IMI 2 - 3rd Call for proposals

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Introduction

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

- 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 report on priority medicines for Europe and the World (2013 update: http://www.who.int/medicines/areas/priority_medicines/en/).

The initiative should therefore seek to involve a broader range of partners, including mid-caps[2], from different sectors e.g. biomedical imaging, medical information technology, diagnostic and/or animal health industries (while ensuring gender matters are considered). 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) is the main reference for the implementation of research priorities for IMI2. Based on the SRA the 2014 scientific priorities for IMI2 have been prepared, which include themes on diabetes, psychiatric diseases, vaccines, and enabling technologies which are addressed in this call.

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

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

A template[3] is available to help applicants provide all the relevant information for the planned clinical studies. Use of this template is not mandatory and the necessary information for experts to evaluate the projects involving clinical trials can also be provided in the regular proposal template.

Before submitting a proposal, applicant consortia should familiarize themselves with all call documents such as the IMI2 Manual for evaluation, submission and grant award, and the IMI2 evaluation criteria. Applicants should refer to the specific templates and evaluation procedures associated with research and innovation actions (RIAs).

[1] The Council Regulation (EU) No 557/2014 of 6 May 2014 establishing the Innovative Medicines Initiative 2 Joint Undertaking.

[2] Under the IMI2 JU, mid-sized companies having an annual turnover of EUR 500 million or less, established in a EU Member State or an associated country, are eligible for funding.

[3] http://ec.europa.eu/research/participants/portal/doc/call/h2020/h2020-phc-2015-two-stage/1620124-essential_information_for_clinical_studies_2015callsv2_18082014_en.pdf

Topic 1: Remote Assessment of Disease and Relapse (RADAR) programme

Introduction to the RADAR Programme

Background and problem statement

With rising health-care costs, all health care stake-holders (payers, physicians, patients) are shifting the onus from a 'pay for intervention' to a 'pay for performance' model. This change in focus towards overall outcomes will drive a paradigm shift towards disease interception, i.e. move from a 'diagnose and treat' to a 'predict and pre-empt' approach. In this model, pre-emption, i.e. intervening early enough in the disease process to prevent serious effects of the disease associated with progression, becomes a critical component of managing chronic disease. Additionally, as the trajectory of chronic diseases is often cyclical, this offers multiple interception opportunities to prevent serious decline — for example, predicting and pre-empting recurrence/suicidality in severe depression, hypoglycaemic event in diabetes , or exacerbations in multiple sclerosis (MS), COPD or asthma.

Measuring physiological and activity-based parameters remotely and continuously via unobtrusive on-body sensors or smartphones has the potential to revolutionise our ability to predict and pre-empt harmful changes in disease trajectory. Developing methods for real-time identification of behavioural and physiological patterns (bio-signatures) that culminate in relapse is of great importance: early detection and communication of "red flags" to both patients, care-givers and providers can prompt help-seeking behaviour and deployment of just-in-time interventions that may prevent relapse episodes, effectively altering one's clinical trajectory.

A platform to acquire data in a real world setting would also enable the development of measures of real world effectiveness of medicines.

RADAR is a multi-topic programme in IMI2 that aims to overcome three key bottlenecks in developing such methods:

1) a lack of fundamental disease understanding into the signals and fluctuations in disease state;

2) the lack of clear policy, guidelines and pathways to develop and license "pre-emptive" therapeutic strategies that use such digital monitoring and remote assessment technology;

3) the maturity of the technology platforms including sensors technology, data exchange standards and the analytical methodology that mean that research is hampered by ad-hoc solutions that are not suitable to develop healthcare product.

Need and opportunity for public-private collaborative research

The RADAR programme aims to test if new pre-emptive therapeutic strategies based on remote continuous monitoring are both scientifically feasible and also practically feasible as part of a wider healthcare system.

Scientific feasibility will be performed via the individual topics of the RADAR programme to focus on the specifics of different disease areas. The first topic, detailed below, will study the fluctuation of the chronic diseases of depression, multiple sclerosis (MS) and epilepsy using remote monitoring technology to provide a foundation for developing a novel paradigm based on prediction and pre-emption. In the future, we intend to add other diseases to the CNS topic, such as pain and schizophrenia, and also add further topics in other disease areas such as airways disease and diabetes. Research in these areas needs to bring together physicians, patient groups, sensor manufactures, ICT providers, data management and analyst specialists with the pharmaceutical industry.

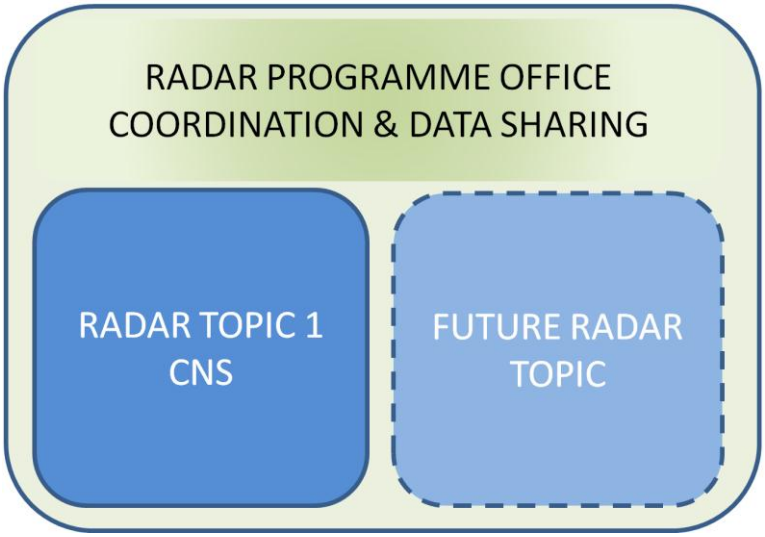
Introducing a therapeutic strategy based on such science and technology requires a second type of public private research to be undertaken to 1) develop policy for the regulatory and licensing pathways to deliver a digital intervention 2) understand and develop a framework to support new digital based interactions between patients and health care providers. This will require key stakeholders such as patient groups, regulators, healthcare providers, communications organisations, device manufactures and infrastructure providers to understand and develop a roadmap of how such interventions can be deployed effectively and safely.

Overall objectives of the RADAR programme

The key objective of the RADAR programme is to develop the foundational components to "Improve patient outcomes through remote assessment". These components will be split into several topics with some cross-cutting themes co-ordinated across all topics. Under IMI2 Call 3, one initial topic will be launched, with more topics added to the programme in the future.

Considering the overall objective of the RADAR programme, the actions stemming from the different topics will be deemed to be complementary[4] to each other. Consequently, the selected consortia will have to conclude collaboration agreements to coordinate their work under the different Grant Agreements.

RADAR programme architecture



The full RADAR programme will consist of several topics that are resourced and managed independently but will share key features such as data, technological approach and overall coordination. Under IMI2 Call 3, one initial topic will be launched in CNS.

RADAR programme office

A key element of the RADAR Programme is coordination across all RADAR topics. This will require applicants to reserve some resource to support the coordination across different topics.

4 Complementarity should be intended as having common objectives or activities as being part of a specific programme. As a minimum, the collaboration agreements must establish that complementary consortia:

- enjoy mutual participation in the actions' governance;
- share project reports;
- grant mutual access rights to projects' results.

RADAR-CNS

The RADAR-CNS project will use a common set of remote assessment technologies to investigate central nervous system based disorders such as depression, multiple sclerosis and epilepsy. This project will be accountable for delivering focused disease research as outlined in the detailed topic description.

As the RADAR-CNS topic includes multiple indications, a critical part of the project will focus on cross cutting themes such as policy and technology standards that are common to all of the disease areas and will be accountable for advancing these themes in collaboration with investigators from future RADAR topics. It is anticipated that elements such as the technology platform or regulatory expertise will be applied in later topics to accelerate and group these reusable experiences.

Future RADAR topics

At a later stage, the IMI2 JU may publish additional topics which will become part of the RADAR programme. In that respect, potential applicants must be aware that all or some of these additional topics, if so foreseen in the applicable annual work plan, and if exceptionally needed to enhance their results and achievements and facilitate the delivery of new treatments to patients, may be restricted to those projects already selected under this call by extending their duration and funding. Consortia will be entitled to open to other beneficiaries as they see fit to fill critical skills gaps in the consortia that reflected the extensions in these work plans.

General principles for all projects conducted under the RADAR programme

Data sharing

Data sharing is paramount to the success of the RADAR programme. The framework supporting this data sharing (i.e., the type of data to be shared and the access governing data sharing) will be fully established during the preparation of the full proposals in line with IMI2 IP policy and considering the overall approach agreed upon in the other RADAR projects. EFPIA members and consortia partners will be committed to sharing all data (clinical, bio-sensor, etc.) available to, or generated by the RADAR program amongst all members of a RADAR topic, and across topics as required. In addition to data, RADAR constituents will also share code, technology, learning and expertise developed in IT architecture, data management, usability, regulatory and policy pathways etc. across the RADAR program and externally as required by IMI policy and procedures.

Dissemination and data standards

The successful applicant consortium will be expected to adhere to the following principles, if inappropriate please provide rationale.

1) Disseminate scientific publications and research data on the basis of open access. Collection, processing and generation of research data is to follow documented data management procedures (see "Guidelines on Open Access to Scientific Publications and Research Data in Horizon 2020" and "Guidelines on Data Management in Horizon 2020"). In order to ensure adherence to the legislation concerning protection of personal data, controlled access digital repositories and data governance will need to be established.

2) IMI2 projects should use well-established data formats and content standards in order to ensure interoperability to quality standards. Preferably, existing standards should be adopted. Should no such standards exist, consideration should be given to adapt or develop novel standards in collaboration with a data standards organization (e.g. CDISC).

RADAR Topic 1: CNS

Topic details

Topic code	IMI2-2015-03-01
Project type	Research and innovation action (RIA)
Submission & evaluation process	2 stages

Background and problem statement

Severe mood disorders (major depression, bipolar disorder) are highly prevalent, chronic, and disabling diseases, with depression alone affecting an estimated 121 million people worldwide. Ranking first in terms of disease burden, as measured by disability adjusted life years (DALYs) in North America and Europe, mood disorders are far ahead of other serious conditions such as ischemic heart disease, chronic obstructive lung disease, and lung cancer.[5] The World Economic Forum (2011) has calculated that mental illnesses will represent the costliest diseases globally in the next two decades (2011-2030), exceeding the cost of cancer, diabetes, and chronic obstructive pulmonary diseases combined. Additionally, neuro-degenerative diseases that include multiple sclerosis (MS), Alzheimer's disease, Parkinson's disease and associated disability and dementia are fast becoming one of the leading challenges for health-care systems due to rapidly aging demographics. For example, the most recent Dementia 2014 report indicates that currently dementia alone costs EUR 33.5 billion a year, whereas a 2013 RAND report[6] put the cost of caring for dementia patients as exceeding the treatment costs due to cancer and heart disease. It should be noted that, in addition to direct costs to healthcare systems, CNS diseases inflict an unprecedented cost and burden on care-givers and family members.

The RADAR-CNS proposal seeks to address/utilise two important aspects of CNS diseases. Firstly, most CNS diseases are dynamic in nature with multiple reoccurrences and relapses each of which accelerate the downward spiral of the underlying disease pathology and lead towards chronification, morbidity and mortality. Secondly, the onset of reoccurrences, exacerbations and relapses in CNS disease causes changes in parameters related to sleep, physical activity, speech, cognition, social connectivity, memory etc.; parameters that can increasingly be measured remotely and passively via unobtrusive on-body biosensors and smartphones. The vision of RADAR-CNS is to reduce cost and trauma to the patient and care-givers and reducing hospitalisations by predicting and pre-empting relapses and reoccurrences via the use of remote assessment technologies. RADAR-CNS will focus initially on unipolar depression, multiple sclerosis (MS) and epilepsy with the main goal of using available clinical information and streaming data from on-body sensors to predict relapse, symptom exacerbations and seizures respectively. Initial RADAR diseases were selected on the basis of unmet need in terms of prevalence, disability caused, feasibility of developing a remote bio-signature predictive of a change in disease state, and the therapeutic interests of contributing EFPIA companies. Depression, MS and epilepsy are prevalent, disabling conditions that effect all age-groups, and are characterised by rapid and distinct changes in disease states at varying time-scales that, if predicted and pre-empted, would result in significant improvement in overall patient outcomes. Furthermore, depression and MS are often co-morbid in a patient, thus offering opportunities to study both diseases in a common population. It should be noted that learnings in terms of sensor development, data management, analytics, privacy, regulatory and health-care policy issues etc. will transfer to other disease areas in this topic. Indeed, the long-term goal is to build upon the learning of the first three diseases and in the future include other disease areas such as bipolar disease, Alzheimer's disease, schizophrenia and pain.

[5] WHO report on Global Burden of Disease

[6] N Engl J Med 2013; 368:1326-1334April 4, 2013DOI: 10.1056/NEJMsa1204629

Need and opportunity for public-private collaborative research

RADAR and RADAR-CNS represent an intersection between diverse areas ranging from telecommunications, bio-sensors, devices, mobile computing, streaming analytics to clinical care, diagnostics and therapeutics development. As such, progress in this area will require cooperation and partnerships between multiple entities from diverse industries and academia. Furthermore, this lies outside the core area of expertise and focus for the pharmaceutical industry, as it does for the telecom/sensor industry and academia. While many projects are already underway in individual disciplines, cross-disciplinary collaborations such as RADAR are not just desirable, but essential, to ensure these rapidly developing technologies can be integrated with clinical and regulatory pathways to make a difference to the day to day lives of patients.

RADAR-CNS objectives

The aim of RADAR-CNS is the characterisation and prediction of changes in disease state in central nervous system (CNS) disorders via non-invasive remote sensing.

This topic is planned to be focused on the three diseases of unipolar depression, multiple sclerosis and epilepsy. For each disease it is proposed that a non-interventional/observational study of subjects is undertaken with three objectives:

- Characterisation of changes in disease state.
- Characterisation of changes in disease state due to drug effects.
- Prediction of change in disease state from remote sensing data.

To co-ordinate across all three disease areas a common set of measures and measurements tools will be used to track the sleep architecture, physical activity, speech, cognition, social connectivity, and memory of subjects of all of the target diseases. We also intend to take advantage of the fact that depression has a high rate of co-morbidity with both MS and epilepsy, and intend to recruit a population that has overlapping morbidity between depression, MS and epilepsy such that we have patients representing each disease as a primary indication, as well as patients who are co-morbid with more than one disease. The overall goal would be to design an observational study, in collaboration with our consortia partners that maximises the power to detect bio-signatures of disease state change and relapse, as well as assess other important considerations such as patient acceptance of wearable devices, adherence, usability and data management.

Potential synergies with existing consortia

Applicants should take in consideration any initiatives already on-going in this field, both in Europe and globally. Synergies with such consortia should be explored to build on their achievements, and to incorporate, when possible, data and lessons learnt, while avoiding unnecessary overlapping and doubling of efforts.

Expected key deliverables

1) Candidate bio-signatures that predict relapse and track disease state changes in MS, depression and epilepsy using at least a common minimal set of metrics: **sleep architecture, physical activity, speech, cognition, social connectivity, and memory.**
2) Development of algorithms and an analytic infrastructure suitable for collecting and analysing data from the RADAR-CNS studies.
3) Proposal of actionable privacy and usability parameters that would drive eventual uptake of, and adherence to, remote assessment solutions in CNS diseases.
4) Delineation of putative regulatory pathways necessary for approval of remote sensing solutions in real-world patients. This deliverable will be developed in consultation with regulators.
5) Delineation of putative clinical care pathways and use cases of remote-sensing solutions and how they impact and interface with stake-holders such as patients, care-givers, case-managers,

physicians etc. This deliverable will be developed in consultation with relevant external stake-holder groups (see above).

Industry consortium

Industry consortium members will bring the following assets and skills to the project:

1) Clinical/ regulatory expertise: Janssen, Lundbeck, BiogenIdec and UCB have years of experience developing therapeutics in CNS disease areas, and will bring expertise related to clinical study design execution and regulatory approval pathways.
2) Clinical data: Industry members will be bringing bio-sensor, clinical and patient self-report data collected in observational studies in relevant patient populations.
3) Data capture/ data management/ analytics/ data mining: Industry consortia members will bring expertise in data management and data-mining through our internal IT and informatics groups.
4) Devices: Industry partners will also bring devices to measure actigraphy, stress (galvanic skin response), cognition and other relevant parameters.

Full details regarding the above contributions will be provided in the full proposal.

EFPIA participants

Janssen, BiogenIdec, UCB, Lundbeck, Merck.

Indicative duration of the project

The indicative duration of the project is 5 years.

Indicative budget

The indicative contribution from EFPIA companies is EUR 11 000 000. Due to the global nature of the participating industry partners it is anticipated that some elements of the contributions will be non EU in kind contribution.

The financial contribution from IMI2 JU will be a maximum of EUR 11 000 000.

Future project expansion

Potential applicants must be aware that the IMI2 JU may publish at a later stage another call for proposals restricted to those projects already selected under this call, if exceptionally needed to enhance their results and achievements and facilitate the delivery of new treatments to patients, by extending their duration and funding. Consortia would then be entitled to open to other beneficiaries as they see fit.

In the context of this topic, such a call could allow the incorporation of other CNS disease areas such as bipolar disease, Alzheimer's disease, schizophrenia and pain. The detailed scope of the call would be described in the relevant annual work plan.

Applicant consortium

Applicant consortium will be multi-disciplinary. We expect device and sensor companies to bring the latest remote assessment technologies that could be further developed or modified for use as intended in CNS diseases. Academic, clinical and disease area experts will help to design the clinical study (end-points, inclusion criteria etc.) and interpret results for clinical significance. IT/ analytics partners will help develop data management architecture, state-of-the-art algorithms to derive bio-signatures of symptoms and relapse from

collected streaming data. Regulatory and health-care systems experts will help define regulatory and clinical-care pathways respectively for the remote assessment solutions. All consortia partners are expected to actively participate in publications to raise awareness and gather further input from the larger scientific community.

Suggested architecture of the full project proposal

We suggest that the RADAR-CNS consortium be organized in the following architecture, though the application consortium is free to propose alternative models, with justification, if they consider them superior.

Work package: Clinical studies

This work package will include the design and execution of the clinical programme of the RADAR-CNS project including protocol development, ethics submission, the operations of clinical observational studies that will include diagnosis and symptom data from physician visits, remote continuous data from wearable devices and other self-reported measures. The exact design of the clinical studies will be developed in consultation with the consortium partners, however, as previously noted, depression and MS are often co-morbid and our goal would be to study these diseases independently, as well as in the same patients to optimize overall study size. Epilepsy will likely be studied in a smaller cohort more focussed on validating and improving existing predictors of seizures. The final allocation of resources between disease clinical studies as well as sensor development and other work-packages will be finalized in consultation with the consortium partners and will reasonably reflect the interests and relative contributions of EFPIA partners.

Work package: Data capture & remote assessment technologies

This work package will be responsible for the remote assessment technology platform that is to be used to measure the core metrics of **sleep architecture, physical activity, speech, cognition, social connectivity, and memory** of subjects across all disease area. This will include preparing and operating the platform in support of the clinical trial and providing data for the data analysis work package. This work package is also responsible for developing the appropriate privacy policies and collaborating with privacy and technology such groups in future RADAR programme topics.

Work package: Data analysis and bio signatures

This work package will be responsible for the analysis of data collected in the clinical trials and identifying candidate bio-signatures of symptoms and relapse. This work package is responsible for the collaborating with the appropriate groups in future RADAR programme topics regarding methodology development.

Work package: Healthcare pathways

This work package will be responsible understanding both the regulatory and healthcare pathways that would enable the use of bio-signatures of disease and relapse to be used in a real world healthcare setting. This work package is responsible for the collaborating with the appropriate groups in future RADAR programme topics regarding regulatory and health care engagement.

Topic 2: Assessing risk and progression of prediabetes and type 2 diabetes to enable disease modification

Topic details

Topic code	IMI2-2015-03-02
Project type	Research and innovation action (RIA)
Submission & evaluation process	2 stages

Background and problem statement

The incidence of type 2 diabetes is increasing at epidemic proportions. The resulting disease burden of diabetes substantially increases morbidity and mortality for citizens in nations within the European Union and worldwide, augments health care expenditures, and reduces economic productivity.

Current therapies for type 2 diabetes largely focus on the control of blood glucose levels rather than the modification of the disease. To attenuate the epidemic rise in the incidence and progression of type 2 diabetes, additional therapeutic approaches will be needed. Multiple gaps exist to enable feasible and successful development of novel therapeutic approaches to either 1) prevent the progression of prediabetes to type 2 diabetes and/or 2) to delay or prevent disease progression in individuals diagnosed with type 2 diabetes. More robust delineation of clinical risk factors, phenotypes, and molecular biomarkers is needed to identify which individuals with prediabetes are at risk for rapid progression to type 2 diabetes for disease prevention therapeutic intervention trials. More intensive phenotyping of individuals with type 2 diabetes is needed to characterize rates of disease progression and to identify and validate biomarkers and/or indicators of “rapid failure” of insulin-producing pancreatic beta cells and of cellular targets of insulin-mediated glucose disposition, including hepatocytes, skeletal muscle, and adipocytes. Validation of robust markers of type 2 diabetes disease progression would facilitate patient segmentation for feasible assessments of new therapeutic options for disease modification. Biomarkers discovered in diabetes-related IMI1-sponsored consortia should be leveraged to support the opportunity within IMI2 for biomarker prioritization, selection, and high throughput assay implementation to enable drug development for diabetes disease modification. Following the future discovery, development, and regulatory approval of effective disease-modifying drugs for diabetes, new patient screening methods will need to be developed and integrated into clinical practice to support appropriate access to therapeutic and public health benefits.

Need and opportunity for public-private collaborative research

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 molecular mechanisms of disease, biopharmaceutical companies which endorse the approach and have a complementary experience and expertise, as well as regulators. This is a program which cannot be successfully administered by an individual research group or company but will require a broad consortium to be successful.

a. Pharmaceutical companies contribute expertise in diabetes drug discovery and development, including understanding of regulatory, economic, and logistical challenges facing drug development for disease prevention and modification. Companies bring unique expertise in biomarker discovery, data analysis, assay development, and prospective clinical trial design.

b. Academic investigators contribute expertise in a range of methods to discover and validate molecular phenotypic biomarkers from human tissues and biofluids, to assess clinical phenotypes, and to

analyze the relationship of molecular phenotypic biomarkers with clinical evaluation of disease progression.

c. Hospitals, clinical research centers, and practicing physicians with access to patients with prediabetes and type 2 diabetes contribute understanding of epidemiology, pathophysiology, clinical and biochemical phenotypes and provide bio banked samples that may be used in combination with novel molecular biomarkers to predict type 2 diabetes disease progression.

d. Patients donate biofluid or tissue samples and participate in clinical research studies to enable more precise molecular understanding of prediabetes and type 2 diabetes.

e. Biotechnology and diagnostics companies facilitate development of high throughput biomarker assays and access to unique technologies.

f. Regulatory authorities contribute expertise in diabetes drug evaluation and approval to enable innovative approaches for developing new therapies for disease prevention or modification in type 2 diabetes.

g. Health care payers and economists provide important perspectives to evaluate the economic impact and value of preventing the onset or delaying the progression of type 2 diabetes.

Overall objectives

The overall aim of the project is to discover and validate a molecular taxonomy of type 2 diabetes to enable feasible patient segmentation, clinical trial design, and regulatory paths for diabetes prevention and for modification of diabetes disease progression.

To fulfil this aim, the following project objectives are proposed:

1) to prioritize and/or validate a panel of human biomarkers or assays of pancreatic beta cell function, stress, mass, and death to enable prospective selection of *a)* subjects with rapid progression from prediabetes to type 2 diabetes and *b)* type 2 diabetes subjects with accelerating pancreatic beta cell dysfunction.

    - Biomarker validation component should explore and assess available predictive biomarkers identified from existing IMI1 diabetes-related consortia (i.e., IMIDIA, SUMMIT, DIRECT, EMIF, StemBanCC), from other cohorts, from published literature, and from discovery studies within this project
    - Biomarker discovery component should leverage a range of technologies including targeted and non-targeted biochemical biomarker discovery in human tissue and/or fluid samples, genomic biomarkers accessible in clinical trials, imaging biomarkers indicative of changes in cellular functions and/or tissue structure, and biomarker discovery from selected preclinical models
    - Validated biomarker panels should encompass multiple mechanisms of pancreatic beta cell stress that may contribute to disease progression, for example oxidative stress, ER stress, nutrient stress, impaired adaptation to changing insulin resistance, apoptosis, and autophagy.

2) to prioritize and/or validate a panel of human biomarkers or assays of hepatic, skeletal muscle, and/or adipose cellular dysfunction derived from or contributing to progression of insulin resistance that enable prospective selection of a) subjects with rapid progression from prediabetes to type 2 diabetes and b) type 2 diabetes subjects with accelerating type 2 diabetes disease progression.

    - Biomarker validation component should explore and assess available predictive biomarkers identified from existing IMI1 diabetes-related consortia (i.e., IMIDIA, SUMMIT, DIRECT, EMIF, StemBanCC), from other cohorts, from published literature, and from discovery studies within this project.

- A range of technologies should be leveraged to assess human samples, ex vivo models, and selected preclinical models to generate a validated biomarker panel reflective of multiple mechanisms of pathophysiology of insulin resistance, including biomarkers reflective of hepatic, skeletal muscle, and adipose cellular dysfunction.

- Biomarker discovery component should emphasize human tissue and/or body fluid biomarkers predictive of environmental contributions to disease progression, including microbiome, toxin exposure, dietary exposure, exercise, and epigenome.

3) to develop innovative potential regulatory approaches in collaboration with regulatory experts, including adaptive clinical trial designs, enabling feasible and robust benefit/risk assessments in clinical trials for a) therapeutic intervention in prediabetes to prevent or delay onset of type 2 diabetes and b) therapeutic interventions in type 2 diabetes for disease modification to reduce the rate of disease progression

4) to model short- and long-term economic and public health morbidity and mortality benefit/risk assessments of a) therapeutic intervention in prediabetes to prevent or delay onset of type 2 diabetes and b) therapeutic interventions in type 2 diabetes for disease modification to reduce the rate of disease progression.

- Modeling should engage multidisciplinary teams of patient advocates, health care economists, and health care payers.

Potential synergies with existing consortia

When developing their short proposal, applicants should take into consideration that there are already several initiatives on-going in the field, both in Europe and globally.

Synergies and complementarities should be considered, building from achievements, and incorporating when possible data and lessons learnt, while avoiding unnecessary overlapping and doubling of efforts.

This project is intended to provide the opportunity within IMI2 to leverage substantial diabetes-related biomarker discovery from multiple IMI1 projects, including IMIDIA, SUMMIT, DIRECT, EMIF, and StemBanCC. Through the data integration work package, this consortium may also enable hosting of secure data repositories of accessible, integrated IMI1 and IMI2 diabetes-related project data. In addition the consortium seeks to leverage research findings, phenotyping, and bio specimens from multiple existing and emerging prediabetes and diabetes longitudinal cohorts, for example, UK Biobank, EU 7th framework supported programs, Interconnect, and EFPIA-sponsored clinical trials.

Collaboration by design should be a cornerstone of the proposed strategy.

Expected key deliverables

- Validation and/or discovery of human phenotypes and biomarker panels predictive of rapid declines in pancreatic beta cell health and function that enable prospective identification of *a)* “rapid progressors” from prediabetes to type 2 diabetes and/or *b)* accelerating type 2 diabetes disease progression for clinical trial recruitment

- Validation and/or discovery of human phenotypes and biomarker panels predictive of rapid declines in insulin action-targeted hepatic, skeletal muscle, and/or adipose cellular functions that enable prospective identification of *a)* “rapid progressors” from prediabetes to type 2 diabetes and *b)* acceleration of type 2 diabetes disease progression for patient identification for clinical trial recruitment or therapeutic intervention

- Prioritization and selection of robust phenotypes and biomarker panels that enable feasible prospective patient segmentation/selection, clinical trial design and regulatory paths to assess new therapeutic options for prevention of *a)* progression from prediabetes to type 2 diabetes and *b)* acceleration of type 2 diabetes disease progression

- Development of new regulatory approaches or standards enabling innovative and feasible clinical trial designs for disease modification in patients with prediabetes or type 2 diabetes

- Models for public health benefit and economic impact of therapeutic intervention to prevent or delay progression from prediabetes to type 2 diabetes

Industry consortium

- Pharmaceutical companies
- Technology and diagnostic providers

EFPIA participants

Lilly (Project- leader), Servier (Project –Co-leader), Janssen, Novo Nordisk, Sanofi

Indicative duration of the project

The indicative duration of the project is 4 years.

Indicative budget

The indicative contribution from the EFPIA companies is estimated at a total of EUR 8 130 000. 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 indicative IMI JU contribution will be up to EUR 8 130 000.

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 call, if exceptionally needed to enhance their results and achievements and facilitate the delivery of new treatments to patients, by extending their duration and funding. Consortia would be entitled to open to other beneficiaries as they see fit.

In the context of this topic, a second phase would most likely have a duration of 3 years and would only be initiated after a futility analysis of the progress of phase 1 and if certain milestones have been passed that justify a Phase 2 of the project to expand knowledge by implementing prospective prevention clinical studies to assess the potential for approved medication(s)

a. to prevent the progression of prediabetes to type 2 diabetes:

    - including assessment of predictive value of biomarkers and clinical assays used for prospective selection or for surrogate markers of disease progression of subjects with prediabetes most likely to rapidly progress to type 2 diabetes

b. to prevent the acceleration of disease progression and worsening of pancreatic beta cell and other cellular function in subjects with type 2 diabetes:

- including assessment of predictive value of biomarkers and clinical assays used for prospective selection or for surrogate markers of disease progression of type 2 diabetes subjects with rapidly accelerating disease progression

A restricted call would allow achieving this in the most efficient way by timely building on the progress and outcomes of the deliverables. The detailed scope of the call for the second phase of the project would be described in the relevant annual work plan.

Applicant consortium

The applicant consortium is expected to address all the research objectives and make key contributions on the defined deliverables in synergy with the industry consortium. This may require to mobilise, as appropriate, expertise in: basic, translational, clinical research; regulatory aspects; economic or public health modelling; as well as project management.

Applicant investigators should include complementary expertise in biomarker discovery and clinical assay implementation across the range of relevant technologies, in human pancreatic beta cell, hepatic, muscle, and adipose biology, in conducting intensive clinical phenotyping of prediabetes and type 2 diabetes patients, and in prospective and retrospective assembly and assessment of large longitudinal cohorts and biobanks from subjects with prediabetes and type 2 diabetes. Applicant investigators should have confirmed access to retrospective cohort collections of biospecimens for use in biomarker discovery and validation.

Investigators should leverage existing retrospective cohorts and collaborations with ongoing studies of individuals with prediabetes and with type 2 diabetes that include clinical phenotype data, biomarker data, longitudinal outcomes data, and available biobank biofluids and/or tissues. These cohorts must be appropriately consented to enable additional biomarker discovery or validation. Individual investigators within the applicant consortium should have a proven track record of productive and highly collaborative basic, translational, and/or clinical research with enthusiasm for working in interconnected private-public research teams. The consortium should also anticipate that results and resources generated by this project will likely interface with and/or be made available to other type 2 diabetes-related projects within the IMI1 and IMI2 frameworks.

Valuable assets that the applicants could provide include:

- Relevant existing datasets and existing clinical studies
- Relevant longitudinal clinical cohorts and registries
- Relevant biobanks and bio-samples
- Involvement of patient organizations and appropriate ethical considerations

Suggested architecture for the full project proposal

The following outline of the architecture for the full proposal is a suggestion; different innovative project designs are welcome, if appropriate.

WP1. Administration, management, and communications

- Provide professional consortium management support
- Secure and facilitate access to data from previous IMI1 consortia
- Foster collaborations and external communications

WP2. Data integration, analysis, and informatics

- Mine and integrate accessible dynamic databases from IMI1 and other available diabetes-related projects
- Identify external biomarkers from literature and other consortia for validation
- Integrate, maintain, and analyze data generated within the consortium

WP3. Pancreatic beta cell predictive biomarker discovery, prioritization, selection, and validation in human samples, ex vivo models, and pre-clinical models reflective of diabetes-related beta cell functions and phenotypes from

- the local islet environment and
- beta cell signalling interactions with other organs
- systemic effects detectable in body fluids

WP4. Insulin action target cell predictive biomarker discovery, prioritization, selection, and validation in human samples, ex vivo models, and pre-clinical models reflective of diabetes-related cellular functions and phenotypes from the following tissues

- liver, including hepatic nutrient handling, NASH, and NAFLD phenotypes
- skeletal muscle
- adipose
- systemic effects detectable in body fluids

WP5. Assays and technologies development

- High throughput assays established to enable convenient and robust use in clinical trials
- Novel technologies leveraged for cellular phenotyping, i.e., innovative imaging
- Diagnostic test development enabled for patient selection for clinical trials and therapeutic intervention

WP6. Regulatory consensus for diabetes disease modification

- Implement a dialogue platform with the European Medicines Agency (EMA) and other non EU regulators, industry, and academic partners
- Enable the development of operational definitions, qualification of biomarker panels and innovative regulatory tools for addressing the challenge of prevention of diabetes or to delay the progression of T2DM, which is an unmet medical need in the aging European population
- Utilise retrospective data to refine population definitions and validate relevant study endpoints

WP7. Modelling economic and public health impact of disease modification

- Explore potential cost effectiveness, cost utility, and economic impact of innovative prediabetes or T2DM disease modification interventions

- Engage a European network of health economists to develop consensus on economic needs for innovative clinical interventions for disease modification in diabetes

- Communicate economic consensus results to decision- and policy-makers

The applicant consortium partners that will provide data and samples from existing study cohorts and registries need to demonstrate in their application that those envisaged resources can be shared among all the partners. Thus the applicants have to document in their short proposal that applicable ethical and data privacy laws allow sharing such data and samples within the consortium.

In addition a plan for interactions with Regulatory Agencies/ Health Technology Assessment bodies with relevant milestones and appropriate resource allocation should be built into the project architecture as well as aspects related to dissemination and sustainability, facilitating continuation beyond the duration of the project.

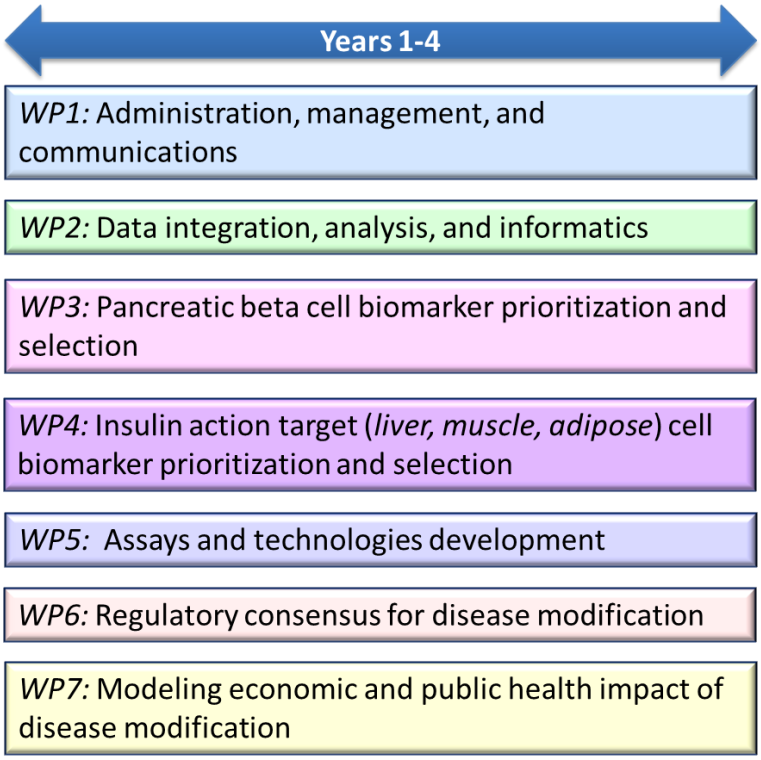
The applicants are requested in their short proposal to consider:

1) Disseminate scientific publications and research data on the basis of open access. Collection, processing and generation of research data is to follow documented data management procedures (see "Guidelines on Open Access to Scientific Publications and Research Data in Horizon 2020" and "Guidelines on Data Management in Horizon 2020"). In order to ensure adherence to the legislation concerning protection of personal data, controlled access digital repositories and data governance will need to be established.

2) Use well-established data format and content standards in order to ensure interoperability to quality standards. Preferably existing standards should be adopted. Should no such standards exist, consideration should be given to adapt or develop novel standards in collaboration with a data standards organization (e.g. CDISC).

Note: Data collection and data management should be conducted according to established data standards and/or in collaboration with a data standards organization (e.g. CDISC), to develop new data standards if no established data standards exist.

Proposed architecture of the full project proposal



Topic 3: Linking clinical neuropsychiatry and quantitative neurobiology

Topic details

Topic code	IMI2-2015-03-03
Project type	Research and innovation action (RIA)
Submission & evaluation process	2 stages

Background and problem statement

The nosology of neuropsychiatric disorders has historically been entirely based upon a clustering of a variety of behavioural symptoms occurring over time using systems such as DSM and ICD. This approach has weaknesses but has allowed a pragmatic approach to treatment choice, regulatory and clinical research processes. However, as a consequence pharmacological research has tended to attempt to identify new drug targets by linking given biological phenomenon to a psychiatric "diagnosis". The fact that psychiatric diagnoses are only descriptive, without biological rationale, has rarely been properly considered.

Almost as a consequence, the development of novel pharmacological treatments for neuropsychiatric disorders has stagnated over the last two decades. This statement holds true across the whole field; cognitive decline in dementia, the control of psychosis, affect etc. The chronicity of these disorders, which is partly a result of lack of specific neuropsychiatric medications, results in a major burden for patient and society. In addition to the need to treat traditional psychiatric patient groups we have an aging population. This group also presents with more complex pathologies and comorbid conditions thus the need for accurate diagnosis, treatment selection and novel therapeutics will become increasingly important and complex. Indeed, if the current efforts to develop disease modifying approaches are successful then these challenges will be faced by potentially a dramatically larger, longer surviving patient population. To reverse this stagnation a new approach is required.

It is a truism, but one rarely voiced, that drugs affect biological substrates not symptoms. Further, that a specific symptom or cluster of symptoms, in different individuals may stem from different aberrant biologies. For instance both in dementia and schizophrenia aberrant cognition, psychosis and affect are observed. These have different presentations but little has been quantified as to the theoretical biology differences. Improved rational prescription of existing compounds, quantitative diagnosis and measurement of treatment response, identification of novel therapeutic hypotheses and hence the development of improved treatment options would all be facilitated by the development of an aetiological, or quantitative biology-, based taxonomy of these disorders.

The development of a quantitative biological approach to the understanding and hence classification of neuropsychiatric diseases should significantly facilitate more successful drug discovery and development. This approach starting from a defined set of symptoms would drive to a quantitative biologic description. Implicitly this would identify the appropriate tools and lead finally to an enhanced diagnostic framework. By linking behavioural symptoms to a quantitative biology the identification of maladaptive brain circuitries, molecular changes, disease stage and genetic risk regardless of any existing disease classification should all be significantly improved. A developing understanding of the biological substrates is thus expected to lead to translatable, quantifiable biomarkers or endophenotypes that allow us to effectively treat the right patient population.

The aim of this call is to initiate the process that is needed to move towards a quantitative biology based framework for neuropsychiatry disorders. This is timely both to reverse the stagnation in the development of treatments for classical psychiatric disorders, but also to address the challenges offered by the need to treat neuropsychiatric issues associated with the increasing burden of neurodegenerative disease.

To complete a systematic quantitative biological review for the whole spectrum of neuropsychiatry is a vast undertaking. This proposal therefore concentrates on providing a structure and framework for the approach while encouraging a focus on two or three areas in the first iteration. Purely for example a proposal might be structured to explore two from; agitation, psychosis, cognition or apathy in Alzheimer's and schizophrenia. This will ensure that proposals can be judged to have realistic aspirations and achievable objectives leading to lasting utility within the time and with resources available.

Need and opportunity for public-private collaborative research

The magnitude of the issue of reclassifying disorders 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 molecular mechanisms of disease, biopharmaceutical companies which endorse the approach and have a complementary experience and expertise, as well as regulators. The potential technical expertise required is likely to involve a broad multidisciplinary consortium bringing together, for example, knowledge and longitudinal samples in "omics", imaging, cognitive and behavioural neuroscience, neuropsychopharmacology, as well as translational, experimental medicine and clinical statistics, bioinformatics and health economics. This is a program which cannot be successfully administered by an individual research group or company but will require a broad consortium to be successful. Paving the way for a new classification by focusing on neuropsychiatric symptom constellations and identifying their biological correlates will lead to an understanding and hence classification of neuropsychiatric diseases which will allow a stratification of patients to enable patient tailored treatment. The project should significantly facilitate more successful drug discovery and development by identification of new hypotheses for therapeutic intervention for specific symptoms.

Overall objectives

The basic concept of the proposal would be to explore, starting from one or more selected symptom constellations, the same set of quantifiable biological parameters across two or more distinctly classified patient groups. Any resultant framework would have the significant potential to alleviate patient burden by improving understanding of biological aetiology of disease, guiding therapeutic decisions and provide novel entry points for treatment development. These studies would be driven from clinical quantitative biology back through appropriate translation to the measurement of homologous pre-clinical quantitative biological indices.

The aims being to:

- Identify and validate clinically relevant biological substrates of neuropsychiatric symptom constellations through the use of quantitative technologies. These might include but are by no means restricted to: Electroencephalography (EEG) (evoked responses, sleep), functional Magnetic Resonance Imaging (fMRI), quantitative neuropsychological testing, Magnetoencephalography (MEG), peripheral biomarkers. A subset of the all possible domains and clusters will be chosen to focus the project in the first instance.

- Identify the best predictive systems- clinical, non-clinical and pre-clinical - for the exploration of the underlying biological process and the identification and development of novel therapies or targets.

- Generate tools that have a beneficial effect on healthcare costs by, for example, enabling more effective identification of the right patient for a given treatment of a specific symptom constellation.

- Pave the way for a new classification by focusing on neuropsychiatric symptom constellations and identifying their biological correlates.

- Provide sufficient proof-of-principle evidence to begin engagement with the regulatory authorities

Potential synergies with existing consortia

In the development of their short proposal, Applicants should consider potential synergies and complementarities with other relevant initiatives, both in Europe and globally, building from achievements, and incorporating when possible data and lessons learnt, while avoiding unnecessary overlapping and doubling of efforts.

Collaboration by design should be a cornerstone of the proposed strategy. Synergies may be sought among others with other ongoing IMI initiatives, (e.g. AETIONOMY, NEWMEDS, EU-AIMS, StemBanCC and EBISC) with other European research projects investigating neurobiological mechanisms of psychiatric disorders as well as European research infrastructure initiatives and non-European initiatives such as the US-National Institute for Mental Health (NIMH), supported Research Domain Criteria (RDoC) Initiative (http://www.nimh.nih.gov/research-priorities/rdoc/nimh-research-domain-criteria-rdoc.shtml).

As much of the framework depends upon the emerging technologies there is a key need to explore synergies with technically orientated companies such as those providing imaging. The initiative could well deliver significant advances in our understanding of “best practice” in the use of these technologies.

Expected key deliverables

- Starting from patients selected by symptom identification of a set of quantitative biological parameters/markers, to allow comparison both between symptom domains and across diseases, for each symptom constellation.
- Analysis of the wide range of parameters measured in this experimental context would aim towards selection and validation of a pragmatic subset useful in everyday diagnosis. These new tools/markers would allow stratification of patients to facilitate more effective treatment and design of clinical trials, including the standardisation of measurement across sites.
- Establish a network of clinical research sites able to perform high quality observational studies in neuropsychiatric syndromes beyond the established classification systems.
- Establish a network of pre-clinical research sites able to perform high quality translatable studies to explore the substrates identified as causal in the clinical studies. The tools validated in the study would also then transferable to general use beyond the initial network.
- Identification of new hypotheses for therapeutic intervention for specific symptom constellations.
- Interaction with regulators and to prepare the regulatory path for acceptance of new metrics and approaches

Industry consortium

- Pharmaceuticals
- Medical imaging and electrophysiology
- Experimental medicine providers
- Statistics and data mining

EFPIA participants

Lilly (Co-coordinator), Boehringer-Ingelheim (Co-coordination), Lundbeck, Pfizer, Novartis, Roche and Takeda.

Indicative duration of the project

The indicative duration of the project is 3 years.

Indicative budget

The indicative contribution from the EFPIA companies is estimated at a total of EUR 8 080 000. 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 indicative IMI JU contribution will be up to EUR 8 080 000.

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 call, if exceptionally needed to enhance their results and achievements and facilitate the delivery of new treatments to patients, by extending their duration and funding. Consortia would then be entitled to open to other beneficiaries as they see fit.

In the context of this topic, a second phase would most likely have a duration of 2 years and would only be initiated after a futility analysis of the progress of collecting data from human subjects but also the progress in the preclinical work package and if certain milestones have been passed that justify a Phase 2 of the project to expand knowledge and to increase statistical power. A restricted call would allow achieving this in the most efficient way by timely building on the progress and outcomes of the deliverables. The detailed scope of the call would be described in the relevant annual work plan.

Applicant consortium

The applicant consortium is expected to address all the research objectives and make key contributions on the defined deliverables in synergy with the industry consortium. This may require to mobilise, as appropriate, expertise in: statistics and study design; clinical study support; IT – Data communication and data basing; quantitative clinical technologies and biomarkers; pre-clinical technologies that are aligned with those identified for use clinically; regulatory expertise translational medicine expertise; and project management. It may also require to mobilise, as appropriate, following resources: existing datasets and existing clinical studies; clinical cohorts and registries; biobanks and bio-samples; engagement of SMEs able to contribute relevant technologies; and involvement of patient organizations and its ethical considerations.

Suggested architecture of the full project proposal

As currently envisaged it is anticipated that the consortia would select two or three symptom constellations, or domains that should be widely present in most disorders, neuropsychiatric and degenerative, therefore if biological substrates were confirmed these would translate in many areas. The following offer examples that would provide the best chance of recruitment of appropriate subjects and reverse translation to pre-clinical approaches:

- Cognition (Working memory, Episodic, Reasoning and Problem solving, Attention), Reward, Stress, Affect, Agitation, Perception and sensory processing.

Appropriate study cohorts of patients could stem from disease populations, for which selected symptom domains are described, such as:

- Neurodegenerative diseases, Alzheimer's disease, Parkinson's disease or FTLD
- Affective disorders such as Major Depressive Disorder/Treatment Resistant Depression or Schizophrenia.

The applicant consortium partners that will provide data and samples from existing study cohorts and registries need to demonstrate in their application that those envisaged resources can be shared among all

the partners. Thus the applicants have to document in their short proposal that applicable ethical and data privacy laws allow sharing such data and samples within the consortium.

In addition a plan for interactions with Regulatory Agencies/Health Technology Assessment bodies with relevant milestones and appropriate resource allocation should be built into the project architecture as well as aspects related to dissemination and sustainability, facilitating continuation beyond the duration of the project.

The successful applicant consortium will be expected to adhere to the following principles, if inappropriate please provide rationale in the short proposal:

1) Disseminate scientific publications and research data on the basis of open access. Collection, processing and generation of research data is to follow documented data management procedures (see "Guidelines on Open Access to Scientific Publications and Research Data in Horizon 2020" and "Guidelines on Data Management in Horizon 2020 "). In order to ensure adherence to the legislation concerning protection of personal data, controlled access digital repositories and data governance will need to be established.

2) Use well-established data format and content standards in order to ensure interoperability to quality standards. Preferably existing standards should be adopted. Should no such standards exist, consideration should be given to adapt or develop novel standards in collaboration with a data standards organization (e.g. CDISC).

The proposal is suggested to be organized in 8 major work packages:

WP1 Consortium management and governance

WP2 Scientific consensus (clinical/pre-clinical) on study designs, instruments and methodology

WP3 Data management and statistics to allow integrated analysis of data sets

WP4 Clinical study implementation and operations

WP5 Clinical harmonization of experimental approaches

In this work-package the applicants should develop and make operational their strategy for selection, validation, standardisation and harmonization of relevant quantitative biology substrates/endpoints. These might include but should not by any means be limited to:

- Imaging
- Electrophysiology
- Bio-samples analysis
- Neuropsychological assessment

WP6 Pre-clinical harmonization of experimental approaches

The activities of this work-package have to be operationally linked to those of the previous one (WP5). In this work-package the Applicants should develop and make operational their strategy for selection, validation, standardisation and harmonization of relevant quantitative biology substrates/endpoints. In analogy to the techniques selected by a consortium above the pre-clinical approaches should all align in a reverse translational manner.

WP7 Engagement with regulatory groups, agencies and other stakeholders

WP8 Dissemination and communication

Topic 4: The consistency approach to quality control in vaccine manufacture

Topic details

Topic code	IMI2-2015-03-04
Project type	Research and innovation action (RIA)
Submission & evaluation process	2 stages

Background and problem statement

In 2010, 79% of the research-based global vaccine companies' production, amounting to 85% of the total market value, took place in Europe. The vaccines sector is therefore a success story for European bioscience, and a key endeavour to ensure public health. But despite its success, it faces a difficult scientific, ethical and economic challenge: the fact that the compulsory testing of vaccines before market release is still relying largely upon traditionally used in vivo methods and many of these are now known to be poor in terms of consistency control by current standards. For some vaccines, this rigorous testing is justified: many already established vaccines are complex mixtures of poorly-defined composition, which forces the regulatory authorities to treat each new batch or lot of vaccine individually, meaning that safety and potency must be tested by the manufacturer and by national authorities before release onto the market. However these have been made the same way for many years so a large amount of consistency and process data exists for them. On the other hand, many modern vaccines of well-defined composition or improved quality and process control of older products might allow certification of product quality without the need for animal experimentation.

In vivo final lot testing for safety and potency of vaccines is slow, expensive, relatively imprecise, and not always sensitive enough to demonstrate product consistency. In addition, some of the tests may be painful and distressing to large numbers of animals required. Elimination of these tests would therefore have significant scientific, economic and ethical benefits.

The development of alternatives to many of these tests has been progressing steadily both in the public and in the private sectors for years. While progress has been made in some directions, for example, in applying ELISA methods for quantitation of antigens, or cell-based methods for measuring residual toxicity of toxoids, the main stumbling block has been conceptual: currently in order to supplant *in vivo* assays, *in vitro* tests are generally required to correlate with the *in vivo* counterpart. But unfortunately, such a 1:1 correlation or replacement is mostly impossible to attain, given the large differences in methods, and the inherent imprecision and variability affecting the *in vivo* methods. Therefore a panel of consistency tests needs to be put in place to ensure that each batch is consistent with what has been shown previously as safe and efficacious. We find ourselves thus in a peculiar situation in which a more precise *in vitro* testing cannot be validated because it will not correlate with a more variable *in vivo* assay.

This is why a shift in paradigm has been proposed: moving away from the question that currently decides the issue – "Can *in vitro* assays mimic the *in-vivo* situation?" – to a new formulation that would lead to radical change: "Can *in vitro* testing ensure that each vaccine batch is of the same quality and consistency as those shown to be safe and efficacious? Can an *in vitro* test or tests ensure that sub-standard final lots of vaccines (i.e. inconsistent, unsafe or sub-potent or over-potent) are detected and therefore not released to the market?".

Such an approach would require a pivotal change in the perspective of the stakeholders involved as it involves not just changing final testing but understanding and controlling the whole production process. This is all about building quality in through the process and not just testing at the end.

Fully *in vitro* release methods are in use by many manufacturers for certain vaccines and the veterinary sector has had success in removing the target animal batch safety tests completely - however, it is far from being a generally accepted paradigm. For established vaccines, a certain level of in-process testing with non-animal methods is conducted but the collected data is not used for lot releases, but as in-house monitoring and trending of production processes. Such in-process testing is generally based on relatively simple, non-animal methods (e.g. trend analysis monitoring flocculation time (Kf), protein nitrogen levels, optical density or tests for residual formalin), and does not cover all aspects of vaccine quality and consistency. These methods monitor the production process and its consistency but information on the effect of antigen/adjuvant interaction after product blending on potency, on product stability and on product safety still requires extensive animal testing.

And yet, the last decades have seen significant progress in *in vitro* methods, so that it could justify a change in the lot release paradigm. In general, seed lots of established vaccines are better characterised and defined than they were in the past, vaccine production processes are optimised, standardised and carefully monitored, and quality systems such as Good Manufacturing Practice (GMP), Quality Assurance (QA) and pharmacovigilance are now in place to oversee consistency in production.

A push towards change in this field is in line with the IMI2 Strategic Research Agenda, which underlines the importance of the acceptance and qualification of novel tools and technologies for processes controlled by the regulatory system. This is highly relevant for vaccine manufacture processes.

Need and opportunity for public-private collaborative research

Recent workshops conducted by the European Partnership for Alternative Approaches to Animal Testing (EPAA) have identified large gaps in the armamentarium and regulatory acceptance of *in vitro* tests that would need to be embedded in any new approach to Quality Control (QC) of vaccine lots to ensure potency and safety. Knowledge comes from the vaccine manufacturers who currently use a mixture of *in-vitro* and *in-vivo* methods in their in-process and final lot testing. The manufacturers also have a considerable amount of historical information on the performance of their production methods and their ability to produce material of consistent quality and composition. The information on past QC is vital for defining alert and acceptance criteria for current and future test methods and process control trend analysis that will avoid final lot testing on animals. The technological gaps hitherto identified vary from vaccine to vaccine, and tests and knowledge need to be developed in such a way as to complement existing processes. This is particularly relevant to veterinary vaccines which are produced by a larger number of smaller manufacturers each adhering to their own in-house processes and the broad range of vaccine targets.

In such an environment, a public-private partnership approach in which multiple stakeholders each play an important role is required to move forward. The private sector role is clear: to identify gaps, to provide test materials (antigens, vaccines) for assay development, to compare *in vivo* and *in vitro* methods, to establish alert and acceptance criteria for new/current in process controls, to pre-validate new tests (e.g. by showing transferability from one manufacturer to another) and to engage the national authorities in validation and regulatory approval.

The public sector and academia's role is to help provide data to support acceptance of new tests and approaches, to participate in the initial proof of concept and to propose innovative approaches to the development of new *in vitro* tests. This includes conducting work to help understand the key parameters for safety and efficacy and therefore consistent quality of an antigen to understand appropriate targets for in vitro tests, and identifying key process parameters for product quality and consistency. This work then translates to collaborative (pre)validation data and interaction with regulatory agencies on acceptance of the newly developed methods. The regulator's role in this partnership is key to assure that the right questions are posed such that the right data can be provided to support regulatory acceptance in the EU, and that all approaches are harmonised and globally acceptable.

Overall objectives

The Consistency Approach (CA) is a new paradigm for improved quality control of established vaccines which moves away from the current focus on testing the final product and high reliance on *in vivo* models, to an integrated in-process and final product quality monitoring programme during vaccine lot production using non-animal methods (in line with 3Rs principle and European Directive 2010/63).

The consistency approach is enabled by the application of a battery of in vitro tests and production consistency controls that leads to the characterisation of structural and functional criteria of a batch by generating a "fingerprint" of the physico-chemical and immunochemical properties instead of reading out end points in animals to demonstrate safety and efficacy of each batch release testing.

The main objective of this project proposal is to demonstrate the proof-of-concept of the Consistency Approach (CA), in the global vaccine manufacturing process, focusing both on human and veterinary vaccines and to facilitate its regulatory acceptance, guidance and implementation.

This objective is going to be achieved through a series of innovations, including:

- predictive technology and methodology innovation in the areas of analytical methods
- *in vitro* models demonstrating functionality of immune responses
- bioinformatics
- a final translation of these new technologies into a general approach to consistency testing that will allow improved monitoring of vaccine quality during production and final formulation.

Depending on the current state of the art, some candidate tests will undergo various stages of pre-validation, and their transferability and inter-laboratory reproducibility will be tested through collaborative studies.

In some cases new tests and methods are required, in others simply a framework for consistency requirements to remove existing redundant tests.

Achieving the main objective would lead to an agreed road map for implementing new CA advanced methodologies and approaches into the regulatory guidance involving relevant international bodies (EDQM BSP, WHO ECBS, EMA BWP/VWP and JEG3Rs, OMCL Network, OIE, ICH/VICH[7], etc…). The project will contribute to overcoming European, but also global regulatory road blocks in harmonisation processes and to improving the problem of structural fragmentation in this area, stepping away from mostly single acting stakeholders and a difficult-to-manage complex framework towards a coordinated, cross-sector, interdisciplinary, long-term, large-scale, trans-national effort.

In addition the project could contribute to the access to medicines, reducing lead time and cost, improving R&D processes beyond vaccine manufacturing, and potentially support any cross-fertilisation opportunity within biologics for convergence of regulations.

Potential synergies with existing consortia

The EPAA working group on the "Application of the 3Rs and the consistency approach for improved vaccine quality control" has been running since 2010 and has conducted a number of workshops and meetings to

[7] EDQM BSP – European Directorate for the Quality of Medicines, Biological Standardisation Programme.

WHO ECBS – World Health Organization, Expert Committee on Biological Standardization.

EMA BWP/VWP – European Medicine Agency, Biological Working Party, Vaccine Working Party.

JEG3Rs – Joint Committee for Medicinal Products for Veterinary Use/Committee for Medicinal Products for Human Use Ad-hoc Expert Group on the Application of the 3Rs in Regulatory Testing of Medicinal Products.

OMCL – Official Medicines Control Laboratories.

OIE - World Organisation for Animal Health.

ICH/VICH - International Conference on Harmonisation / Veterinary International Conference on Harmonization.

identify priority vaccines. Members of the working group encompass the main European manufacturers (GSK, MSD, Zoetis, Sanofi-Pasteur, Novartis) and its strength lies in the additional involvement of national and international regulatory bodies (EMA, EDQM, FDA, USDA, Health Canada, Canadian Centre for Veterinary Biologics, WHO), European validation and standard bodies (EDQM, EURL ECVAM) and OMCLs from several European countries, many of which are engaged in research on alternatives. Furthermore, the EPAA working group is closely connected to those involved in validation and regulatory approval of alternatives and is likely to provide a useful platform for further dissemination of project outcomes with regards to tests and guidance.

There may also be opportunities with other IMI projects such as the project currently under preparation from the IMI 10th Call for Proposals "Immunological assay standardisation and development for use in assessments of correlates of protection for influenza vaccines", and the FP7 project ADITEC (www.aditecproject.eu).

Expected key deliverables

1) Demonstration of **proof-of-concept** for use of non-animal assays and techniques/key process parameters leading to an integrated end to end quality and safety monitoring programme during vaccine lot production for a number of model vaccines.

    - Proof of concept for in vitro tests for a range of human and veterinary vaccines, for instance: safety tests for toxoid products (diphtheria and clostridials), potency tests for viral vaccines (rabies) and bacterial vaccines (pertussis and erysipelas), etc.

    - A set of non-animal methods for which proof-of-concept has been demonstrated for model vaccines and that could also be used for other vaccines after optimisation and evaluation. This could include key process parameters to be monitored, antigen assays, adjuvant assays and other consistency measures.

2) Development, optimisation and evaluation of techniques to be used in the CA for vaccine lot release testing. Depending on the vaccine to be controlled, one or more of the following:

    - **Physicochemical techniques** to ensure the consistent conformation of the antigen

    - **Immunochemical methods** to analyse epitopes important for the induction of functional/protective cellular or humoral responses as well as to assess antigenicity and adsorption in adjuvanted formulations

    - ***In vitro* functional methods** to demonstrate functional immunological responses

    - **Genomics and proteomics** assays to monitor genetic profiles of specific toxicity.

    The assays will be selected to cover the key parameters for demonstrating vaccine consistency and assuring release of potent and safe products.

3) Global dissemination of knowledge and training for stakeholders on those new methodologies and approaches.

4) Input into improvements of existing or development of new regulatory guidance to facilitate consistency approach to vaccine release testing.

Industry consortium – EFPIA participants

Boehringer-Ingelheim, GlaxoSmithKline, Merck/MSD Animal Health, Merial, Novartis Vaccines, Sanofi-Pasteur, Zoetis.

Indicative duration of the project

The indicative duration of the project is five years.

Indicative budget

The indicative contribution from EFPIA companies is EUR 7 850 000.

The financial contribution from IMI2 JU will be a maximum of EUR 7 850 000.

Justification for non-EU in-kind contribution

Whilst vaccine marketing authorization processes are still regulated regionally, vaccines are often designed and developed globally. In addition, animal reduction can only effectively be pursued if regional differences in regulatory requirements and different release testing programs can be gradually reduced. The successful implementation of the objectives will therefore require the participation of non-EU laboratory and manufacturing sites of Boehringer-Ingelheim, Merck, Sanofi Pasteur and Zoetis.

Applicant consortium

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.

The Applicant Consortium is expected to provide both pre-clinical (safety, CMC, assay development) and clinical expertise and ability for interdisciplinary and inter-sectorial work and to cover the following critical fields:

1) Physicochemical techniques for conformational fingerprinting of antigens
2) Proteolytic susceptibility of antigens to mimic APC action
3) Immunochemical assay development
4) Manufacturing processes and production consistency
5) Antigen-adjuvant interactions
6) *In vitro* cell models of immune responses
7) Genomic and proteomic profiling
8) Regulatory expertise
9) Understanding of GLP, QA
10) Animal models and laboratory animal science

This may require to mobilise, as appropriate, partners from regulatory authorities (European or national, in line with the objectives), academia, National Control Laboratories, and SMEs.

Suggested architecture of the full project proposal

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

A plan for interactions with Regulatory Agencies/health technology assessment bodies with relevant milestones, and appropriate resources allocation, should be built into the project architecture as well as aspects related to dissemination and sustainability, facilitating continuation beyond the duration of the project.

Data collection and data management should be conducted according to established data standards and/or in collaboration with a data standards organisation (e.g. CDISC), to develop new data standards if no established data standards exist.

Work Package 1: Physicochemical methods for consistency testing

This WP will focus on:

- Development of physicochemical methods for conformational fingerprinting.
- Development of non-animal proteolytic assays to mimic antigen processing.

EFPIA contribution: Supply of materials e.g. adjuvanted and non-adjuvanted toxoid, technology transfer, inter-laboratory evaluation, comparison of in vitro and in vivo tests, if relevant.

Expected Applicant consortium contribution: Fluorescence and CD spectroscopy for conformational fingerprinting, electrophoresis and mass spectroscopy for antigen processing.

Deliverables:

- Protocols for the conformational analysis of single antigens in final formulations, regardless of composition to address presence of B-cell epitopes.
- Assays to measure the proteolytic sensitivity of antigen described to address T-cell epitope formation.

Work Package 2: Immunochemical methods for consistency testing

This WP will focus on:

- Development and optimisation of immunochemical assays, development of methods for determining antigen content of adjuvanted vaccines.

EFPIA contribution: Supply of materials and reagents including mAbs, standards and vaccines, comparison of in vitro and in vivo tests.

Expected Applicant consortium contribution: Development of suitable assays e.g. ELISA for intermediate and final lot testing (including adjuvanted vaccines) and stability testing, characterisation of the panel of monoclonal antibodies used, e.g. epitope mapping.

Deliverables:

- A list of suitable methods, together with full SOPs, for subsequent inclusion in inter-laboratory evaluation and transfer studies.
- Full report and analysis describing the extent of concordance between the current *in vivo* methods and the immunochemical methods for selected vaccines.

Work Package 3: In vitro functional models for consistency testing

This WP will focus on:

- Development and optimisation of *in vitro* models to monitor parameters that are closely linked to the functionality of vaccines (i.e. capability to induce a protective immune response).

EFPIA contribution: Supply of materials, comparison of in vitro and in vivo tests.

Expected Applicant consortium contribution: Expertise in cell culture of monocytic cell lines and primary monocytes, dendritic cells and PBMCs; Co-culture of APCs and T cells; Cytokine secretion and cell surface marker expressions assays, FACS.

Deliverables:

- A primary validated cell based and a cell-line based APC assay system that can be used to evaluate vaccine quality for regulatory consistency test(s).
- Validated human and murine T cell activation assays that can be used to evaluate vaccine quality for regulatory consistency test(s).
- Comparison of the in vivo and in vitro performance of (sub)potent vaccines in murine models.

Work Package 4: Bioinformatics

This WP will focus on:

- Development of genomics and bioinformatics techniques to evaluate the safety of toxoid vaccines.

EFPIA contribution: Supply of materials (vaccine production intermediates and final lots). Inter-laboratory evaluation.

Expected Application consortium contribution: Gene expression analysis, QPCR, proteomics (mass spec).

Deliverables:

- Optimise, perform in house-validation and do technology transfer of a genomic derived *in vitro* safety test for selected toxoid vaccines.

Work Package 5: Validation criteria, transferability and inter-laboratory reproducibility of consistency approach methods

This WP will focus on:

- Definition of validation criteria for consistency approach methods, design and coordination of small-scale collaborative studies evaluating the transferability and inter-laboratory reproducibility of the methods identified;

EFPIA contribution: Supply of materials, participation in transferability and inter-laboratory reproducibility studies.

Expected Applicant consortium contribution: Participation in transferability and inter-laboratory reproducibility studies. Curation of test samples and reagents, coding and shipping.

Deliverables:

- Definition of validation criteria.
- Results of the collaborative studies (including inventory of methods developed and standardised and recommendations for further studies).

Work package 6: Promotion of consistency testing to regulatory acceptance

This WP will focus on:

- Definition of a roadmap for regulatory acceptance of the consistency approach with the goal of providing a basis for guidance on regulatory implementation of new tests developed for the CA

EFPIA contribution: Participation in meetings to develop the roadmap.

Expected Applicant consortium contribution: Development of the roadmap and engagement of relevant international regulatory and standards bodies.

Deliverables:

- Roadmap conference.
- General guidance for acceptance and implementation of the CA.
- Publication and communication activities.

Work package 7: Consortium management

This work package will focus on:

- Consortium and project management, facilitation and streamlining of cooperation between the different partners of the project and between work packages

- Communication and dissemination activities

Topic 5: Pertussis vaccination research

Topic details

Topic code	IMI2-2015-03-05
Project type	Research and innovation action (RIA)
Submission & evaluation process	2 stages

Background & problem statement

Globally, CDC estimated that there are 16 million pertussis cases and about 195,000 pertussis deaths in children per year, making it one of the leading causes of vaccine-preventable deaths. While there is a resurgence of the disease in Europe, US and Australia, the heaviest burden is in children in low-income countries.

Since its introduction in the 1940's, vaccination against Bordetella pertussis (B. pertussis) infection has been demonstrated to be effective in preventing infection and disease. An impressive 99% reduction of whooping cough was observed in infants in European countries during the 1950's and 1960's, as a result of the wide use of whole cell pertussis vaccine, wP (a suspension of formalin inactivated B. pertussis with Alum salts). In the 1990's, the advent of biotechnology resulted in the introduction of second generation pertussis vaccines, containing well-defined combinations of highly purified antigens formulated in Alum adjuvant. These vaccines, termed acellular pertussis vaccines, aP, show a much more acceptable local reactogenicity profile than wP vaccines and still offer high levels of protection. Acellular vaccines are primarily used in industrialised countries, while many developing and emergent economies are still using the whole cell vaccines. The WHO recommends vaccination minimally as a primary series of at least three doses of high quality aP or wP pertussis vaccine in infants. Paediatric vaccination schedules in industrialised countries typically include recommendations for additional doses of the aP vaccines to ensure boosting of immunity through schooling years and prevent transmission to younger siblings, who are yet to complete their primary vaccination series. Moreover, some countries offer an additional one-dose aP booster vaccine to adolescents and adults, commonly administered in combination with diphtheria and tetanus toxoids (Tdap vaccines, Tetanus Toxoid, Reduced Diphtheria Toxoid and Acellular Pertussis Vaccine). wP vaccines are not recommended for use as booster vaccines in older children, adolescents or adults because an increase in local reactogenicity has been observed with age and repetitive administration.

Despite the success and relatively large vaccination coverage with pertussis vaccines in industrialised countries, there has been an increase in the incidence of pertussis in certain countries since the early 2000's. USA [CDC], Australia and the UK have declared epidemic outbreaks [Sheridan et al. 2014]. In fact, the largest numbers of annual cases of B. pertussis in over half a century were reported recently in the USA [Cherry 2012]. In Europe, a resurgence of the disease has been described in the Netherlands, Norway, Germany, the United Kingdom, Spain and Slovenia [ECDC; Sizaire et al, 2014]. Following a resurgence of infant pertussis-related deaths, maternal immunization programs were successfully adopted in the US, UK, and several other countries [Amirthalingam 2014]. WHO has since recommended that countries with a high pertussis burden adopt maternal immunization as the most cost-effective intervention strategy to reduce neonatal pertussis disease [WHO-SAGE 2014]. The pattern of disease resurgence in school-aged children, adolescents and adults is understood to be related to a waning of immunity with age.

Although the effectiveness of current aP vaccines in infants (at risk population) and the benefit of Tdap booster vaccines are not questioned, there is a clear need to investigate the underlying causes of the observed increase in incidence of pertussis disease in certain populations, in particular with regards to the role played by immunological memory and the differences between aP and wP vaccines in generating long-term protection. This will provide the research community, manufacturers and health authorities with valuable

information on what is needed to increase the effectiveness of vaccination in the affected population cohorts. It could also pave the way for refining vaccination schedules with currently available vaccines as well as for improving or developing novel formulations.

Need and opportunity for public-private collaborative research

While the effectiveness of current aP vaccines in infants (at risk population) and the benefit of Tdap booster vaccines are not questioned, the changing epidemiology of pertussis calls for action. The joint effort of vaccine manufacturers, academic researchers, government, public health bodies and regulatory authorities is needed to increase our scientific understanding of human immunity to pertussis and the role of vaccination in tackling this phenomenon. Ultimately the potential modification of current vaccine formulations and/or immunisation schedules and the development of novel vaccines will be impacted by the outcome of this collaborative research program.

Moreover, this public-private consortium of industrial and academic stakeholders would become a unique platform for interaction and consultation with Regulatory Authorities and Public Health Institutions. Indeed, the validation and acceptance of new biomarkers, new disease models, new vaccines and/or formulations, as well as new vaccination schedules will be a critical step in implementing the results of this project for the benefit of public health.

Overall objectives

The overall objectives of the project are to pursue the identification and validation of biomarkers of protective immunity to pertussis and the establishment of models of pertussis infection that will enable the refinement of current vaccination schedules and expedite the development and testing of novel or improved vaccine formulations.

In particular, the project aims will be:

- Gaining a more thorough scientific understanding of the pathogenesis of B. pertussis and of the underlying molecular mechanisms and biomarkers of protective immunity to pertussis in humans.
- Investigating differences between whole cell and acellular pertussis vaccines, in particular with regards to their ability to generate protection against infection, disease, carriage and transmission, the role of maternal antibody in modulating immune responses to pertussis vaccination in infants, as well as to establish long term immunological memory
- Strengthening our technological means of testing novel vaccine candidates and immunisation regimes in animal and human models of pertussis disease and immunisation
- Interacting closely with Regulatory Authorities and Public Health Institutions including those involved in vaccination and the monitoring and control of infectious diseases to ensure that the results obtained can be translated into relevant regulatory guidance as well as public health and clinical practice.

Potential synergies with existing consortia

Applicants should include considerations in their proposal on how interactions with ongoing IMI and other projects are envisaged, if applicable. The following IMI and European Commission funded projects might be considered:

The European research programme for improved pertussis strain characterisation and surveillance (EUPERTSTRAIN), http://www.2020-horizon.com/EUPERTSTRAIN-European-research-programme-for-improved-pertussis-strain-characterisation-and-surveillance-(EUPERTSTRAIN)(EUPERTSTRAIN)-s45262.html

Other IMI projects in the field of infectious diseases and vaccines, such as projects running under the IMI New Drugs for Bad Bugs (ND4BB) programme, the projects BioVacSafe (www.biovacsafe.eu), RAPP-ID (www.rapp-id.eu), ADVANCE (www.advance-vaccines.eu), as well as the project resulting from the topic "The consistency approach to quality control in vaccine manufacture" of the present Call

The FP7 project ADITEC, www.aditecproject.eu

The US National Institutes of Health funded Human Immune Phenotyping Consortium and the Bill and Melinda Gates Foundation funded Systems Biology/Immunology Consortium in the US

In general, the applicant consortium should ensure that all activities that are already ongoing in the field covered by this topic and all expertise that already exists in the EU and elsewhere are leveraged to maximise the potential impact of this action.

Expected key deliverables

The following key deliverables are expected:

1) Immunological biomarkers that could reliably be used to streamline vaccine clinical trials:
   - Harmonised classic and novel bioassays to measure immune responses against pertussis, such as In vitro functional killing assays (i.e. bactericidal and opsonophagocytic antibody)
   - Biomarkers that can be used to predict protection against pertussis
   - Biomarkers that can be used to assess long lasting immunological memory to pertussis
   - Biomarkers that can be used to detect early signs of the waning of immunological memory to pertussis
   - Identification of putative correlates of protection that can be studied in future efficacy trials, with an overarching goal to define, in such trials, correlate(s) of protection that are suitable as endpoints for future pertussis vaccine registration
   - Development of a rapid and reliable point of care diagnostic test development may also be considered
2) An understanding of the difference in immune response profiles generated by natural pertussis infection and aP and wP vaccines in selected population cohorts (school age children, adolescents, younger adults, older adults) through:
   - A molecular dissection of the immune response to *B. pertussis* including:
     1. Dissection of the memory B-cell responses
     2. Dissection of the T-cell response, including the validation in humans of differences in T helper cell response profiles observed in animal models with the vaccines
   - Information on the effect of vaccination on *B. pertussis* colonisation, carriage and transmission
3) The laboratory network and technological expertise in Europe to perform preclinical immunisation and B. pertussis challenge studies in predictive pre-clinical models, considered relevant models of the disease. This can be used to test experimental vaccines and aid in the identification of biomarkers of vaccine efficacy and immunological memory.

4) A molecular understanding of the progression of B. pertussis colonisation, infection and disease in the presence or absence of pre-existing immunity, acquired through studies in human cohorts naturally exposed to pertussis and/or via control challenge studies in human adult volunteers (a human challenge model that would need to be developed). Epidemiological studies that could cast light on the resurgence of pertussis may also be considered (aP and wP vaccines countries)

5) A close interaction, collaboration and consultation with Regulatory Authorities and Public Health Institutions to ensure assessment, acceptance and validation of the results of the project so they can be translated into Regulatory Guidance and public health and clinical practice.

6) An understanding of the role of maternal antibody in modulating immune responses to pertussis vaccination in infants, so that recommendations could be made for adoption of maternal immunisation programs in low-income countries.

Expected impact

The information and knowledge acquired through this program will be useful in understanding the reasons underlying the resurgence of pertussis disease in school age children, adolescents, and younger adults and ultimately provide clues as to how current vaccines and vaccination schedules can be modified to enhance protection in these populations.

The availability of reliable preclinical models in Europe, in which to test the immunogenicity and efficacy of novel vaccine formulations, will increase the ability of academic researchers, biotechnology and pharmaceutical companies all over the world to screen vaccine candidates and select the most successful for clinical development.

The establishment of a human model of pertussis infection via control challenge studies in volunteers could permit the early evaluation of experimental vaccines for protective efficacy, thus accelerate the development of novel and improved vaccine formulations.

The identification of reliable biomarkers of immunological memory and vaccine efficacy validated by regulatory authorities will facilitate vaccine efficacy trials and streamline clinical development programs.

A concerted effort of the pharmaceutical industry in coming together with academia and public bodies to resolve a pressing public health issue will have an overall positive impact globally. This unique public-private consortium will act as an exceptional interlocutor with Regulatory Authorities and Public Health Institutions allowing a concerted evaluation, validation and acceptance of new biomarkers, new models, new vaccines and/or formulations as well as new vaccination schedules to help combat pertussis disease around the world.

By ultimately understanding and explaining the resurgence in pertussis observed in the face of wide vaccine use, the program is expected to help prevent a further reduction in the public's confidence in vaccination in Europe and increase the coverage of life-saving vaccines around the world.

Industry consortium

The industry consortium will comprise vaccine developers and manufacturers. They will be contributing:

- Licensed pertussis vaccine for prospective clinical studies
- Know-how on clinical development of vaccines
- Expertise in *in vitro*, preclinical and clinical *B. pertussis* research, pertussis vaccination and pertussis epidemiology

- Expertise in the identification of human biomarkers of infectious disease progression, immunological memory and/or vaccine efficacy
- Expertise in molecular epidemiology and use of *in silico* tools to investigate pathogen biodiversity
- Expertise and access to epidemiological data on pertussis disease and effectiveness of pertussis vaccination

EFPIA participants and associated partners

- Sanofi Pasteur, GSK, Bill & Melinda Gates Foundation and Novartis.
- The Bill & Melinda Gates Foundation (BMGF) works to help all people lead healthy, productive lives, particularly those in most need. While pertussis is a growing concern in Europe and the US, its heaviest burden is in children in low-income countries. BMGF's aim in this pertussis vaccine research project is to ensure that findings and results from the project can make the biggest public health impact in at risk populations globally.
- The BMGF participates in the present topic as Associated Partner to IMI2.

Indicative duration of the project

The indicative duration of the project is 5 years.

Indicative budget

The indicative contribution from EFPIA companies and IMI2 JU Associated Partners is EUR 14 000 000. The financial contribution from IMI2 JU will be a maximum of EUR 14 000 000.

Applicant consortium

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. The research objectives may require:

- Expertise in *in vitro*, preclinical and clinical *B. pertussis* research or pertussis vaccination
- Expertise in the development of bioassays or immunoassays suitable to assess pertussis infection and functional and memory immune responses to pertussis vaccination.
- Expertise in the identification of human biomarkers of infectious disease progression, immunological memory and/or vaccine efficacy
- Expertise in molecular epidemiology and use on *in silico* tools to investigate pathogen biodiversity and epidemiology of infectious disease
- Expertise and infrastructure needed to set up preclinical disease models, including in non-human primates
- Expertise and infrastructure to perform prospective clinical studies with licensed pertussis vaccines, as well as access to relevant vaccination cohorts
- Institutional expertise /infrastructure to develop and perform control bacterial/respiratory pathogen challenge studies in human volunteers

- Expertise or access to epidemiological data on pertussis disease and effectiveness of pertussis vaccination

- Banking and Documenting clinical isolates of *B. pertussis* or biological samples from infected or vaccinated individuals

This may require to mobilise, as appropriate, stakeholders such as:

- Academic or public research participants with established and well recognised experience in the field of pertussis research, vaccine research and/or human biomarker identification.

- Clinical investigators with the expertise and infrastructure to perform prospective clinical studies with licensed pertussis vaccines in relevant vaccination cohorts

- Clinical investigators with the expertise and infrastructure to conduct controlled challenge studies with respiratory pathogens in human volunteers

- Academic or public research participants with expertise and support infrastructure in the development of preclinical *in vivo* models of pathogens

- SMEs interested in the development of novel pertussis vaccines and/or in developing and validating novel technologies for identification or testing of biomarkers following infection or vaccination (this might also include development of point of care diagnostic tools)

- Regulatory Authorities and Public Health Institutions involved in vaccination and the control of infectious diseases

- Regulatory bodies involved in the regulation of clinical trials and the licensure of new vaccines

- Regulatory bodies involved in the authorisation of clinical trials of new vaccines

The successful applicant consortium will be expected to adhere to the following principles, if inappropriate please provide rationale in the short proposal:

- Disseminate scientific publications and research data on the basis of open access. Collection, processing and generation of research data is to follow documented data management procedures (see "Guidelines on Open Access to Scientific Publications and Research Data in Horizon 2020" and "Guidelines on Data Management in Horizon 2020 "). In order to ensure adherence to the legislation concerning protection of personal data, controlled access digital repositories and data governance will need to be established.

- Use well-established data format and content standards in order to ensure interoperability to quality standards. Preferably existing standards should be adopted. Should no such standards exist, consideration should be given to adapt or develop novel standards in collaboration with a data standards organization (e.g. CDISC).

Suggested architecture of the full proposal

The work packages that will make up the architecture of this project should be interacting closely with each other to ensure the project achieves all its objectives and has the impact expected. The proposed work package list is the following:

- WP1: Development of a preclinical in vivo model of pertussis vaccination and challenge to be used in research of aP and wP vaccines and development of novel pertussis vaccines

- WP2: Immunological studies of pertussis infection in human volunteers naturally exposed to pertussis or via control challenge studies

- WP3: Investigation of the difference in immune response profiles to aP and wP vaccines in selected population cohorts

- WP4: Regulatory affairs and Public Health impact of the research, including interfacing with relevant authorities and bodies to ensure the acceptance and validation of biomarkers and their translation into regulatory guidance

- WP5: Identification and assessment of immunological biomarkers of long lasting immunity and vaccine efficacy that could reliably be used to streamline vaccine clinical trials

- WP6: Project coordination and management. To cover all aspects of project governance, management and coordination.

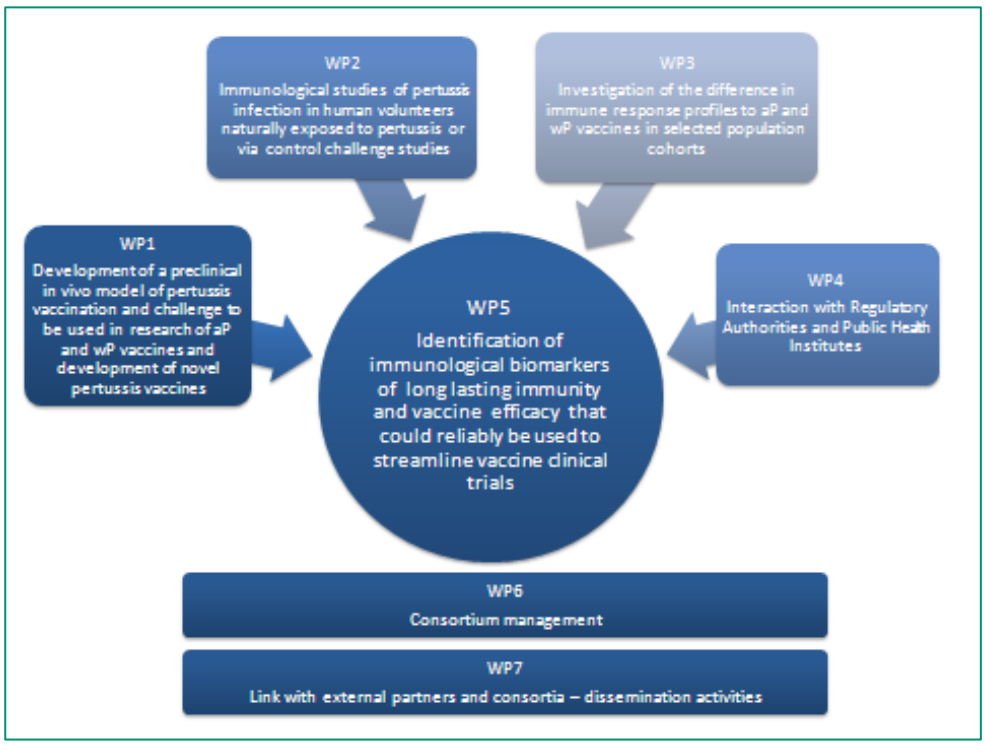
- WP7: Dissemination activities. To cover all aspects of the dissemination of results, and communication strategy

Work packages 1, 2, 3 and 4 should run in parallel as much as possible with the objective to feed results to WP5 that will ultimately lead to the assessment and identification of immunological biomarkers of long lasting immunity and vaccine efficacy . Each work package team, as applicable, is expected to be comprised of academic researchers, industry, and regulatory experts and experts from public health or other institutions to ensure acceptance of results.

A full project plan with suitable milestones resource allocation and timeline shall be included in the proposal. In particular, a plan for interactions with Regulatory Agencies/Public Health bodies should be built into the project architecture of the project. The plan shall also address aspects related to dissemination and sustainability, facilitating continuation beyond the duration of the project.

Data collection and data management should be conducted according to established data standards and/or in collaboration with a data standards organization (e.g. CDISC), to develop new data standards if no established data standards exist.

A suggested architecture is shown in the scheme below. Please note that the suggested outline of the architecture for the full proposal is a suggestion; different innovative project designs are welcome, if appropriate.



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Topic 6: Knowledge repository to enable patient focused medicine development

Topic details

Topic code	IMI2-2015-03-06
Project type	Research and innovation action (RIA)
Submission & evaluation process	2 stages

Background and problem statement

In order to achieve successful patient integration in medicines development, individual players from the pharmaceutical industry must work together and develop an open dialogue on a peer-to-peer basis with patient representatives. To this end a multi-national collaboration with an initial emphasis on the patient-industry relationship was formed: *Patient Focused Medicines Development* (PFMD).

The ultimate goal is to make medicines development faster and more efficient through systematic patient involvement. This can only be accomplished when a rational, structured process for integrated patient involvement is developed and accepted by all stakeholders.

In order to achieve routine patient involvement, all stakeholders need to work together to achieve a meaningful outcome. These include: industry; regulators; patients, patient associations and advocacy groups; purchasers of medicines (including pharmacies and hospitals); healthcare professionals; politicians and legal advisors; HTA agencies; and academia and topic-related think-tanks.

There are a substantial number of organizations and initiatives aiming to improve patient involvement – indicating that this is a common priority. However there is no organized information repository to share best practices, standards and approaches. Real time, searchable information sharing is critical to develop standard approaches and guidance which are shared and embraced by multiple constituents.

A key step is the creation of a knowledge repository and supporting network of stakeholders to capture current approaches, standards, regulatory provisions and best practices to optimize patient engagement information from—and for – stakeholders. A centralized Patient-Inspired Knowledge Hub (PIKH) would capture when patient engagement occurs, and details and standards of how stakeholders are involving patients from early discovery throughout the research and development cycles towards, and following approval. This shared repository will make research leaders more focused on unmet health needs of patients and hence more targeted toward what "end users of healthcare" really want and need.

Need and opportunity for public-private collaborative research

A PIKH will respond to the critical need for more patient involvement in medicines R&D and expand opportunities for supporting such involvement and important role of patients in the industry R&D and regulatory processes.

The development of an open platform like a PIKH requires contributions from multiple stakeholders including patient organizations, companies, regulators and academia.

To ensure neutrality and broad acceptance of the new platform it should be hosted by a public partner / institution in the consortium.

Overall objectives

The overall objective is to have a Patient Inspired Knowledge Hub (PIKH) that enables sharing non-competitive information with and by users from patient groups, regulators, health authorities, academia and industry. The project is a response to the lack of a uniform process to engage patients in the drug development process. The PIKH will facilitate and enable the incorporation of patient input into the drug development processes, used broadly by stakeholders in a uniform (standardized) way among a range of stakeholder organizations.

Potential synergies with existing consortia

This proposed IMI2 project is expected to develop synergies and avoid duplication of effort with existing consortia (e.g. EUPATI) and other relevant initiatives. The details of these interactions will have to be defined at the full proposal stage and agreed with the EFPIA partners. However, the application should include considerations how the interactions with ongoing consortia and other initiatives, such as the following are envisaged and particularly what / which ones would add most value to the project.

The project may also be aided by:

- The recently developed Chief Medical Officers (CMO)-Roundtable think tank focused on fostering cooperation between Patient Organizations and Industry (PFMD) including MSD, Pfizer, GSK, Novartis, UCB, National Health Council etc.
- Several organizational stakeholders (Patient-Centered Outcomes Research Institute (PCORI), Health Technology Assessment International (HTAi), Brookings Institute, Institute of Medicine) are developing validation methodology and standard approaches for patient input into research.
- The IMI project EUPATI - in parallel to its focus on the development of R&D information programs for patients - has started to identify best practice examples for patient involvement along the whole R&D process and to develop best practice guidance for the interaction / collaboration of stakeholders (Patient Organisations, Ethics Committees, HTA bodies, Academia / Hospitals, Industry, Regulatory Authorities). PIKH would complement these activities and the sustainability plans of the project.
- Another IMI project, EMTRAIN, has developed and enhances a searchable course and information portal (on-course®) for the biomedical sciences, particularly for the pharmaceutical industry, (a section for Patient Organisations via EUPATI is planned) and a collaboration and synergistic use of the database could be explored.

Expected key deliverables

A centralized Patient-Inspired Knowledge Hub (PIKH) that captures when patient engagement occurs, details and standards of how stakeholders are involving patients from early discovery throughout the research and development cycles towards, and following approval.

PIKH will enable and support the following key deliverables according to the three major work streams:

- Identifying the appropriate points in time to interact with patients for development of medicine, including: risks and benefits of interactions, required capabilities, anticipated enabling changes in regulatory affairs and more.
- Standardizing a framework to be used for patient engagement in medicine development
- Providing the ecosystem and mechanisms for stakeholders, for example pharmaceutical companies and patient advocacy groups, regulators, to discuss and share frameworks, methods and knowledge.

A risk assessment and evaluation report of conflict of interest in such a cooperation between industry and patients.

Provide a sustainable service specifically for patient organisations and industry to identify possibilities of interaction/collaboration.

Furthermore by providing data and knowledge management services this consortium will enable:

- Making the framework available for broad use
- Populating the framework
- Improving the framework through group learning

EFPIA participants

MSD (coordinator), Pfizer, UCB, Bayer

Indicative duration of the project

The indicative duration of the project is 3 years

Indicative budget

The indicative contribution from EFPIA companies is EUR 7 370 000.

The indicative financial contribution from IMI2 JU is a maximum of EUR 7 370 000

Applicant consortium

The successful applicant consortium will be expected to adhere to the following principles, if inappropriate please provide rationale in the short proposal:

1) Disseminate scientific publications and research data on the basis of open access. Collection, processing and generation of research data is to follow documented data management procedures (see "Guidelines on Open Access to Scientific Publications and Research Data in Horizon 2020" and "Guidelines on Data Management in Horizon 2020"). In order to ensure adherence to the legislation concerning protection of personal data, controlled access digital repositories and data governance will need to be established.
2) Use well-established data format and content standards in order to ensure interoperability to quality standards. Preferably existing standards should be adopted. Should no such standards exist, consideration should be given to adapt or develop novel standards in collaboration with a data standards organization (e.g. CDISC).

The applicant consortium is expected to consider how the input from special populations such as the paediatric population and older adults etc. can systematically be included in patient informed medicines development.

The applicant consortium is expected to address all the research objectives and contribute on the defined deliverables in synergy with the EFPIA consortium. This may require to mobilise, as appropriate, expertise in:

- Experience with Patient Advocacy
- Regulatory Expertise
- Health Services Research
- Clinical Informatics
- Infrastructure and Software
- Advanced Knowledge Management
- Point of Care Know-how and Integration
- Community Education and Learning
- Education Systems

- Learning and training Management
- Analysis and complex clinical workflow experience
- Drug Development Life Cycle
- Innovation
- Requirements Engineering
- Product Development

Industry profiles assigned to the project will be as follows:

- Clinical
- Business Operations
- Medical Affairs
- Data and Knowledge Management
- Product Development
- Project Execution – Non Technical
- Project Execution – Technical

Suggested architecture of the full proposal

The below architecture for the full proposal is a suggestion, different innovative project designs are possible.

WP1 Evaluate needs & existing landscape

- Review existing state of patient engagement in drug development including perspective and needs from: patients, patient advocacy groups, regulatory, pharmaceutical industry, delivery system, and business.
- Review the ethical, legal and regulatory landscape in Europe
- Identify the features and requirements needed for next-generation patient engagement into drug development.

WP2 Platform roadmap and strategic planning

- Develop a roadmap for the patient engagement platform focusing on the benefit/risk for patients, public-private capability development, and wide-industry dissemination & adoption.
- Develop a sustain business model that would facilitate the platform becoming an industry-standard tool with global sources of revenue.

WP3 Patient advocacy engagement

- Define, design, and build the processes and platforms necessary for systematic patient input into drug development.
- Influence industry practices, regulatory decision making, and patient participation

WP4 Regulatory engagement

- Define, design, and build the processes and platforms necessary for systematic patient input into drug development.
- Influence industry practices and patient participation

WP5 Academic engagement

- Define, design, and build the processes and platforms necessary for systematic patient input into drug development.
- Influence industry practices and introduce evidence-based science and best-practices.

WP6 Architecture and integration

- Define the architecture of platform, implementation and oversee the overall platform integration and operation.

WP7 Semantic interoperability

- Provide tools and services for semantic interoperability between varying data sources, enabling uniform interpretation of data.

WP8 Data protection, privacy & security

- Provide security services for the platform and ensure processes are enhanced for data protection and compliance.

WP9 Platform services

- Design and implement end-to-end solutions (tools and services) that address the requirements.

WP10 Pilots

- Demonstrate the functionality of the tools and services provided by Work Packages 3-9 and to evaluate the patient engagement platform in terms of usefulness for facilitating better patient-pharma industry interaction.
- Pilot evaluations will occur for a specific population(s), disease area(s) and pharma company workflow(s)

WP11 Dissemination and standardization

- Plan dissemination strategy and incorporate it into the design of the platform to ensure high rates of framework adoption.
- Work with pharma companies to integrate platform into their business processes

WP12 Commercialization and business model generation

- Identify problem areas in the healthcare ecosystem that could benefit from application of platform.
- Propose new value propositions for the users and incorporate into product development
- Identify market segments and monetization path for platform to become financially sustainable post-funding.

WP11 Project communication

- Support the communication and training between all Work Package Groups and prepare for platform execution.
- Widely disseminate platform outcomes and communicate with other EC FP or IMI projects in Europe and globally

WP12 Project management

- Coordinate project work, administer day-to-day operations, manage the collaborative efforts of the Work Packages

- Ensure that the scientific work being conducted is delivered on time and on budgets through optimal project management, including quality monitoring, planning, reporting and financial control

WP13 Product management

- Coordinate platform and operations design, and development, ensuring resulting products adhere to best-practice design standards, are well-built and easy to use.

Conditions for this call

Applicants intending to submit a short proposal in response to the IMI2 Call 3 should read the topic text, above, the IMI2 Manual for submission, evaluation and grant award and the IMI2 Evaluation Criteria.

Call Identifier: H2020-JTI-IMI2-2015-03-two-stage
Type of action: Research and innovation action
Publication Date: 17 December 2014
Stage 1 Submission start date: 17 December 2014
Stage 1 Submission deadline: 24 March 2015 – 17:00:00 Brussels time

Indicative Budget:
From EFPIA companies and IMI2 JU Associated Partners: EUR 56 430 000
From the IMI2 JU: EUR 56 430 000

Call topics

IMI2-2015-03-01	The indicative contribution from EFPIA companies is EUR 11 000 000. The financial contribution from IMI2 JU is a maximum of EUR 11 000 000.	Research and Innovation action. Two stage submission and evaluation process. Only the applicant consortium whose proposal is ranked first at the first stage is invited for the second stage.
IMI2-2015-03-02	The indicative contribution from EFPIA companies is EUR 8 130 000. The financial contribution from IMI2 JU is a maximum of EUR 8 130 000	Research and Innovation action. Two stage submission and evaluation process. Only the applicant consortium whose proposal is ranked first at the first stage is invited for the second stage.
IMI2-2015-03-03	The indicative contribution from EFPIA companies is EUR 8 080 000. The financial contribution from IMI2 JU is a maximum of EUR 8 080 000	Research and Innovation action. Two stage submission and evaluation process. Only the applicant consortium whose proposal is ranked first at the first stage is invited for the second stage.
IMI2-2015-03-04	The indicative contribution from EFPIA companies is EUR 7 850 000. The financial contribution from IMI2 JU is a maximum of EUR 7 850 000	Research and Innovation action. Two stage submission and evaluation process. Only the applicant consortium whose proposal is ranked first at the first stage is invited for the second stage.

IMI2-2015-03-05	The indicative contribution from EFPIA companies is EUR 7 000 000 The indicative contribution from IMI2 JU Associated Partners is EUR 7 000 000 The financial contribution from IMI2 JU is a maximum of EUR 14 000 000	Research and Innovation action. Two stage submission and evaluation process. Only the applicant consortium whose proposal is ranked first at the first stage is invited for the second stage.
IMI2-2015-03-06	The indicative contribution from EFPIA companies is EUR 7 370 000. The financial contribution from IMI2 JU is a maximum of EUR 7 370 000	Research and Innovation action. Two stage submission and evaluation process. Only the applicant consortium whose proposal is ranked first at the first stage is invited for the second stage.

Indicative timetable for evaluation and grant agreement

	Information on the outcome of the evaluation (first stage)	Information on the outcome of the evaluation (second stage)	Indicative date for the signing of grant agreements
IMI2-2015-03-01 IMI2-2015-03-02 IMI2-2015-03-03 IMI2-2015-03-04 IMI2-2015-03-05 IMI2-2015-03-06	Maximum 5 months from the date of submission to the first stage.	Maximum 5 months from the date of submission to the second stage.	Maximum 3 months from the date of informing the applicants following the second stage evaluation.

Consortium agreements

In line with the Rules for Participation and Dissemination applicable to IMI2 actions8 and the IMI2 model grant agreement, participants in research and innovation actions are required to conclude a consortium agreement prior to grant agreement.

[8] Regulation (EU) No 1290/2013 of 11 December 2013 and Commission Delegated Regulation (EU) No 622/2014 of 14 February 2014.