical information in healthy volunteers to monitor for vascular safety in early clinical trials to help inform dose level selection, dose escalation, or decision on continuation of dosing.

Approaches and biomarkers of interest:

1. A panel of biomarkers will be selected from candidate biomarkers identified by SAFE-T and PSTC [10]. The panel includes endothelial, smooth muscle and inflammation markers. The performance of the panel will be assessed in subjects with existing vascular diseases to evaluate the ability of a biomarker panel to detect vascular injury specifically and the role of the presence of co-morbidities. Although immunoassay technology may be supplementary, the applicant consortium should explore LC-MS analytical technology for biomarker assay development. LC-MS technology is important for smooth muscle biomarker assay development, cross-species translation and low sample volume requirements. The applicant consortium should build on progress of LC-MS assay development and validation made by the PSTC consortium.

Sufficient level of assay validation should be completed prior to generating biomarker results beyond the learning phase.

2. The second objective is to explore a more accurate means to measure active vascular injury against which to qualify the emerging biomarker panel in humans, as currently we lack a standard, non-invasive, specific biomarker for vascular injury [11]. This may include optical coherence tomography (OCT), fluorescein angiography (FA), ultra-widefield FA, and fundus photographic evaluations in the ophthalmic vascular disease manifestations or imaging with contrast or bio labelled agents, such as PET tracers, in systemic vascular disease manifestations.

Specific goals:

1. **Select subset of vascular injury biomarkers in learning phase and use to advance the clinical qualification in patients with systemic vascular conditions to detect acute vascular injury:**

   The patient populations should include systemic vasculitides especially focused on active and untreated patients with non-infectious cutaneous leukocytoclastic vasculitis, anti-neutrophil cytoplasmic antibody-associated (ANCA+) vasculitis (PR3-ANCA+ and MPO-ANCA+ subtypes of granulomatosis with polyangitis [GPA] and microscopic polyangitis [MPA], giant cell arteritis and Takayasu's Disease, as well as balloon angioplasty (acute mechanical injury) as previously evaluated [9][10][12]. For those patients with ocular vascular injury manifestations of these vasculitides, this presents the opportunity to also measure the biomarkers against ocular vascular injury endpoints (see goal 4). The learning phase should be focused on a subset of these patients to provide a robust data set by which to select a subset of the panel of biomarkers to be used in the confirmatory phase, as well as the subsequent goals.

   Industry contribution:

   Expertise in data analysis and analytical support.

   Expected Applicant consortium contribution:

   Expertise in clinical vasculitides and/or dermatology research and access to unique cohorts of patients with the clinical vasculitides of interest, conducting observational cohort studies, clinical outcomes research, or pilot clinical projects that may contribute to the confirmatory data set. The clinical vasculitides academic collaborators should also have expertise or ready access to expertise in ophthalmology, as outlined in goal 4. Additionally, collaborators can provide analytical support.

2. **Augment healthy volunteer reference range data:**

   The panel of biomarkers selected in the learning phase of goal 1 will be assessed in subjects without detectable disease across age, gender and ethnic cohorts and with lower body mass index.

   Industry contribution:

   Industry members will provide samples from normal healthy volunteers with relevant metadata for sample analysis.

   Expected Applicant consortium contribution:

   Academic collaborators with access to unique cohorts of normal healthy volunteers (e.g. ethnic background, pediatric, or elderly samples) may contribute to the assessment of sample sets, as well as provide analytical support for the generation of these baseline assessments.

3. **Complement the clinical qualification of vascular injury biomarkers with imaging tools:**

   Generate an exploratory data set to provide foundation for future confirmatory studies to enable clinical qualification of non-invasive imaging tools to support diagnosis and monitoring of clinical vasculitis, preferably PR3-ANCA+ vasculitis in combination with a panel of circulating vascular injury biomarkers

(from goal 1). Imaging tools will include biomarkers already with compelling performance, such as MMP3, or that provide increased specificity to the vascular bed, such as an endothelial-specific tracer.

Expected Applicant consortium contribution:

Expertise in clinical vasculitides research and access to unique cohorts of patients with clinical vasculitis, preferably PR3-ANCA+ vasculitis, conducting observational cohort studies, clinical outcomes research, or clinical projects that may contribute to the exploratory data set. Academic collaborators would provide analytical support and clinical imaging capabilities to support a small scale exploratory clinical study to assess the diagnostic performance/value of a novel imaging agent of PR3-ANCA-associated vasculitis in combination with circulating vascular injury biomarkers. Additionally, academic collaborators with radiochemistry or medicinal/synthetic organic chemistry resources could also support the development and evaluation of potential radionuclides for vascular imaging.

Industry contribution:

Industry members will provide the exploratory MMP3-based imaging tools or support academic imaging candidates with a foundational preclinical qualification package demonstrating proof of concept in animal models and preclinical studies required to enable the clinical use of the imaging tool.

4. **Augment the clinical qualification of vascular injury biomarkers in patients with acute non-infectious ocular diseases with vascular injury** [13]**:**

This exploratory data set may enable an easier, more sensitive monitoring scheme and a patient population without underlying chronic vascular injury to support the clinical regulatory qualification outlined in goal #1. The biomarker levels in circulation may be compared to those in the ocular fluid. Diseases of interest include those with pathophysiology of vasculitis and microangiopathy with vascular leak that are not of infectious origin, including wet acute macular degeneration (AMD) diabetic retinopathy (DR) and various forms of acute uveitis (iritis, iridocyclitis, choroiditis, retinal vasculitis, chorioretinitis, anterior/intermediate/posterior uveitis, and drug-induced/idiopathic/immune-mediated uveitis). Clinical evaluation can be augmented by preclinical evaluation especially for drug-induced uveitis.

Expected Applicant consortium contribution:

Expertise in ophthalmology diagnostics (to include ultra-widefield FA, FA, OCT and fundus photographic evaluations), research, and access to unique cohorts of patients with the clinical ocular diseases of interest, conducting observational cohort studies, clinical outcomes research, or clinical projects that may contribute to the exploratory data set. Additionally, collaborators can provide analytical support.

Industry contribution:

Expertise in data analysis and analytical support and samples from ophthalmology programs.

Work package 5 – Biomarkers of CNS injury

Context of use:

The recent tragedy associated with the BIAL clinical trials in France underscores the critical need for more sensitive preclinical biomarkers predictive of neurotoxicity that can be readily translated to clinical trials. Thus, the goal of the current proposal is to evaluate the potential of non-invasive, fluid-based biomarkers (in human blood, urine, and/or CSF) to predict clinical neurotoxicity risk.

Approach and biomarkers of interest:

Several fluid-based biomarkers have been studied in attempts to improve diagnosis and prognosis of CNS injury and disease. Some of these biomarkers have also been studied in preclinical models of neurotoxicity. However, none have been qualified for a specific clinical use. One of the reasons for this is that these candidate biomarkers have not been thoroughly evaluated in large enough numbers of human samples in order to fully characterise background variation or the influence of age, sex, body weight, ethnicity,

comorbidities, drug treatments, etc. The successful applicant consortium will have: 1) demonstrated clinical experience with CNS injury/disease biomarkers and associated assays, 2) past experience with bioanalytical method validation of assays per Industry guidance; 3) the capacity to obtain relevant clinical samples for analysis.

Specific goals:

1. **Select and validate a panel of biomarker assays consisting of 4-5 proteins (e.g. GFAP, UCH-L1, tau) and 4-5 cytokines (e.g. IL1-β, TNF, IL10, TGF-β2) for use with human blood (serum or plasma), CSF or urine samples.**

   Other classes of biomarkers (e.g. isoprostanes) may also be proposed. The focus should be on achieving GLP/GCP standard validation (full or partial as needed) of up to 10 assays.

   Industry contribution:

   Expertise in development of biomarkers of CNS injury, analytical expertise, samples from clinical studies (healthy volunteers), data from preclinical studies.

   Expected Applicant consortium contribution:

   Expertise in CNS biomarkers, development and validation of biomarker assays, access to relevant samples.

2. **Fully characterise the baseline variation of biomarkers in samples from "healthy" volunteers using assays validated in Goal 1 to establish reference ranges including assessing the influence of age, sex, body weight, ethnicity, etc.**

   Depending on sample availability this objective will require up to 500 samples for each assay from volunteers with no known CNS disease or injury. In collaboration with the Liquid Biopsies work package, specific miRNA biomarkers (4-5 miRNAs) will also be identified for further evaluation.

   Industry contribution:

   Expertise in the development of biomarkers of CNS injury, samples from clinical trials (healthy volunteers).

   Expected Applicant consortium contribution:

   Clinical expertise in development of biomarkers of the CNS and access to samples from healthy subjects across various populations.

3. **Evaluate the influence of 2-3 injury/disease states and 1 neurotoxic chemical treatment on biomarkers identified in stages 1 and 2: this will include samples from patients with brain injury (e.g. stroke, TBI), neurodegenerative disease (e.g. AD, MS, etc.) and chemical-induced neurotoxicity.**

   Depending on sample availability, this objective will utilise ~100 samples from each type of patient.

   Industry contribution:

   Expertise in the development of biomarkers of CNS injury.

   Expected Applicant consortium contribution:

   Clinical expertise in appropriate disease phenotypes, ability to identify and access relevant samples from subjects with appropriate disease phenotypes, conduct biomarker studies.

Work package 6 – Liquid biopsies

Availability of non-invasive methods capable of differentiating underlying mechanisms of toxicity and/or disease is an unmet medical need. Micro RNAs (miRNAs) are regarded as a promising source of tissue-specific biomarkers that are released to circulation as a result of tissue damage and/or active secretion. Although some miRs showed promise as tissue specific leakage biomarkers [14] the recent progress in multiplexing technologies and next generation sequencing uncovered a paradigm changing potential of miRs to provide insights into pathogenesis of disease and/or mechanism of toxicity. Thus measuring miR profiles or signatures has been proposed as liquid biopsies capable of detecting injury in distal tissues including their mechanistic context [15]. It has been shown that , panels of miRs were able to differentiate APAP overdose from ischemic liver injury [16], diagnose types of diabetes [17], chronic heart failure [18], and Parkinson and Alzheimer disease [19][20]. Recently, next generation sequencing enabled unbiased interrogation of the whole miRNome including structural modifications of miRNAs, also called isomiRs. Interestingly, changes in the relative isomiR distribution have been associated with specific developmental stages and disease progression [21], APAP-induced liver injury [22] and hepatocellular carcinoma tissues [23] and a variety of liver impairments [15]. Therefore the proposed project will focus on evaluation of miR profiles as liquid biopsies that would be applicable for interrogation of mechanisms of toxicity and etiology and pathogenesis of diseases. Since liquid biopsies WP will require the development of new innovative approaches that include sequencing of a large number of serum samples and development of bioinformatic tools, it is expected that significant resources up (to 40%) will be committed to this WP.

Specific goals:

1. **Characterization of NextGen platform:**

   There are at least three categories of concern with miRNA sequencing which need to be addressed by the consortium such as (a) ligase bias, (b) effect of potential inhibitors of cDNA synthesis and qPCR present in serum and/or plasma samples and (c) characterisation of NextGen sequencing method performance. It is expected that the applicants will justify the selected sequencing platform with available published data and when not available outline studies that will sufficiently characterise selected sequencing technology.

   Industry contribution:

   Expertise in method development and validation.

   Expected Applicant consortium contribution:

   Nextgen sequencing methodology and data analysis expertise.

2. **Characterise circulating miRnome in healthy subjects:**

   The interpretation of the miR-based liquid biopsy approach is dependent on detailed characterization of the circulating miRNome in healthy subjects including evaluating the potential influence of age, sex, ethnicity, longitudinal variability, inter and intra-individual variability, effect of food etc. Since the characterization of circulating miR-nome will provide a foundation for the development of tissue damage-specific signatures, a large cohorts of subjects (500-2000) will need to be interrogated.

   Industry contribution:

   Serum samples from healthy volunteers of various specifications, expertise in design of studies, data interpretation, bioinformatics.

   Expected Applicant consortium contribution:

   Serum samples from healthy subjects (ages, sex, ethnic groups), Next gen sequencing methodology and data analysis.

3. **Develop specific target organ injury miR signatures:**

   This will require obtaining a sufficient number of samples from subjects with characterised impairments of various aetiologies. The focus of this specific goal is expected to be in line with target organ WP. If tissue biopsies are available, tissue and liquid biopsy miRNA profiles will be compared. To be successful large numbers of subjects will need to be included in this project.

   Industry contribution:

   Serum samples from healthy volunteers of various specifications, expertise in design of studies, data interpretation, bioinformatics.

   Expected Applicant consortium contribution:

   Serum samples from subjects with specific diseases, Next gen sequencing methodology and data analysis.

4. **Develop an informatics platform that allows the deconvolution of miR based signatures to pathways and mechanisms:**

   The goal is to develop a user-friendly system that will enable researchers to interrogate miR profiles for meaningful mechanistic information. This objective will need to utilise available databases of miR tissue distribution across human and non-clinical species that are available publicly or from member companies.

   Industry contribution:

   Data from existing databases (miR atlas), expertise in design of studies, data interpretation, bioinformatics.

   Expected Applicant consortium contribution:

   Bioinformatic expertise, development of databases and search engine approaches for data mining.

Work package 7 – Assay development, sample and data management, and statistical support

This WP will be integrated with individual WPs and provide backbone support for other WP activities. This might be an opportunity for including SMEs with appropriate expertise. Availability of robust assays that are transferable to research and ultimately to clinical laboratories for commercial use is essential for implementation of safety biomarkers in clinical trials and diagnosis of diseases. It is important to note that the level of validation will need to reflect the stage of the biomarker candidate [24]. For example, a kidney marker intended for regulatory review differs from the qualification of an emerging vascular or CNS biomarker candidate. These issues will be addressed through assay validation plans co-authored by consortia partners and the SME or laboratory performing a particular validation. This WP will provide opportunity to engage SMEs to standardise assay methodologies for particular stages of development and potentially develop commercially available diagnostics. Furthermore, appropriate sample and data management tools that are compliant with data management and patient privacy standards and statistical support will be essential for TransBioLine success. This WP will provide necessary support across individual target organ- and liquid biopsies-based WPs.

Specific goals:

1. **Coordinate the development of standardised validation procedures and SOPs for all biomarker assays and sample management**;

2. **Prioritise most impactful biomarker assays for development of diagnostics as laboratory developed tests (LDTs) or potentially as in vitro diagnostics (IVDs);**

   Industry contribution:

Assay validation, SOP and quality control.

Expected Applicant consortium contribution:

Assay development, validation, LDT and potentially IVD development capabilities.

3. **Provide sample and data management support for TransBioLine project;**

Industry contribution:

Expertise in compliance.

Expected Applicant consortium contribution:

Sample management and distribution across laboratories. Data warehousing in compliant databases.

4. **Statistical support for individual WPs.**

Industry contribution:

Expertise and conduct of statistical analysis**.**

Expected Applicant consortium contribution:

Expertise and conduct of statistical analysis.

Work package 8 – Regulatory acceptance of biomarkers

Achieving regulatory acceptance of emerging safety biomarkers by EMA, FDA and PMDA is essential for their application in clinical trials and diagnosis of disease. Although the biomarker qualification process utilises evidentiary standards that were recently formalised [1][24], it is necessary to develop and maintain a dialog and collaborative relationship with regulatory agencies via consultations, meetings and workshops. In addition, establishing connections and relationships with stakeholders from wider scientific and health care communities will be essential for dissemination of and implementation of novel biomarkers in clinical practice.

Specific goals:

1. **Develop biomarker qualification strategy for all safety biomarkers in the TransBioLine project;**
2. **Develop individual biomarker qualification packages and manage submissions to regulatory agencies as part of the routine regulatory interactions;**
3. **Organise annual workshops with regulatory agencies to discuss biomarker qualification**.

Industry contribution:

Support writing regulatory documents, expertise in regulatory interactions.

Expected Applicant consortium contribution:

Expertise in regulatory science, managing submissions to regulatory agencies, organizing workshops and meetings with regulatory agencies.

Work package 9 – Project management

The goal of this work package is the overall project coordination, integration and dissemination.

Specific goals:

1. **Financial management, maintain timelines, and execute on deliverables and milestones;**
2. **Legal and contractual management;**
3. **Communication to the scientific community and the public.**

Industry contribution:

Programme co-leadership, WP co-leadership of all aspects of the project; contribution to application and valorisation aspects, project and financial management, contribution to communication and dissemination.

Expected Applicant consortium contribution:

Programme co-leadership, WP co-leadership; proven record of professional project management capabilities; expertise and experience in managing complex and long lasting projects including financial management; previous experience with management of IMI projects including scientific and technical programme coordination and reporting to the commission; contribution to communication and dissemination.

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Pilot programme on a Clinical Compound Bank for Repurposing

Topic 12: Cardiovascular diseases and diabetes

Topic 13: Respiratory diseases

Topic 14: Neurodegenerative diseases

Topic 15: Rare/orphan diseases

Topic details

Topic code	IMI2-2017-13-12 IMI2-2017-13-13 IMI2-2017-13-14 IMI2-2017-13-15
Action type	Research and Innovation Action (RIA)
Submission and evaluation process	2 stages

Specific challenges to be addressed

On average it takes about 14 years for a new drug to travel from the research lab to market approval at an average cost of ≥€2 billion. Only 10% of compounds that enter preclinical testing ever make it into clinical trials, with only 20% of these achieving marketing approval [1][2].

A number of innovative programmes have been established over the last few years between research funding agencies and industry to provide academic researchers with access to high-quality pharmaceutical industry compounds that have stalled at some stage during research or development. Many of these compounds have already undergone preliminary testing in humans, but have not been progressed further because they were not found to be sufficiently effective in the indication for which they were originally developed.

These compounds represent valuable tools that researchers can use to test their novel hypotheses for alternative therapeutic indications, with the ultimate aim of identifying alternative uses for these compounds in other indications ('repurposing', 'repositioning'). Since partial preclinical and clinical documentation packages have been developed for these assets, any positive findings hold the opportunity to progress towards the market more quickly and cost-effectively, with the ultimate goal of benefiting patients in diseases of high unmet need. Examples of ongoing open innovation schemes include the National Institute of Health/National Center for Advancing Translational Sciences (NIH/NCATS), the New Therapeutic Uses program in the US[24], the Medical Research Council (MRC) industry asset sharing initiative in the UK[25] and the ERA-Net E-Rare

[24] https://ncats.nih.gov/ntu/about?_sm_au_=iDVNkL6Rk8jPqH55
[25] https://www.mrc.ac.uk/news/browse/world-s-largest-collection-of-deprioritised-pharma-compounds-opens-to-researchers/

2016 call[26] in which many EFPIA members already provide previously unprecedented access to a subset of their assets. Expanding this asset-sharing repurposing programme through IMI2 JU aims to provide researchers across the EU with the same opportunity to form hypothesis, to engage in collaborative research with industry and to access discontinued compounds that have already passed through several stages of the drug development process.

In this call, a number of compounds are made available for exploration in specific therapy areas: cardiovascular diseases and diabetes, respiratory diseases, neurodegenerative diseases and rare/orphan diseases.

The pharmaceutical small molecule compounds made available are listed in the Appendix, together with key information on mechanism of action, pharmacology, safety, tolerability and exclusions relating to these compounds. The applicants will submit proposals to utilise these assets to test their hypotheses for alternative indications within the above-mentioned therapeutic areas, to generate clinical data and, if needed, prerequisite preclinical data, with the ultimate aim of taking these assets to the market in alternative indications to those that they were originally developed for.

If these pilot topics on drug repurposing are successful, the programme will be expanded in future calls.

Need and opportunity for public-private collaborative research

The European research organisations, including universities, hospitals and small and medium-sized enterprises (SMEs) are renowned for their cutting-edge science and innovative spirit, yet often do not have the tools nor the expertise to develop their discoveries towards the clinic and regulatory approval. The pharmaceutical industry has built up significant experience, knowledge and research and development (R&D) information for a large number of deprioritised or disused compounds arising from terminated programmes. Public-private collaboration enables the investigation of scientific advances within research organisations using drugs and drug candidates from industry. Academic organisations benefit from access to clinic-ready assets and prior R&D information. This includes predefined preclinical and clinical dosing regimens, toxicological and pharmakokinetic/pharacodynamic data packages which help to ensure their studies are designed with the best possible chance of success, alongside the industrial guidance on the data package needed to support development and transition towards the market.

By collaborating and bringing the strengths of European research communities and pharmaceutical companies together, it may be possible to accelerate the research in drug repurposing and potentially speed up the development of new treatments and giving patients access to these new therapies.

Parallel grant-funding schemes with the NIH/NCATS, MRC and selected institutions around the world, contain many examples of preclinical and clinical proof-of-concept studies in which the academic and industry collaboration has provided the opportunity for a rapid transition towards clinical development. This model has also previously provided the opportunity to spin out new SMEs based on positive repositioning data, enabling funds to be raised to progress to later stages of clinical development. All of these advantages have the long-term effect of getting drugs to the market quicker and more cost effectively for the benefit of patients.

A private-public partnership like IMI2 JU provides the opportunity to test interesting compounds in new indications that may not be otherwise tested. In addition, IMI2 JU provides an exciting possibility for translational research funding accessible to researchers across the EU and H2020 Associated Countries.

[26] http://www.erare.eu/previous-calls

Scope

The overall objective of this pilot programme is to take one of the nine previously deprioritised clinical compounds listed in the Appendix – and investigate their therapeutic potential in new clinical indications in areas of high unmet need.

Under the Clinical Compound Bank for Repurposing pilot programme, there will be four separate topics, one for each disease area listed below:

- **TOPIC 12 : Cardiovascular diseases and diabetes**
- **TOPIC 13 : Respiratory diseases**
- **TOPIC 14 : Neurodegenerative diseases**
- **TOPIC 15 : Rare/orphan diseases**

Potential applicants must be aware that only the compounds identified in the Appendix are within the scope of these four topics. These compounds are listed therein together with key information including mechanism of action, original indication, route of administration pharmacology, safety, tolerability and links to previous clinical studies and publications, to facilitate idea generation by investigators with hypotheses for novel uses. The listed compounds have all been through clinical phase 1 studies.

All proposals submitted under one topic will be evaluated by a panel of independent experts and ranked together. For each topic, only one proposal will be eventually retained and a grant agreement will be signed.

- Proposals should cover clinical Phase 2A proof of concept studies, though larger Phase 2 studies are also in scope if these are within the budget. Clinical submissions should aim at moving towards the next stage of development and positive data should be a starting point for further investment into developing a drug towards clinic and regulatory approval.
- If preclinical work is deemed necessary to provide additional support and confidence before moving into a clinical study in an alternative indication, proof-of-concept/feasibility preclinical studies of up to a year in duration can be included in the proposal. These studies should have clear go/no-go criteria for progressing in to the clinical phase of the project.

Important note: This programme intends to support only innovative clinical development for the compounds listed in the Appendix. This means that proposals for clinical development should not be considered in an indication which has been already tested (i.e. original primary indication or additional studies) or if there are already ongoing or planned clinical studies on identical or related disease indications with the compound or with a compound with overlapping mechanism of action that impacts the novelty of a given proposal.

Information on original primary indications, already tested indications, ongoing and/or planned clinical studies for each of these nine compounds can be found in the Appendix.

Therefore, applicants must demonstrate in their stage 1 application (short proposal) that the proposed study is innovative for the chosen compound.

Expected key deliverables

Proposals should have the potential to identify a new indication for the compound chosen among those made available within this pilot programme. Each selected project must aim at making clear scientific advances within a given disease area.

Key deliverables for each selected project include:

- initiation and completion of new Phase 2A clinical proof-of-concept study in the chosen indication which was not previously investigated with the specific compound;

- preclinical data to support a go/no-go decision for initiation of the clinical study in the new indication, if this is deemed necessary for the selected project;
- dissemination of the results in high-impact publications.

Expected impact

The expected impact is as follows:

- achieving early proof-of-concept for new mechanisms with the potential to rapidly bring novel drugs to patients in areas of high unmet need and/or those with greatest disease burden;
- generation of ideas and/or data licensed from the research organisation, leading to further development of the compound in the new indication;
- added value by repurposing pharmaceutical assets which have already passed through several stages of the R&D process. This can offer significant time, cost and risk savings over embarking on discovery programmes with novel targets;
- supporting EU academic institutions to conduct well-designed and high-standard translational and drug development research with quality compounds under GCP conditions, resulting in high impact publications and patents when possible;
- pooling of resources and greater collaboration between the public and private sectors, with the potential for pharmaceutical involvement or establishment of SMEs following in/out-licencing;
- boosting the discovery and development of therapeutics in the areas of cardiovascular diseases and diabetes, respiratory diseases, neurodegenerative diseases and rare/orphan diseases using a more cost-effective approach to drug development;
- advancing science and knowledge of disease (patho)physiology through testing of new hypothesis;
- boosting European competiveness by contributing to the establishment of closer links between industry and academia across the EU, and ensuring Europe is competitive in line with initiatives already in place in other leading scientific regions around the world.

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 tools/models and lessons learned where possible, thus avoiding unnecessary overlap and duplication of effort.

The projects generated from this topic will be complementary to other ongoing similar initiatives in other parts of the world.

Industry consortium

The industry consortium is composed of the following EFPIA companies:

- AstraZeneca (lead)
- Servier

The industry consortium will contribute the following expertise and assets:

AstraZeneca and Servier will supply compounds for these pilot topics. The EFPIA companies will cover the costs associated with manufacturing, supply and delivery of active pharmaceutical ingredient (API) required for a given study. Clinical studies costs associated with supply, packaging and distribution of drug product will

also be covered by the EFPIA companies. The EFPIA companies will provide expert support for e.g. study design, protocol writing, study oversight, pharmacovigilance, as well as expert support throughout the duration of the funded studies with the aim of working with the consortium to move positive data towards the next stage of development. Under each topic, only one of the two contributing companies listed above will be involved in the full proposal and selected project. This will depend on the clinical compound which will be developed under a new indication.

Indicative duration of the action

The indicative duration of the action is 48 months.

Clinical studies are anticipated to have a maximum duration of 36 months per action. If preceded by a preclinical study, this study should have a maximum duration of 12 months, giving a maximum of total 48 months per action.

Indicative budget

The indicative EFPIA in-kind contribution is EUR 4 160 000.

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

The financial contribution from IMI2 JU is a maximum of EUR 4 160 000.

Under each topic, the maximum IMI2 JU contribution is EUR 1 000 000 per clinical study and an additional EUR 40 000 if a preceding preclinical study is proposed.

Applicant consortium

The applicant consortium will be selected on the basis of the submitted short proposals. Applicants are expected to form consortia with other investigators to bring in relevant expertise and ensure study recruitment targets are met in the clinical studies. All experimentation should be undertaken within the investigators' research institutions and/or their linked third parties.

The proposals should be based on a strong scientific rationale from prior preclinical and/or clinical data. The planned studies should have the potential for improvement of currently available treatments and it is also important that the proposed clinical studies in the projects have a clear feasibility for further clinical development and commercialisation of the compounds in the suggested indications, beyond the project duration.

The applicant consortium is expected to address all the research objectives and make key contributions to the defined deliverables in synergy with the relevant contributing company from the industry consortium which will join the selected applicant consortium for preparation of the full proposal in stage 2.

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

- experience and capability to conduct all aspects of a clinical trial using an investigational medicinal product (including data analysis and reporting) under good clinical practice (GCP) in the proposed indication;
- clinical and preclinical expertise as necessary for the scope of a given study;
- expertise in the science of drug development including aspects of clinical pharmacology, study design and conduct;

- experience and capability to submit an application for clinical trial authorisation with the European Medicines Agency (EMA)/ national regulatory authorities in all member countries of a given consortium;
- capacity to recruit sufficient number of patients within a few clinical study centers;
- strong project management and communication expertise.

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 contributing company participation including its contributions and expertise.

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

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

References

[1] Frail DE, Brady M, Escott KJ, Holt A, Sanganee HJ, Pangalos MN, Watkins C, Wegner CD. Pioneering government-sponsored drug repositioning collaborations: progress and learning. 2015. Nat Rev Drug Discov:14(12):833-41.

[2] Hughes JP, Rees S, Kalindjian SB, Philpott KL. Principles of early drug discovery. 2011. Br J Pharmacol: 162(6):1239-49

Appendix – Compound information sheets

	Compound name: AZD0328
Mechanism of action	Nicotinic acetylcholine receptor alpha 7 (α7 nAChR) agonist
Overview	AZD0328 is a stereo-selective, potent, full agonist of the human α7 nAChR (binding IC50 of 3 nM; activation of whole cell current (half maximal inhibitory concentration) IC50 of 2.9 μM; intrinsic activity = 101% compared with acetylcholine). It is ~20-fold selective to the α1β1γδ nAChR, 1000-fold selective to other nicotinic receptors and a panel of other targets (inhibition of radioligand binding), and is equipotent with the structurally related serotonin 5HT3 receptor (2 μM). Oral administration of AZD0328 significantly improves operant conditioning and long-term potentiation in rats. In rhesus monkeys, spatial working memory is enhanced at doses above 0.001 mg/kg (plasma compound levels of ~0.2 x whole cell current IC50).
Additional information	In a 14 day phase 2A clinical study in patients with schizophrenia, concurrently taking an additional anti-psychotic drug, AZD0328 (0.00093 to 0.675mg; plasma levels ~5 x IC50 at 0.675mg dose), did not show a statistically significant improvement in cognition nor other secondary endpoints.
Safety/Tolerability	In single and multiple ascending dose clinical studies, where AZD0328 was studied at up to 2 mg and 1.35 mg (for 13 days), respectively, the most common adverse events reported were nausea, facial flushing and gastrointestinal disturbances; nausea limited clinical tolerability at doses ≥1.35 mg. In a phase 2A study, AZD0328 at concentrations of up to 0.675 mg once daily for 14 days, did not show any major safety or tolerability concerns in subjects with schizophrenia other than a dose-related incidence of nausea. The (maximum tolerated dose) MTD for multiple dose administration in the context of the original indication was determined to be 1 mg. Preclinical studies of up to 6-month duration have been performed.
Suitable for and Exclusions	The reproductive toxicology package indicates a risk of fetal toxicity. The inclusion of women of child-bearing potential would need to be assessed for any proposal based on the risk-benefit and the use of appropriate highly effective contraception. AZD0328 is renally cleared and, therefore, future studies will require an assessment of the risk-benefit for subjects with renal impairment.
▪ **Clinical trials** ▪ **Previous, ongoing and planned**	Link to clinicaltrials.gov Original indication: schizophrenia
Additional characteristics: ▪ Central nervous system (CNS) penetrance ▪ Pediatric diseases	 Yes Not studied
Publications	Pubmed AZD0328

	Compound name: AZD0530 (saracatinib)
Mechanism of action	Src tyrosine kinase family inhibitor
Overview	Saracatinib (AZD0530) is a potent inhibitor of the Src family of tyrosine kinases (IC50 of 2.7 – 5 nM) with >250-fold selectivity over other tyrosine kinase families. AZD0530 has sub-micromolar activity in a variety of cellular assays of human tumour cell proliferation and inhibits tumour growth in murine and rat allografts and xenografts at compound levels of ~2 x IC50 in plasma when dosed orally.
Safety/Tolerability	In healthy human volunteers, AZD0530 was tolerated in single dose studies up to 1000 mg and in 14 day multiple dose studies at up to 250 mg. A maximum tolerated dose in oncology patients of 175mg per day has been determined. Adverse events across various patient groups include: anemia, nausea, anorexia, asthenia, pyrexia, vomiting, diarrhea, and pneumonitis. Preclinical safety studies to support clinical dosing up to 12 months in duration have been performed. These reveal haematological changes and proliferative, hypertrophic and degenerative changes in multiple organs which were mild in severity and showed evidence of reversal. All changes were considered generally to be consistent with SRC inhibition.
Additional information	Target coverage has been demonstrated in patients by decreased phosphorylation of focal adhesion kinase and paxilin in tumour biopsies. In healthy volunteers and patients, reduction in serum βCTX, a marker of bone resorption, was evident at doses of 125 & 175 mg (125 mg achieves plasma levels of ~5 x IC50 at Cmin steady state). To date no effect on survival has been observed in a number of oncology trials with AZD0530 as monotherapy (at doses of up to 175 mg).
Suitable for and Exclusions	The reproductive toxicology package indicates a risk of fetal toxicity. AZD0530 is a moderately potent CYP3A4 inhibitor; concomitant administration of compounds / medicines that are metabolised by this route should be avoided. Unsuitable for further oncology researches in respiratory indications is also excluded.
▪ **Clinical trials** ▪ **Previous, ongoing and planned**	European Clinical Trials Register Clinicaltrials.gov Oncology, Alzheimer's disease, metastatic bone pain, alcohol abuse, Parkinson's disease.
Additional characteristics: ▪ CNS penetrance ▪ Pediatric disease	 Yes Not suitable
Publications	Pubmed AZD0530

	Compound name: AZD1981
Mechanism of action	Chemoattractant receptor-homologous molecule expressed on Th2 cells (CRTh2) antagonist [prostaglandin D2 (DP2) receptor antagonist]
Overview	AZD1981 is a potent (binding IC50 of 4 nM), fully reversible, functionally non-competitive antagonist of human CRTh2. It blocks agonist-induced human eosinophil CD11b expression, shape change (including in whole blood), and chemotaxis as well as basophil shape change and Th2-cell chemotaxis at IC_{50}'s of 8.5 – 50 nM. Potency is similar across species as is plasma protein binding (~97%). AZD1981 is a weak (10's of µM) inhibitor *in vitro* of CYP2C9, OATP1B1 and UGT1A1 as well as inducer of CYP3A4. These potential DDI effects appear to translate to in vivo at super pharmacologic doses/exposures (see below).
Safety/Tolerability	AZD1981 has been found to be generally well tolerated in healthy volunteers (single oral dose up to 4000 mg; multiple doses up to 2000 mg (twice a day) BID for 2 wks), asthma or COPD patients (up to 100 mg, BID for 4 wks), and asthmatics (up to 400 mg BID for 12 wks). A small percentage of patients treated with AZD1981 had notable elevations of (alanine aminotransferase) ALT and (aspartate aminotransferase) AST without notable increase in total bilirubin. Results suggest a dose-response relationship with the highest percentage of subjects having identified LFT abnormalities in the AZD1981 400 mg BID group (~2 – 3% above placebo). In all cases, transaminases returned to baseline after AZD1981 was stopped. However, the possibility that AZD1981 may be associated with an increased risk of liver injury cannot be excluded. In completed DDI studies, AZD1981 at 400 or 500 mg BID, but not at 100 mg BID (where tested), increased the plasma exposure of ethinyl estradiol in female volunteers receiving a combined oral contraceptive (COC), warfarin (CYP2C9 substrate), and pravastatin (OATP1B1 substrate), while decreasing midazolam (CYP3A4 substrate). Preclinical safety studies of up to 12-month duration have been performed.
Additional information	Target engagement was demonstrated in the (single ascending dose) SAD and (multiple ascending dose) MAD phase 1 studies using an *ex vivo* whole blood PGD_2-induced eosinophil shape change assay (A_2 = 35nM). Data from these as well as asthma efficacy studies indicate effective target coverage at doses of 40 – 80 mg BID or (three times a day) TID.
Suitable for and Exclusions	Preclinical reprotoxicology data are available and have not identified any specific risks. Women of child-bearing potential using highly effective contraception can be included. Given the potential for DDI and LFT effects (see above), dosing regimen (level and duration) as well as inclusion/exclusion criteria should be selected carefully to support a favourable risk-benefit.
▪ **Clinical trials** ▪ **Previous, ongoing and planned**	clinicaltrials.gov Asthma, chronic sinusitis with nasal polyps, chronic idiopathic urticarial, diabetes.
Additional characteristics: ▪ CNS penetrance ▪ Pediatric diseases	Low CNS penetrance. There are currently no clinical data to support use in pediatric populations below 12 years of age, although existing preclinical data would support clinical studies in a pediatric population of >5 years.
Publications	pubmed azd1981

	Compound name: AZD4017
Mechanism of action	11-beta-hydroxysteroid dehydrogenase type 1 (11β-HSD1) inhibitor
Overview	AZD4017 is a competitive, fully reversible inhibitor of human recombinant 11β-HSD1 (IC_{50} of 2 nM) and of 11β-HSD1 activity in isolated human adipocytes (1.8 nM) with cortisone as substrate. It is selective (>2000x) over human recombinant 11β-HSD2 and other closely homologous enzymes *in vitro*. AZD4017 has limited activity in pre-clinical species other than cynomolgus monkey. However, related tool compounds with activity in all species are available; e.g., in diet-induced obese mice, a rodent-active AZ 11β-HSD1 inhibitor induced significant, and approximately half-maximal, reduction in adipose mass and weight gain when compound exposure was ~1 x IC_{50}.
Safety/Tolerability	In single ascending dose studies, Caucasian and Japanese volunteers were exposed to AZD4017 dosed up to 750 mg BID. In a MAD study, volunteers received single doses of AZD4017 followed by repeated doses ranging from 75 mg QD up to 900 mg BID for 9 days. A few subjects on treatment had transient increased liver enzyme levels above ULN (>3 x ULN in one subject) with no concurrent increase in bilirubin. An activation of the HPA axis was demonstrated by an increase in ACTH and DHEAs levels and by an increase of total urinary glucocorticoid metabolites. However, s-cortisol and testosterone levels were not changed. In a phase 2a glaucoma study, a number of subjects had incidences of raised liver enzymes at 1 x ULN, but with no associated adverse events. Preclinical toxicity studies of up to 3 month duration have been performed in rat and non human primate. Changes in adrenal glands were noted in both preclinical species but were considered an adaptive response of this organ to altered function. Findings in the liver and the thyroid gland of rat were also considered adaptive and not degenerative in nature.
Additional information	In a 9-day proof of mechanism study, AZD4017 (1200 mg QD) significantly inhibited hepatic 11β-HSD1 activity as measured by an oral prednisone challenge. Measurements of urine glucocorticoid metabolites further indicate an inhibitory effect on the whole body 11β-HSD1 activity. Regarding the 11β-HSD1 inhibitory effect in adipose tissue, a MAD and PoM study in abdominally obese subjects demonstrated inhibition of 11β-HSD1 after single dosing, yet no sustained inhibitory effect after repeated doses at the tested dose levels. However, *ex vivo* investigations suggest the possibility to obtain an inhibition after repeated dosing at high AZD4017 concentrations. In a 28 day phase 2a study in patients with raised intraocular pressure, AZD4017 dosed at 400mg BID, produced no change in IOP when compared to placebo (plasma concentrations of ~10 x IC_{50}).
Suitable for and Exclusions	Preclinical reprotoxicology data are not available for this compound. The inclusion of women of child-bearing potential using highly effective contraception in trials of modest size and duration could be considered based on the risk benefit and in accordance with territory specific requirements. Preclinical safety studies support future clinical studies of up to 3-month duration with the need for monitoring liver enzymes, thyroid, and adrenal function.
▪ **Clinical trials** ▪ **Previous, ongoing and planned**	clinicaltrials.gov Post-menopausal osteopenia, idiopathic intracranial hypertension, glaucoma, iatrogenic Cushing's syndrome, diabetic wound healing, metabolic disorders.
Additional characteristics: ▪ CNS penetrance ▪ Pediatric diseases	 Low CNS penetrance Not studied
Publications	pubmed AZD4017

	Compound name: AZD7325
Mechanism of action	Gamma-aminobutyric acid receptor A alpha 2 & 3 ($GABA_{Aα2,3}$) positive modulator
Overview	AZD7325 is a high affinity, selective modulator of the $GABA_A$ receptor system, with differential binding and modulatory properties dependent on the particular GABAA subtype. Binding affinity is high at $GABAA_{α1}$, $_{α2}$ and $_{α3}$ (Ki of 0.5, 0.3 and 1.3 nM, respectively), but not $GABA_{Aα5}$ (230 nM). Using whole cell electrophysiology after specific expression of a $GABA_A$ subunit in Xenopus oocytes, AZD7325 did not display intrinsic agonist activity at any subtype, but potentiated the response of diazepam at Aα2 and Aα3 (43 and 45%, respectively at 100 nM), but not Aα1 or Aα5. In contrast, AZD7325 acted as a full antagonist of zolpidem at Aα1 consistent with a lack of sedative liabilities in vivo. Selectivity was >100-fold in a panel of 160 other receptors, ion channels and enzymes, with the closest secondary pharmacology target being melatonin MT1 receptor antagonism (IC_{50} of 126nM). AZD7325 also potentiated native GABA responses in neurones prepared from the rat prefrontal cortex, occupied brain binding sites in non human primates as assessed by PET (approximately 50% receptor occupancy at plasma levels of ~1 x Ki), and demonstrated efficacy in a number of rat anxiety models.
Safety/Tolerability	AZD7325 has been administered to healthy volunteers at single doses of up to 100 mg and repeated doses up to 50 mg for 7 days. Adverse events were CNS in nature, and included dizziness, feeling of relaxation, euphoric mood, somnolence, and headache. These were transient, mild, and related to peak plasma concentrations. In patients dosed for up to 28 days, AZD7325 was generally well tolerated with the most frequent adverse events being dizziness, headache, and somnolence although one grand mal convulsion was also reported and considered to be treatment related. Preclinical toxicity studies of up to 3-month duration have been performed. These have identified pharmacologically mediated changes in behavior and, additionally, changes to heart rate, increases in cholesterol, AST and ALT, and also changes in hematology parameters. No compound related histopathogical changes were found.
Additional information	Receptor occupancy was measured by PET imaging in healthy volunteers; maximal occupancy was achieved at doses of 10mg, 20mg and 30 mg. Two phase 2a GAD studies have been conducted. In the first, AZD7325 was dosed at either 2 or 5 mg BID or 10mg QD for 28 days, achieving compound plasma exposures of ~4 x K_i. In the second, it was dosed at either 5 or 15mg BID and compared with lorazepam. While the primary objective of greater efficacy vs. placebo and/or lorazepam, as assessed by the Hamilton Anxiety scale, was not met at any of the doses tested, the placebo response rate was considered to be high and reduction in other anxiety endpoints at 10 mg and depression (Montgomery-Asberg depression scale) MADRS score were noted.
Suitable for and Exclusions	Preclinical reprotoxicology data are available and have not identified any specific risks. Women of child-bearing potential using highly effective contraception can be included. Subjects with past or present symptoms of alcohol or drug abuse/dependence and/or subjects suspected of abusing alcohol or illicit or prescription medications should be excluded. Subjects with past or present history of seizures or convulsions should be excluded.
▪ **Clinical trials** ▪ **Previous, ongoing and planned**	clinicaltrials.gov Generalised Anxiety Disorder, fragile X syndrome, peripheral sensory neuropathy, dystonia, autistic spectrum disorder

Additional characteristics: ▪ CNS penetrance ▪ Pediatric diseases	 Yes Not studied
Publications	pubmed AZD7325

	Compound name: AZD1656
Mechanism of action	Glucokinase (GK; hexokinase 4) activator
Overview	AZD1656 is a potent, selective (>100-fold versus hexokinase 1 and 2 and a pharmacology screening panel), activator of human and rat glucokinase *in vitro*; EC_{50}'s = 0.057 and 0.072 µM, respectively, for the recombinant enzymes, which translates into cellular systems (EC_{50}'s = 1.39 and 0.47 µM in human and rat hepatocytes, respectively). AZD1656 reduces plasma glucose levels in a dose-dependent fashion, with a rapid onset of action, in normo-glycaemic insulin resistant rats and diabetic mice, when dosed acutely and when dosed once daily for up to 28 days.
Safety/Tolerability	AZD1656 has been studied in single doses of up to 180mg and multiple doses to 150mg BID for 8 days in healthy volunteers as well as alone and in combination with other blood glucose control agents in diabetic patients at 200 mg daily for up to 6 months duration. In both healthy volunteers and diabetic patients no significant clinical effects other than glucose lowering were noted. Preclinical studies of up to 12-month duration have been performed. These revealed a potent glucose lowering effect, and thereby, the results of chronic toxicology studies in healthy animals were confounded by severe hypoglycaemia at higher doses and sequelae such as Wallerian type nerve degeneration and skeletal muscle fibre degeneration. Additional changes, also considered secondary to hypoglycaemia, were seen in the liver (loss of hepatocellular glycogen).
Additional information	In a phase 2 study in Japanese type 2 diabetic subjects, AZD1656, given BID at high (40 – 200 mg/day), medium (20 – 140 mg/day) and low (10 – 80 mg/day) doses over a 4-month period, has been found to lower HbA1c and fasting plasma blood (FPG) glucose levels with a 50 mg dose producing compound levels of ~2 x EC_{50} in plasma. However, this effect was transient trending towards pre-dose levels between weeks 8 and 16 and there was no statistically significant change in either HbA1c or FPG from baseline at 4 months.
Suitable for and Exclusions	Preclinical reprotoxicology data are available and have not identified any specific risks. Women of child-bearing potential using highly effective contraception can be included. Proposed indications should be evaluated against the risk of hypoglycaemia in non-diabetic subjects.
▪ **Clinical trials** ▪ **Previous, ongoing and planned**	clinicaltrials.gov European Clinical Trials Register Diabetes / metabolic disease
Additional characteristics: ▪ CNS penetrance ▪ Pediatric diseases	 Low CNS penetrance Not studied
Publications	pubmed AZD1656

	Compound name: AZD5904
Mechanism of action	Myeloperoxidase (MPO) inhibitor
Overview	AZD5904 is a potent (IC_{50} of 140 nM), irreversible inhibitor of human MPO with similar potency in mouse and rat. It is 10 to 19-fold selective compared to the closely related lactoperoxidase and thyroid peroxidase; >70-fold to a broad panel of other enzymes, ion channels, and receptors. In isolated human neutrophils, 1 µM inhibited PMA stimulated HOCl by >90%. In rats, a plasma concentration of ~5 µM decreased the *in vivo* formation of glutathione sulphonamide (a product of the reaction of HOCl with glutathione) from *in situ* zymosan activated peritoneum neutrophils.
Safety/Tolerability	AZD5904 has been administered orally to healthy volunteers in single doses of up to 1200 mg (1400 mg with extended release (ER) formulation) and multiple doses of up to 325 mg TID (600 mg BID for 10 days with ER formulation). In total, 181 subjects have been dosed in five phase 1 studies. No overtly drug-related adverse event has yet been identified, although a minimal effect on free P-Thyroxin (T4) and free P-Triiodothyronine (T3) could not be ruled out in the first multiple ascending dose study. Preclinical studies of up 12 month duration have been performed.
Additional information	Via both standard (TID) and extended release (BID) oral formulations, 300 mg yielded blood concentrations of ~30 µM peak, ~4 µM trough, and 12 -16 µM C_{avg}. The main route of clearance is renal, possibly via active transport. Plasma protein binding is 44%. *In vitro* studies indicate CYP2C19 inhibition and P-gp substrate as well as low (blood–brain barrier) BBB penetration.
Suitable for and Exclusions	The reproductive toxicology package indicates a risk of fetal toxicity. The inclusion of women of child-bearing potential would need to be assessed for any proposal based on the risk-benefit and the use of appropriate highly effective contraception. AZD5904 is renally cleared, thus, requiring caution and (pharmacokinetics) PK monitoring if dosed to subjects with impaired renal function. As AZD5904 has only previously been dosed for up to 10 days, clinical studies with dosing duration of no longer than 4 months are advised. Proposals for HFpEF will not be considered.
▪ **Clinical trials** ▪ **Previous, ongoing and planned**	No ongoing studies. Original indication: inflammation
Additional characteristics: ▪ CNS penetrance ▪ Pediatric diseases	 Low CNS penetrance Not studied
Publications	Pubmed MPO inhibitors

	Compound name: S 38093
Mechanism of action	Moderate antagonist/inverse agonist at histaminergic H_3 receptors Moderate antagonist at adrenergic α_{1A} and Sigma 1 receptors
Overview	In adult or aged rodents and monkeys, S 38093 (0.3 mg/kg p.o. or i.p.) demonstrates memory-enhancing properties in several models of working memory and episodic memory with an activity comparable to that of donepezil. S 38093 also displays positive effects on attention and cognitive flexibility as evidenced in monkeys. In addition, combination studies with S 38093 and AChEI (donepezil, rivastigmine or galantamine) or memantine in a mouse model of age-related episodic memory deficit have shown a synergistic beneficial effect of the combination compared to each drug given alone. Moreover, S 38093 (0.3 to 3 mg/kg p.o.) possesses beneficial effects on 3 pain symptoms (mechanical hyperalgesia, mechanical and thermal allodynia) in different neuropathic pain models in rat. On the whole, the kinetics and size of effect of S 38093 are comparable to those of positive controls gabapentin and/or pregabalin. In healthy young subjects submitted to a sleep deprivation procedure, S 38093 demonstrated a transitory effect on alertness at the highest tested dose of 100 mg and attentional properties at lower doses of 20 and 50 mg In healthy elderly volunteers, S 38093 showed a statistical significant activation in fMRI in several areas involved in working memory at 5 mg and in several areas involved in declarative/episodic memory at 5 and 20 mg. No beneficial effect of S 38093 alone or in combination with donepezil was observed on cognitive performance in patients with mild or moderate Alzheimer's disease.
Safety/Tolerability	• In animals: no cardiovascular or respiratory warning, no addictive potential. CNS and endocrine effects may occur, but only at higher doses / plasmatic concentrations than in pharmacological studies: potentiation of PTZ- or ECS-induced seizures in rat, increase in prolactin release. S 38093 was clinically well tolerated in rats and in monkeys in long-term toxicity studies; targets organs in rats at the high dose being female genital system, mammary glands and prostate. In repro toxicity study, no effect was observed on male fertility but S 38093 decreased global fecundity of females and increased post–implantation loss rate. • During phase I studies, S 38093 (up to 100 mg/d) was administered as a single or repeated administration to young (males) and elderly (males and females) volunteers (n>300). Clinical overall acceptability was good. Main observed adverse events were mild or moderate sleep disorders (nightmares and insomnia), asthenia, diarrhoea and orthostatic hypotension. Two phases IIa and two phases IIb studies were performed with S 38093 (5 to 50 mg/d) in patients with mild or moderate Alzheimer's disease (n > 1000). These studies confirmed a global good tolerance of S 38093 alone or in add on to donepezil in patients. Main adverse events were falls, headaches, dizziness and depression. The review of overall safety data since the beginning of the development program for S38093 lead to consider seizure, orthostatic hypotension, fall and prolactin increase as expected for the S 38093.
Additional information	Favourable PK (almost complete absorption, high absolute bioavailability, linear pharmacokinetics, elimination terminal half-life in humans: 20h to 40h).

	Main enzymes involved in metabolism: CYP2C19 for 80-85%, CYP2C8 for 5-10% and amidases for 5-10%.
Suitable for and Exclusions	S 38093 should be avoided in pregnant and breast-feeding women and in subjects with history of epilepsy or history of a solitary seizure. Poor metabolisers and treatments known to inhibit CYP 2C19 activity are authorised due to low impact on PK. Suitable for indications in which there is a cognitive deficit (Alzheimer's disease excluded) and pain, in particular neuropathic. Not optimal for treatment of arousal disturbance (narcolepsy for instance).
▪ **Clinical trials** ▪ **Previous, ongoing and planned**	Link to EU Clinical Trial register
Additional characteristics: ▪ CNS penetrance ▪ Pediatric diseases	In rat and mouse, the brain distribution of S 38093 is rapid and high. Waiver asked for children (Alzheimer's disease indication)
Publications	▪ Mechanistic characterization of S 38093, a novel inverse agonist at histamine H3 receptors. Sors A, Panayi F, Bert L, Favale D, Nosjean O, Audinot V, Arrang JM, Buisson B, Steidl E, Delbos JM, Huhtala T, Kontkanen O, Chollet AM, Casara P, Lestage P. Eur J Pharmacol. 2017 May 15;803:11-23. ▪ *In vivo* pharmacological profile of S 38093, a novel histamine H3 receptor inverse agonist. Panayi F, Sors A, Bert L, Martin B, Rollin-Jego G, Billiras R, Carrié I, Albinet K, Danober L, Rogez N, Thomas JY, Pira L, Bertaina-Anglade V, Lestage P. Eur J Pharmacol. 2017 May 15;803:1-10. ▪ The Synergistic Enhancing-Memory Effect of Donepezil and S 38093 (a Histamine H3 Antagonist) Is Mediated by Increased Neural Activity in the Septo-hippocampal Circuitry in Middle-Aged Mice. Sors A, Krazem A, Kehr J, Yoshitake T, Dominguez G, Henkous N, Letondor C, Mocaer E, Béracochéa DJ. Front Pharmacol. 2016 Dec 22;7:492. ▪ S 38093, a histamine H₃ antagonist/inverse agonist, promotes hippocampal neurogenesis and improves context discrimination task in aged mice. Guilloux JP, Samuels BA, Mendez-David I, Hu A, Levinstein M, Faye C, Mekiri M, Mocaer E, Gardier AM, Hen R, Sors A, David DJ. Sci Rep. 2017 Feb 20;7:42946. ▪ Effects of S 38093, an antagonist/inverse agonist of histamine H3 receptors, in models of neuropathic pain in rats. Chaumette T, Chapuy E, Berrocoso E, Llorca-Torralba M, Bravo L, Mico JA, Chalus M, Eschalier A, Ardid D, Marchand F, Sors A. Eur J Pain. 2017 Sep 6.

	Compound name: S 47445
Mechanism of action	S 47445 is a positive allosteric modulator of alpha-amino-3-hydroxy-5-methyl-4-isoxazole-propionic acid (AMPA) receptors (AMPA-PAM). It has no effect alone, no effect on NMDA nor kainate receptors. S 47445 (10µM) showed no interaction up to 10^{-5}M on about a hundred of receptors, enzymes and ion-channels tested. No difference of potentiation among the different AMPA receptors subtypes (GluA1/2/4 flip and flop variants) (EC_{50} between 2.5-5.4 µM), except a higher EC_{50} value for GluA4 flop (0.7 µM) and a greater amount of potentiation on GluA1 flop. S 47445 did not increase the release of monoamines in the frontal cortex after 5 days of oral administration of 40 mg/kg in mice in a microdialysis experiment. S 47445 at 10 mg/kg p.o. in awake mice in anesthetised rats enhanced the long-term potentiation (LTP) and reversed the deficit of LTP observed in middle-aged mice at 10mg/kg, p.o. It presented neurotrophic properties *in vitro* (on BDNF) and *in vivo* in hippocampus and cortex of adult rats in basal conditions and submitted to a mild stress and also in aged rats of 18 months old (from 1 to 10mg/kg p.o.).
Overview	Pharmacological data from animal models: *In vivo*, S 47445 has shown memory-enhancing properties in adult rats, adult, middle-aged and aged mice in 5 models of episodic memory tests after acute and chronic administration, and 3 rodent models of working memory, at pharmacologically-active doses between 0.3 and 3 mg/kg p.o. S 47445 presented antidepressant-like activity after repeated administration in 4 depression-like behaviour models, the chronic mild stress and the prenatal stress in rats, the corticosterone model and the olfactory bulbectomy in mice. In two of these models (the corticosterone model in mice and the prenatal stress in rats), it also presented anxiolytic-like activity. At 30 mg/kg i.p., S 47445 showed a neuroprotective effect on delayed hippocampal neuronal death induced by a global transient ischemia in rats and in an excitotoxic brain model in neonates at 0.1 and 0.3 mg/kg i.p. S 47445 significantly increased neurogenesis of neural progenitors in the dentate gyrus of the hippocampus of adult mice treated with corticosterone at antidepressant-active doses. This effect was associated with an increase of dendritic length and number of intersections of neural progenitors of dentate gyrus. Pharmacodynamics data in healthy volunteers: S 47445 at 5 mg facilitates interactions between task-positive networks during a cognitive task compared to placebo. In the posterior cingulate cortex, S 47445 at 5mg and 20mg induced a significant increase of glutamate (excitatory neurotransmission) in elderly women. S 47445 showed a statistically significant increase in plasma BDNF protein at pooled doses 20 and 50 mg after a 10-day treatment in young. Two parallel developments were considered for this drug: 1/“symptomatic treatment of mild to moderate Alzheimer’s disease (AD) in patients with depressive symptoms” and 2/-“adjunctive treatment of (major depressive disorder) MDD patients with inadequate response to an initial antidepressant treatment”.
Safety/Tolerability	Safety pharmacology: No cause of concern up to 1000 mg/kg p.o. on behaviour, body temperature, locomotion, coordination, autonomic function and respiratory function in rats. A possible proconvulsant potential noted at 200 and 1000 mg/kg p.o. in the rat PTZ-induced seizure model: induction of a slight but statistically significant decreases of the time required for initiation of PTZ-induced seizures. Up to 30mg/kg p.o., single dose did not show addictive potential in rats trained on cocaine in a drug discrimination procedure. No difference in clinical observations in combination with donepezil or SSRI or SNRI. Concerning the integrated cardiac risk assessment: no *in vitro* effects were observed on hERG assay and no *in vivo* cardiovascular effects (haemodynamic and ECG parameters) were observed in telemetered primates, up to 150 mg/kg p.o.

	Toxicology: Administered orally during 26 weeks in rats and 39 weeks in monkeys, no toxicological findings were observed up to 1000 mg/kg/day inclusive of S 47445-11. No target organ for toxicity was observed in both species. S 47445-11 was devoid of genotoxic potential in 3 tests, phototoxic potential in an *in vitro* test and immunotoxic potential in a 4-week rat study. In reproduction toxicity studies, S 47445-11 did not show any effect on male and female fertility in the rat and on embryo-foetal development including teratogenicity in the rat and the rabbit. Clinical studies: Phase I studies: In the single dose studies, S 47445 was administered at doses from 5 to 800 mg. Clinical and biological tolerance was good up to the dose of 800 mg. In the repeated 21-day administration studies, S 47445 was administered at 5 mg (elderly volunteers), 20 and 50 mg (young and elderly volunteers) and at 100 mg (young volunteers). Clinical and biological tolerance was good up to the dose of 100 mg. The Maximal Tolerated Dose was not reached either after single or repeated administration in these studies. Phase II studies: No specific and/or unexpected safety signal was observed in any of the S47445 arms compared to placebo in AD patients or in any of the S47445 arms compared to placebo (SSRI) in MDD patients.
Additional information	Pharmacokinetics and metabolism in human: Moderate bioavailability, high protein binding; mean apparent terminal elimination half-life value ranges between 30h to 40h after single and repeated oral administrations. The steady-state is reached after about 8-10 days after repeated oral administration in young and elderly volunteers with an accumulation ratio of about 2.5. Mainly eliminated through metabolism and the renal clearance is very low. *In vivo*, CYP1A2 is the major enzyme involved in S 47445 metabolism. According to pharmacokinetics data, concomitant use of S 47445 with potent CYP1A2 inhibitors (e.g. fluvoxamine, ciprofloxacin) and BCRP substrates are not recommended. S 47445 C_{max} and AUC increase less than proportionally with the dose.
Suitable for and Exclusions	
▪ **Clinical trials** ▪ **Previous, ongoing and planned**	Link to Clinical Trial.gov NCT02805439: Efficacy and Safety of **S 47445** Versus Placebo as Adjunctive Treatment in Depressed Patients Not Fully Recovered From Depressive Symptoms With a Current Antidepressant Treatment NCT02626572: Efficacy and Safety of 3 Doses of **S 47445** Versus Placebo in Patients With Alzheimer's Disease at Mild to Moderate Stages With Depressive Symptoms.
Additional characteristics:	
▪ CNS penetrance	Yes. After repeated administration, Kp between brain and blood was high: in rat >7 and in mice ~ 4 to 5. Ratio $AUC_{T_{CSF/blood}}$ is similar after 20 and 50 mg doses: around 4 %.
▪ Pediatric diseases	No data in pediatric disease: biowaiver related to developed clinical indications (Alzheimer's disease and MDD in adjunctive therapy).
▪ Other	In models predictive of antipsychotic activities such as prepulse inhibition in normal and PCP-treated rats, hyperactivity induced by amphetamine or amnesia induced by MK-801, S 47445 has shown no effect alone and no synergy of effect in presence of clozapine. S 47445 presented no impact on ventilatory response in neonate mice after single administration in normoxia and hypercapnia conditions (5% CO_2). Moreover, no modifications of the ventilatory response by S 47445 were

	observed after administration of the opiate fentanyl in pup mice.
Publications	▪ Calabrese F et al. Upregulation of neurotrophins by S 47445, a novel positive allosteric modulator of AMPA receptors in aged rats. Pharmacol Res. 2017 Apr 23;121:59-69. ▪ Guilloux JP et al. S 47445 produces antidepressant and anxiolytic-like effects through neurogenesis dependent and independent mechanisms Front Pharmacol. 2017; 8:462. ▪ Giralt A et al. The AMPA receptor positive allosteric modulator S 47445 rescues *in vivo* CA3-CA1 long-term potentiation and structural synaptic changes in old mice. Neuropharmacology. 2017 Sep 1;123:395-409. ▪ Bretin S. et al. Pharmacological characterisation of S 47445, a novel positive allosteric modulator of AMPA receptors. PLoS One. 2017 Sep 8;12(9):e0184429.

Conditions for this Call for proposals

All proposals must conform to the conditions set out in the H2020 Rules for Participation (https://ec.europa.eu/research/participants/portal/doc/call/h2020/common/1595113-h2020-rules-participation_oj_en.pdf) and the Commission Delegated Regulation with regard to IMI2 JU http://eur-lex.europa.eu/legal-content/EN/TXT/PDF/?uri=CELEX:32014R0622&from=EN.

The following conditions shall apply to this IMI2 JU Call for Proposals:

Applicants intending to submit a Short proposal in response to the IMI2 Call 13 should read this topics text, the IMI2 JU Manual for submission, evaluation and grant award and other relevant documents (e.g. IMI2 JU Model Grant Agreement).

Call Identifier	**H2020-JTI-IMI2-2017-13-two-stage**
Type of actions	**Research and Innovation Action (RIA)** **Coordination and Support Action (CSA)**
Publication Date	**30 November 2017**
Stage 1 Submission start date	**30 November 2017**
Stage 1 Submission deadline	**28 February 2018 (17:00:00 Brussels time)**
Stage 2 Submission deadline	**6 September 2018**
Indicative Budget From EFPIA companies and IMI2 JU Associated Partners	EUR 106 629 000
From the IMI2 JU	EUR 116 421 000

Call Topics

IMI2-2017-13-01	The indicative contribution from EFPIA companies will be EUR 6 000 000 The financial contribution from IMI2 JU will be a maximum of EUR 6 700 000	Research and Innovation Action (RIA) Two-stage submission and evaluation process. Only the applicant consortium whose proposal is ranked first at the first stage is invited for the second stage.
IMI2-2017-13-02	The indicative contribution from EFPIA companies will be EUR 8 300 000 The financial contribution from IMI2 JU will be a maximum of EUR 10 500 000	Research and Innovation Action (RIA) Two-stage submission and evaluation process. Only the applicant consortium whose proposal is ranked first at the first stage is invited for the second stage.

IMI2-2017-13-03	The indicative contribution from EFPIA companies will be EUR 1 945 000 The indicative IMI2 JU Associated Partners contribution will be EUR 4 855 000 The financial contribution from IMI2 JU will be a maximum of EUR 6 800 000	Research and Innovation Action (RIA) Two-stage submission and evaluation process. Only the applicant consortium whose proposal is ranked first at the first stage is invited for the second stage.
IMI2-2017-13-04	The indicative contribution from EFPIA companies will be EUR 3 120 000 The indicative IMI2 JU Associated Partners contribution will be EUR 168 000 The financial contribution from IMI2 JU will be a maximum of EUR 4 500 000	Research and Innovation Action (RIA) Two-stage submission and evaluation process. Only the applicant consortium whose proposal is ranked first at the first stage is invited for the second stage.
IMI2-2017-13-05	The indicative contribution from EFPIA companies will be EUR 1 056 000 The indicative IMI2 JU Associated Partners contribution will be EUR 144 000 The financial contribution from IMI2 JU will be a maximum of EUR 1 200 000	Coordination and Suppert Action (CSA) 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.
IMI2-2017-13-06	The indicative contribution from EFPIA companies will be EUR 4 000 000 The financial contribution from IMI2 JU will be a maximum of EUR 4 600 000	Research and Innovation Action (RIA) Two-stage submission and evaluation process. Only the applicant consortium whose proposal is ranked first at the first stage is invited for the second stage.
IMI2-2017-13-07	The indicative contribution from EFPIA companies will be EUR 24 700 000 The financial contribution from IMI2 JU will be a maximum of EUR 25 500 000	Research and Innovation Action (RIA) Two-stage submission and evaluation process. Only the applicant consortium whose proposal is ranked first at the first stage is invited for the second stage.
IMI2-2017-13-08	The indicative contribution from EFPIA companies will be EUR 16 350 000 The financial contribution from IMI2 JU will be a maximum of EUR 17 830 000	Research and Innovation Action (RIA) Two-stage submission and evaluation process. Only the applicant consortium whose proposal is ranked first at the first stage is invited for the second stage.

IMI2-2017-13-09	The indicative contribution from EFPIA companies will be EUR 13 500 000 The financial contribution from IMI2 JU will be a maximum of EUR 15 300 000	Research and Innovation Action (RIA) Two-stage submission and evaluation process. Only the applicant consortium whose proposal is ranked first at the first stage is invited for the second stage.
IMI2-2017-13-10	The indicative contribution from EFPIA companies will be EUR 4 331 000 The financial contribution from IMI2 JU will be a maximum of EUR 5 331 000	Research and Innovation Action (RIA) Two-stage submission and evaluation process. Only the applicant consortium whose proposal is ranked first at the first stage is invited for the second stage.
IMI2-2017-13-11	The indicative contribution from EFPIA companies will be EUR 14 000 000 The financial contribution from IMI2 JU will be a maximum of EUR 14 000 000	Research and Innovation Action (RIA) Two-stage submission and evaluation process. Only the applicant consortium whose proposal is ranked first at the first stage is invited for the second stage.
IMI2-2017-13-12 -> 15	The indicative contribution from EFPIA companies will be EUR 4 160 000 The financial contribution from IMI2 JU will be a maximum of EUR 4 160 000	Research and Innovation Action (RIA) Two-stage submission and evaluation process. Only the applicant consortium whose proposal is ranked first at the first stage is invited for the second stage.

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

The following general conditions shall apply to the IMI2 JU Calls for Proposals:

LIST OF COUNTRIES AND APPLICABLE RULES FOR FUNDING

By way of derogation[27] 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:

[27] 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

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

(ii) secondary and higher education establishments;

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

(c) the Joint Research Centre;

(d) international European interest organisations.

Participating legal entities listed in (b) above established in a third country may receive funding from the IMI 2 JU provided their participation is deemed essential for carrying out the action by the IMI 2 JU or when such funding is provided for under a bilateral scientific and technological agreement or any other arrangement between the Union and the country in which the legal entity is established[28].

STANDARD ADMISSIBILITY CONDITIONS AND RELATED REQUIREMENTS

Part B of the General Annexes to the Horizon 2020 -Work Programme 2016– 2017[29] shall apply mutatis mutandis for the actions covered by this Work Plan.

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

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

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

ELIGIBILITY CONDITIONS

Part C of the General Annexes to the Horizon 2020 - Work Programme 2016– 2017 shall apply mutatis mutandis for the actions covered by this Work Plan.

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

The participants from EFPIA constituent entities and affiliated entities and other Associated Partners which are pre-defined in the topics - under the section 'Industry consortium' – of a call for proposals do not apply at the stage 1 of the call. The applicant consortium selected from the stage 1 of the Call for Proposals is merged at the stage 2 with the EFPIA constituent entities or their affiliated entities and other Associated Partners.[30]

TYPES OF ACTION: SPECIFIC PROVISIONS AND FUNDING RATES

Part D of the General Annexes to the Horizon 2020 - Work Programme 2016– 2017 shall apply mutatis mutandis for the actions covered by this Work Plan.

TECHNOLOGY READINESS LEVELS (TRL)

Part G of the General Annexes to Horizon 2020 - Work Programme 2016–2017 shall apply mutatis mutandis for the actions covered by this Work Plan.

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

[29] http://ec.europa.eu/research/participants/data/ref/h2020/other/wp/2016-2017/annexes/h2020-wp1617-annex-ga_en.pdf

[30] 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 RULES

Part H of the General Annexes to the Horizon 2020 - Work Programme 2016–2017 shall apply *mutatis mutandis* for the actions covered by this Work Plan with the following additions:

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

Award criteria and scores:

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

Type of action	Excellence	Impact	Quality and efficiency of the implementation*
RIA and IA **1st stage evaluation**	The following aspects will be taken into account, to the extent that the proposed work corresponds to the topic description in the call for proposals and referred to in the IMI2 JU 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 following aspects will be taken into account, to the extent to which the outputs of the project should contribute at the European and/or International level: ▪ The expected impacts of the proposed approach as mentioned in the call for proposals ▪ Added value from the public private partnership approach on R&D, regulatory, clinical and healthcare practice as relevant; ▪ Strengthening the competitiveness and industrial leadership and/or addressing specific societal challenges; ▪ Improving European citizens' health and wellbeing and contribute to the IMI2 objectives[31].	The following aspects will be taken into account: ▪ Coherence and effectiveness of the outline of the project work plan, including appropriateness of the roles and allocation of tasks, resources, timelines and approximate budget; ▪ Complementarity of the participants within the consortium (where relevant) and strategy to create a successful partnership with the industry consortium as mentioned in the topic description in the Call for proposal; ▪ Appropriateness of the proposed management structures and procedures, including manageability of the consortium.
RIA and IA	The following aspects will be taken into account, to	The following aspects will be taken into account, to the extent	The following aspects will be taken into account:

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

Type of action	Excellence	Impact	Quality and efficiency of the implementation*
Single stage, and 2nd stage evaluation	the extent that the proposed work corresponds to the topic description in the call for proposals and referred to in the IMI2 JU Annual Work Plan and is consistent with the stage 1 proposal: ▪ Clarity and pertinence of the proposal to meet all key objectives of the topic; ▪ Credibility of the proposed approach; ▪ Soundness of the concept, including trans-disciplinary considerations, where relevant; ▪ Extent that proposed work is ambitious, has innovation potential, and is beyond the state of the art; ▪ Mobilisation of the necessary expertise to achieve the objectives of the topic, ensure engagement of all relevant key stakeholders.	to which the outputs of the project should contribute at the European and/or International level: ▪ The expected impacts of the proposed approach as mentioned in the call for proposals; ▪ Added value from the public private partnership approach on R&D, regulatory, clinical and healthcare practice as relevant; ▪ Enhancing innovation capacity and integration of new knowledge; ▪ Strengthening the competitiveness and industrial leadership and/or addressing specific societal challenges; ▪ Improving European citizens' health and wellbeing and contribute to the IMI2 objectives;[31] ▪ 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.	▪ Coherence and effectiveness of the project work plan, including appropriateness of the roles and allocation of tasks, resources, timelines and budget; ▪ Complementarity of the participants within the consortium (where relevant); ▪ Clearly defined contribution to the project plan of the industrial partners (where relevant); ▪ Appropriateness of the management structures and procedures, including manageability of the consortium, risk and innovation management and sustainability plan.
Type of action	**Excellence**	**Impact**	**Quality and efficiency of the implementation***
CSA **1st stage evaluation**	The following aspects will be taken into account, to the extent that the proposed work corresponds to the topic description in the Call for proposal and referred to in the IMI2 JU Annual Work Plan: ▪ Clarity and pertinence of the proposal to meet all key objectives of the topic	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 proposal; ▪ Added value from the public private partnership approach	The following aspects will be taken into account: ▪ Coherence and effectiveness of the outline of the project work plan, including appropriateness of the roles and allocation of tasks, resources, timelines and approximate budget; ▪ Complementarity of the

Type of action	Excellence	Impact	Quality and efficiency of the implementation*
	▪ Credibility of the proposed approach; ▪ Soundness of the concept, including trans-disciplinary considerations, where relevant; ▪ Quality of the proposed coordination and/or support measures. ▪ Mobilisation of the necessary expertise to achieve the objectives of the topic, ensure engagement of all relevant key stakeholders.	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[32].	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.
CSA **Single stage and 2nd stage evaluation**	The following aspects will be taken into account, to the extent that the proposed work corresponds to the topic description in the Call for proposal and referred to in the IMI2 JU Annual Work Plan and is consistent with the stage 1 proposal: ▪ Clarity and pertinence of the proposal to meet all key objectives of the topic; ▪ Credibility of the proposed approach; ▪ Soundness of the concept, including trans-disciplinary considerations, ▪ where relevant;	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 proposal; ▪ Added value from the public private partnership approach on R&D, regulatory, clinical and health care practice as relevant ▪ Strengthening the competitiveness and industrial leadership and/or addressing specific societal challenges; ▪ Improving European citizens' health and wellbeing and	The following aspects will be taken into account: ▪ Coherence and effectiveness of the project work plan, including appropriateness of the roles and allocation of tasks, resources, timelines and budget; ▪ Complementarity of the participants within the consortium (where relevant); ▪ Clearly defined contribution to the project plan of the industrial partners (where relevant); ▪ Appropriateness of the management structures

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

Type of action	Excellence	Impact	Quality and efficiency of the implementation*
	▪ Quality of the proposed coordination and/or support measures. ▪ Mobilisation of the necessary expertise to achieve the objectives of the topic and to ensure engagement of all relevant key stakeholders.	contribute to the IMI2 objectives33. ▪ 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.	and procedures, including manageability of the consortium, risk and innovation management and sustainability plan.

* In a single-stage, or in the second-stage of a two-stage evaluation procedure, experts will also be asked to assess the operational capacity of applicants to carry out the proposed work.

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

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

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

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

The full evaluation procedure is described in the IMI2 JU Manual for submission, evaluation and grant award in line with the H2020 Rules for Participation.[34]

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

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

Under the two-stage evaluation procedure, and on the basis of the outcome of the first stage evaluation, the applicant consortium of the highest ranked short proposal[35] (first stage) for each topic[36] will be invited to discuss with the relevant industry consortium the feasibility of jointly developing a full proposal (second stage).

[33] 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)

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

[35] Under exceptional circumstances, and subject to objective criteria based on grounds which could not be reasonably expected to be known by the evaluation panel, the IMI2 JU Governing Board may decide by motivated decision to invite the next-ranked applicant consortium in priority order.

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

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

As part of the panel deliberations, the IMI2 JU may organise hearings with the applicants to:
clarify the proposals and help the panel establish their final assessment and scores, or
improve the experts' understanding of the proposal.

INDICATIVE TIMETABLE FOR EVALUATION AND GRANT AGREEMENT

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

BUDGET FLEXIBILITY

Part I of the General Annexes to the Horizon 2020 - Work Programme 2016–2017 shall apply mutatis mutandis for the actions covered by this Work Plan.

ACTIONS INVOLVING FINANCIAL SUPPORT TO THIRD PARTIES

Part K of the General Annexes to the Horizon 2020 - Work Programme 2016–2017 shall apply mutatis mutandis for the actions selected under topics covered by this Work Plan.

CONDITIONS RELATED TO OPEN ACCESS TO RESEARCH DATA

[36] In cases clearly identified in the relevant call for proposals where a given topic is composed of two or more sub-topics, one short proposal per sub-topic will be invited

Part L of the General Annexes to the Horizon 2020 - Work Programme 2016–2017 shall apply mutatis mutandis for the actions covered by this Work Plan.

However, should a project "opt-out" of these provisions, a Data Management Plan must still be prepared. Guidelines for the Data Management Plan including a template are available on the H2020 Participant portal.[37]

SUBMISSION TOOL

Proposals in response to a topic of the IMI2 JU Call for proposals must be submitted on-line, before the call deadline, by the coordinator via the Electronic Submission Service of the Participant Portal:

http://ec.europa.eu/research/participants/portal/desktop/en/home.html

No other means of submission will be accepted.

OTHERS

For proposals including clinical trials/studies/investigations, a specific template to help applicants to provide essential information on clinical studies in a standardised format is available under:

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

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

Ethical issues should be duly addressed in each submitted proposal to ensure that the proposed activities comply with ethical principles and relevant national, Union and international legislation. Any proposal that contravenes ethical principles or which does not fulfil the conditions set out in the H2020 Rules for Participation, or in the IMI2 JU Annual Work Plan shall not be selected. [38]

In order to ensure excellence in data and knowledge management consortia will be requested to Disseminate scientific publications on the basis of open access[39] (see "Guidelines on Open Access to Scientific Publications and Research Data in Horizon 2020").

Full proposals must contain a draft plan for the exploitation and dissemination of the results.

Applicants intending to submit a proposal in response to the IMI2 JU Calls should also read the topic text, the IMI2 JU Manual for submission, evaluation and grant award, and other relevant documents[40] (e.g. IMI2 JU Model Grant Agreement).

CONSORTIUM AGREEMENTS

In line with the Rules for Participation and Dissemination applicable to IMI2 actions[41] and the IMI2 JU Model Grant Agreement, participants in IMI2 actions are required to conclude a consortium agreement prior to grant agreement.

[37] Additional information and guidance are also available at: https://www.openaire.eu/what-is-the-open-research-data-pilot
[38] Article 19 of Horizon 2020 Framework Programme, and Articles 13 and 14 of the Horizon 2020 Rules for Participation.
[39] 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
[40] http://www.imi.europa.eu/content/documents#calls_for_proposals_-_imi_2_programme
[41] Regulation (EU) No 1290/2013 of 11 December 2013 and Commission Delegated Regulation (EU) No 622/2014 of 14 February 2014.

LIST OF ACRONYMS

Acronym	Meaning
3Rs	Reduction/Refinement/Replacement
AD	Atopic Dermatitis
ADLs	Activities of daily living
ALT	Alanine transaminase
AMR	Antimicrobial resistance
API	Active Pharmaceutical Ingredient
ARTI	Acute Respiratory Tract Infection
ASP	Antibiotic stewardship programmes
BBB	Blood Brain Barrier
BD4BO	IMI2 Big Data for Better Outcomes Programme
BMI	Body Mass Index
BSEP	Bile Salt Export Pump
BUN	Blood urea nitrogen
CA-ARTI	Community-Acquired Acute Respiratory Tract Infection)
CDISC	Clinical Data Interchange Standards Consortium
CHF	Congestive Heart Failure
CKD	Chronic kidney disease
CNFD	Conreal nerve fiber density
CNS	Central Nervous System
COPD	Chronic obstructive pulmonary disease
CRISP/CAS	Clustered Regularly Interspaced Short Palindromic Repeats/associated
CRP	C-reactive Protein
CSA	Coordination and Support Action
CSF	Cerebrospinal fluid
ctDNA, ctRNA	Circulating Tumour DNA / RNA
CyTOF	Methodology for single cell mass cytometry
DALA	Drug Abuse Liability Assessment
DILI	Drug-Induced Liver Injury
DMC	Data monitoring committee
EEG	Electroencephalography
EFPIA	European Federation of Pharmaceutical Industries and Associations
eGFR	Estimated Glomerular Flitration Rate
EMA	European Medicines Agency
EMIF	European Medical Information Framework
ER	Endoplasmic Reticulum
eTRIKS	IMI1 consortium on Delivering European Translational Information & Knowledge

EU	European Union
FA	Fluorescein Angiography
FACS	Fluorescence-activated cell sorting
FDA	Food and Drug Administration
FNIH	Foundation for the National Institutes of Health
FTE	Full Time Equivalent
GCP	Good Clinical Practice
GWAS	Genome Wide Association Studies
H2020	Horizon 2020
HA	Heath Authorities
HCP	healthcare professionals
HEOR	Health Economics and Outcomes Research
HFpEF	Heart Failure with preserved Ejection Fraction
HMGB1	high mobility group box 1
HIV	Human Immunodeficiency Virus
HNV	Healthy normal volunteer
HTA	Health Technology Assessment
I/O	Immunooncology
ICF	Informed Consent Forms
ICH	International Council for Harmonisation
ICI	Immune Checkpoint Inhibitor
ICT	Information and Communication Technology
IEFD	Intra-Epidermal Fiber Density
IF	Immunofluorescence
IHC	Immunohistochemistry
IMI	Innovative Medicines Initiative
IND	Investigational New Drug
IPCF	Informed Patient Consent Form
iPSC	Induced Pluripotent Stem Cell
IVD	In Vitro Diagnostics
LC-MS	Liquid Chromatography-Mass Spectrometry
LDT	Laboratory Developed Test
MAH	Marketing Authorisation Holder
MCSFR1	Macrophage Colony Stimulating Factor Receptor 1
MS	Management Services
MRC	Medical Research Council
MRI	Magnetic Resonance Imaging
MS status	Microsatellite status
mTOR	Mechanistic Target of Rapamycin
NASH	Non-alcoholic Steatohepatitis

ND4BB	New Drugs for Bad Bugs
NHVs	Normal Healthy Volunteers
NIH/NCATS	National Institute of Health/National Center for Advancing Translational Sciences
NMJ	Neuro Muscular Junction
OCT	Ooptical Coherence Tomography
PBMC	Peripheral blood mononuclear cell
PBPK	Physiologically Based Pharmacokinetics
PD	Parkinson's disease
PD-1	Programmed cell death protein-1 (CD279)
PD-L1	Programmed death-ligand 1 (CD274)
PK/PD/TD	Pharmacokinetic/Pharmacodynamic/Toxicodynamic
PLLR	Pregnancy and Lactation Labelling Rule
PMDA	Pharmaceuticals and Medical Devices Agency
PNS	Peripheral Nervous System
Pso	Psoriasis
PSTC	Predictive Safety Testing Consortium
PV	Pharmacovigilance
QC	Quality Controlled
R&D	Research and Development
RNA	Ribonucleic acid
RNAseq	RNA sequencing
RUO	Research Use Only
RWE	Real World Evidence
RWS	Real-world walking speed, gait speed in a home environment
SAB	Scientific advisory board
sCr	Serum creatinine
SGLT	Sodium Glucose Co-Transporter
SME	Small- and Medium-sized Enterprise
SNP	Single-nucleotide polymorphism
STE	Speckle Tracking Echo-cardiograph
SVM	Support Vector Machine
SWOT	Strengths, Weaknesses, Opportunities, Threats
T2DM	Diabetes Mellitus Type 2
Tg	Transgenic
TME	Tumour microenvironment
TBIL	Total Bilirubin
WHO	World Health Organisation
WP	Work package