IMI2
9th Call for proposals

Approved by the IMI2 Governing Board of the Innovative Medicines Initiative 2 Joint Undertaking on 20.04.2016

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Contents

Introduction

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

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

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

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

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

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

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

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

[1] Council Regulation (EU) No 557/2014 of 6 May 2014 establishing the Innovative Medicines Initiative 2 Joint Undertaking (IMI2 JU).
[2] http://www.who.int/medicines/areas/priority_medicines/en/
[3] Under IMI2 JU, mid-sized companies having an annual turnover of EUR 500 million or less, established in an EU Member State or an associated country, are eligible for funding.
[4] http://www.imi.europa.eu/sites/default/files/uploads/documents/IMI2_SRA_March2014.pdf
[5] Directive 95/46/EC on the protection of individuals with regard to the processing of personal data and the free movement of such data and implementing national laws: http://eur-lex.europa.eu/legal-content/EN/TXT/?uri=celex:31995L0046
[6] http://www.imi.europa.eu/sites/default/files/uploads/documents/IMI2_CallDocs/IMI2_Manual_submission_evaluation_grant_v1.3_April2016.pdf

Topic 1: Addressing the clinical burden of *Clostridium difficile* infection (CDI): Evaluation of the burden, current practices and set-up of a European research platform

(Part of the IMI New Drugs for Bad Bugs (ND4BB) programme)

Topic details

Topic code	IMI2-2016-09-01
Action type	Research and Innovation Actions (RIA)
Submission & evaluation process	2 Stages

Specific challenges to be addressed

Infection with *Clostridium difficile*, a Gram-positive spore-forming anaerobe, is the most common cause of nosocomial diarrhoea in developed countries and leads to symptoms that range from self-limiting mild-moderate watery diarrhoea to severe fulminant diarrhoea, abdominal pain and pseudomembranous colitis. In some patients it may progress to toxic megacolon, colonic perforation and death [2]. *C. difficile* spores are resistant to most non-bleach based disinfectants and are shed into the hospital environment by both symptomatic patients and asymptomatically colonised carriers [15].

The annual reported rate of CDI has greatly increased since 2001, coincident with the emergence of hypervirulent and epidemic strains [18] [17] [12]. Over 500 000 new cases of *C. difficile* infection occur each year in the US [13] and 172 000 cases in Europe [9], although large variations between countries in the frequency of testing and the sensitivity of diagnostic tests mean that the true incidence is likely to be much higher [6]. Furthermore, although current robust epidemiological data is very limited, there is a widespread belief within the medical community that the burden of CDI outside of the acute care hospital environment, particularly in nursing homes and long-term care facilities, is greatly underestimated [11]. CDI therefore represents a substantial burden of morbidity, mortality, and healthcare resource consumption that calls for more effective prevention and treatment strategies [19].

CDI is most common in elderly patients with comorbidities – a fragile population – and infections are typically subsequent to treatment with broad-spectrum antibiotics [21]. Antibiotic-mediated disruption of the beneficial colonic microflora allows colonisation and infection with *C. difficile* [1]. The two antibiotics most commonly used to treat CDI, metronidazole and vancomycin, both have broad spectrum activity against many of the protective anaerobic bacteria resident in the colon and therefore prolong the period of dysbiosis. This is believed to contribute to the increased rate of infection recurrence following cessation of antibiotic therapy, occurring in around 20-25% of patients [13].

The susceptibility of any patient to developing CDI or experiencing recurrent infection is based on the confluence of three basic factors:

1) exposure to *C. difficile* spores either from the environment, other patients, healthcare professionals or persisting from a prior episode;
2) dysbiosis and disruption of the protective colonic microflora which allows germination of spores, overgrowth of vegetative cells and production of toxin;

3) failure to mount a sufficient immune response to neutralise the toxins and also to neutralise the surface components involved in the colonisation process, leading to damage to the mucosal barrier, inflammation and disease.

In isolation, one or two of these factors will not lead to disease (although they may allow asymptomatic colonisation and shedding of spores). However, when all three are present, a patient is at high risk of developing CDI. Furthermore, subsequent recurrences are highly likely until such time that these factors are addressed.

Need and opportunity for public-private collaborative research

A collaborative approach is required to develop a robust assessment of the burden of CDI and current practices in Europe and to carry out research which will provide evidence to support effective control and prevention strategies.

A collaborative IMI-based approach will ensure that different perspectives and a broad range of diverse evidence sources are gathered and synthesised. As described in the table below, various stakeholders are key to the success of the development and implementation of this public private partnership.

Function	Contribution
Public health	Understand the burden associated with CDI (including epidemiology and cost associated with disease burden both in the hospital and wider long-term care facility/community sectors), establish public health priority and develop infection control/antibiotic stewardship initiatives to minimise risk of CDI. Identify data sources to track epidemiology and surveillance.
Industry	Conduct research to identify patients and populations at risk of CDI and recurrent infection. Gather disease-related data to support research and development (R&D) for new preventive and treatment approaches.
Academia	Advance current research into CDI pathogenesis and models of transmission.
Clinical societies	Provide the clinical description of the need for enhanced surveillance, point of care diagnostics, prevention, and treatment of CDI.
Government and payers	Develop evidence base and frameworks for the assessment of preventative symptom reduction and curative approaches, as well as establishing the cost burden of CDI.
Patients/society	Communicate on the societal impact of CDI and its impact on patients, public health, and society as a whole.

This project builds on previous and ongoing efforts sponsored by both international public health bodies and national governments such as Centers for Disease Control and Prevention (CDC) sponsored epidemiology research [13], European Centre for Disease Prevention and Control (ECDC) sponsored ECDIS survey [3] and ECDIS-Net project (2010-2014), the ECDC study on European surveillance of *C. difficile* infections [7]; UK registry studies [20]; industry-sponsored initiatives such as the EUCLID epidemiology study [6] and ClosER resistance surveillance study [10], as well as 221 completed or ongoing clinical studies [4] and analyses of healthcare databases (claims and other databases).

Scope

The objective is to develop a detailed understanding of the epidemiology and clinical impact of CDI. More specifically, this project aims to:

- align and understand the unmet public health needs relating to CDI;
- identify the direct and long-term burden on healthcare systems;
- set up an EU research platform that will provide support for potential proof-of-concept studies of new prevention and treatment strategies.

This project will attempt to synthesise all efforts made at EU level so far to understand the epidemiology and clinical impact of CDI at multinational, national and local levels and fill in key remaining gaps that are key to supporting effective control and prevention strategies.

The project resulting from this action will be part of the IMI New Drugs for Bad Bugs (ND4BB) programme launched in May 2012 in response to the challenge of rising antimicrobial resistance in Europe[7].

Expected key deliverables

- Create and communicate a multifaceted understanding of CDI epidemiology across the European region.
- Provide insights into the differences in incidence, strain prevalence, reporting and testing practices, current control measures, diagnosis and treatment variations within and between countries.
- Quantify the burden of disease (including primary infections and recurrence) and outcomes related to the disease in acute hospital, nursing home/long-term care facility and community settings.
- Identify potential reservoirs of CDI spread (community paediatrics, food/agriculture and environment) and the drivers for transmission between and within community and healthcare settings.
- Identify opportunities for innovative prevention and treatment strategies.
- Establish a pan-European multidisciplinary-based research platform.

Expected impact

The better understanding of CDI burden, transmission and control practices across Europe will provide a basis for the further development of public health intervention and practices. It will provide information so that the CDI issue is addressed with the level of priority it deserves. In addition, the research platform will help in speeding up the development of alternative prevention and treatment approaches.

Potential synergies with existing consortia

Applicants should take into consideration, while preparing their short proposal, relevant national, European (both research projects as well as research infrastructure initiatives), and non-European initiatives. In particular, the applicants should seek alignment with the ECDC initiatives listed below so that there is no duplication of effort and findings from these initiatives can inform project deliverables:

- European surveillance of CDI in acute care hospitals, launched in January 2016;

[7] http://www.imi.europa.eu/content/nd4bb

- project ‘Microbiological support to European surveillance of *Clostridium difficile* infections’, 2016-2018;
- point prevalence survey of healthcare-associated infections and antimicrobial use in acute care hospitals, 2011-2012 and 2016-2017;
- point prevalence survey of healthcare-associated infections and antimicrobial use in long-term care facilities (HALT-3 project), 2016-2017;
- project ‘HAI-Net mortality review validity and reproducibility study’, including validation of direct review of attributable mortality in patients with CDI.

Synergies and complementarities should be considered, building on achievements, and, when possible, incorporating data and lessons learned while avoiding unnecessary overlapping and doubling of efforts. In particular, the project should attempt to build on previous initiatives both sponsored by the ECDC, local governments or industry sponsored initiatives. Potential synergies with the outcomes of the EPIWORK FP7 should also be explored.

Being part of the IMI ND4BB programme, it is expected that close interactions and collaboration with other ND4BB projects will take place, especially with the COMBACTE projects which are establishing networks including the epidemiology network EPI-Net, and the TRANSLOCATION project for the use of and contribution to the ND4BB Joint Information Centre.

Industry consortium

- Sanofi Pasteur (lead)
- Astellas
- AstraZeneca
- GSK
- Merck
- Pfizer

The industry consortium will contribute knowledge and expertise in all project work packages in areas like infectious diseases, and more specifically *C. difficile* epidemiology and surveillance, drug development, outcome research, and health economics.

Indicative duration of the project

The indicative duration of the project is 36 months.

Future project expansion

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

Such further work would be the natural progression of the project leveraging any success achieved. Building on these prior successes and positive results would maximise the long term impact of the larger project. Any proposed project extension would also take advantage of already established collaborations and networks forged in the overall project, thereby maximising efficiency on time and resources. A restricted Call would

achieve this in the most efficient way. The detailed scope of the restricted Call shall be described in the relevant Annual Work Plan.

Indicative budget

The indicative EFPIA in-kind contribution will be EUR 3 000 000.

The IMI2 contribution will be a maximum of EUR 3 000 000.

Applicant consortium

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

The applicant consortium is expected to address all the research objectives and make key contributions to the defined deliverables in synergy with the industry consortium which will join the selected applicant consortium in preparation of the full proposal for stage 2. This may require to mobilise at the minimum the following expertise, originating in academic institutions, public health bodies and policy makers.

- access to healthcare databases and surveillance data (including molecular data);
- understanding of the limitations of historical datasets and approaches to minimise these issues;
- experience of handling and analysing large and complex data sets from multiple sources;
- experience with prospective data collection;
- infectious disease modelling expertise;
- ability to establish links with partner organisations to access diverse data sources;
- expertise in testing practice, treatment approach;
- public health programme evaluation expertise;
- expertise in cost analysis;
- ability to coordinate large research initiatives and to create a scientific network;
- experience in developing proof of concept for new prevention and treatment approaches;
- ability to attract external funding;
- proven project management skills;
- ability to assemble and coordinate multi-stakeholder discussions form both the public and the private sector and resolve blocks;
- experience with public health issue management and communication of key public health messages.

Suggested architecture of the full proposal

The applicant consortia should include in their short proposal their suggestions for creating the full proposal architecture, taking into consideration the industry contributions and expertise as indicated.

The final architecture of the full proposal will be defined together with the industry consortium and should enable activities designed to achieve all objectives and deliverables as indicated in the previous relevant

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

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

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

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

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

Work package 1: Epidemiology of *C. difficile*

In order to develop a more complete understanding of CDI epidemiology and burden of disease, this work package should address the following topics across selected European countries:

- CDI incidence in hospital, community and nursing home / long-term care facilities (LTCF);
- strain distribution;
- identification of high-risk groups for CDI, recurrences and negative outcomes;
- rate of recurrence, morbidity and mortality (including attributable mortality) for the general population and subgroups identified above;
- disease transmission model.

To avoid any duplication of work, the consortium should take into consideration existing projects/initiatives and establish potential collaborations to ensure understanding of best practices, to fill in gaps in data/research, and to extend studies/efforts.

EFPIA partner contribution: Industry has substantial experience in developing approaches to data collection and analysis for infectious disease burden estimation.

Work package 2: Disease detection and management

In order to better understand EU-wide practices in relation to CDI, this work package should address the following topics:

- heterogeneity in testing density and in following the existing guidance (including identification of missed diagnoses and empiric treatment approach practices);
- current surveillance practices and ways to improve them;
- current guidelines for disease detection, notification and management/control;
- treatment pathway for patients with CDI infection and recurrences;

- impact of CDI management on the healthcare system;
- costs of CDI, including management of multiples episodes and re-hospitalisation (healthcare perspectives including indirect financial impact on the healthcare system);
- impact of current control measures (infection control/antibiotic stewardship).

Data collection should explicitly address the broad population as well as specific sub-populations at high risk of developing complications due to CDI infection (as identified within work package 1).

EFPIA partner contribution: Industry has substantial experience in developing approaches to assess the cost of disease.

Work package 3: Build a research network and platform

We propose the creation of a multidisciplinary EU-based research platform. The platform will consist of researchers, medical and scientific societies, patients, R&D companies and venture capital (VC) firms interested and engaged in CDI. By assembling all the key stakeholders and ensuring positive synergies, communication and alignment of the various research projects, this research platform will enhance and speed up leading-edge research on CDI. It will provide support for potential proof-of-concept studies through easy access to laboratory facilities, clinical trial sites, etc.

This work package will deliver proposals for suitable models of governance, a comprehensive mapping of the relevant stakeholders and their potential role in this platform, and mechanisms to attract funding to ensure the sustainability of the initiative. Synergies with other networks like COMBACTE's CLIN-NET and EPI-NET will be explored.

Work package 3 will also ensure effective communication of the project's activities and the final results of this project to key stakeholders to attract external partners and to position the platform as an essential partner in areas related to CDI.

EFPIA partner contribution: Industry has substantial experience in partnership building around business development, proof-of-concept infrastructure needs and interaction with venture capitalists.

Work package 4: Coordination and project management

Work package 4 will establish effective governance and internal communication procedures to allow for the flow of information within the project as well. Efficient coordination of all elements of this in the project is key, given the inter-connectedness of all work packages. This work package will also fulfil the administrative tasks associated with management of this project.

EFPIA partner contribution: Project/alliance management, personnel, meeting facilities, communication expertise.

A division of the budget is suggested below, although the budget should be viewed holistically since work packages are inter-related:

Work Packages	EFPIA (in € m)	IMI JU (in € m)
WP1: Epidemiology of CDI	1.5	1.5
WP2: Disease detection and management	0.8	0.8
WP3: Build a research platform and network	0.5	0.5
WP4: Coordination and project management	0.2	0.2
TOTAL	**3**	**3**

Glossary

CDC	Centers for Disease Control and Prevention
CDI	*Clostridium difficile* infection
ECDC	European Centre for Disease Prevention and Control
EFPIA	European Federation of Pharmaceutical Industries and Associations
EU	European Union
ND4BB	New Drugs for Bad Bugs
LTCF	Long-Term Care Facilities
WP	Work package

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Topic 2: Development of immune tolerance therapies for the treatment of rheumatic diseases

Topic details

Topic code	IMI2-2016-09-02
Action type	Research and Innovation Actions (RIA)
Submission & evaluation process	2 Stages

Specific challenges to be addressed

Autoimmune diseases cover over 100 distinct diseases and syndromes, together affecting approximately 5% of the population of Europe, with two-thirds of the patients being female. The burden of autoimmune disease crosses medical and scientific boundaries, and requires cross-functional collaboration by scientists and physicians with interests in diseases of widely differing organ systems. A rather large number of therapeutic agents for rheumatoid arthritis (RA) have been developed and approved during the last 15 years, and these agents have substantially improved the disease outcome for RA patients, in particular when used early in the course of the disease. Despite recent advances in the treatment of RA using a range of biological therapies (for example anti-TNF, CTLA-4 & anti-B-cell therapies), under 30% of patients achieve long-term clinical remission, even when therapies are instituted early. A major challenge for research and drug development is now to go beyond current treatment paradigms and find ways to dramatically change the outcome, with the aim of reaching sustained remission or cure in a large majority of patients. Patients that benefit from biological therapies are treated with monthly injections and continued use of oral methotrexate, which often causes unpleasant side-effects, and sometimes leads to serious and life-threatening adverse effects due to the suppression of the immune system that is required for normal immune defence. The ultimate therapeutic ambition for rheumatologists is to provide drug-free remission for all patients. Theoretically this could be achieved using a short course or infrequent (vaccine-like) treatment to restore normal immunity and prevent further synovial damage to maintain joint function. Such a therapy would not only benefit patients with established RA, it could also be used before the onset of RA to halt the disease process at the early immune initiation phase of the disease, before any joint damage has occurred. Furthermore, insights into patients' immune status may allow stratification of patient groups to select the most appropriate treatment. This may lead to more personalised treatment of patients with RA.

Recent advances in understanding the specific immune response that drives the inflammatory pathology in RA include a rapidly emerging understanding of the fine specificity of a patient's auto-antibody and T cell response and the precise pathological role of individual antibodies. This potentially allows the identification of the major autoantigens driving a particular patient's disease and raises the possibility of tailored immunotherapies aimed specifically at modulating disease-causing immunity. Improved understanding of the role of regulatory T-cells and dendritic cells in suppressing the immune response may also lead to novel therapeutics to induce immune tolerance. Immune tolerance could be achieved using a combination of existing therapies, novel drugs and cell-based therapies and peptide immunotherapy to re-regulate and suppress the pathogenic immune response in RA. RA is an ideal disease setting for the study of tolerance-inducing therapies. This is due to recent insights into the immunology of RA, coupled with advances in autoantibody identification and T and B-cell monitoring. Furthermore, a number of potential therapies exist or are being developed in pharma & biotech companies, which could be investigated using the methods developed within this project.

Need and opportunity for public-private collaborative research

The proposed work will focus on a key set of immune-mediated diseases or disease mechanisms where working in partnership will benefit the knowledge base and accelerate delivery of drug treatments to patients.

Drug free remission through immune tolerance is the 'holy grail' of immunology research and such a challenging ambition can only be achieved through extensive collaboration between patients, industry partners, SMEs, clinical investigators, and scientists.

There is a critical need for methods to allow patient stratification and personalised treatment of patients, to achieve remission in rheumatoid arthritis. Collaborative efforts in a public-private partnership are most likely to achieve this ambitious goal. The development of biomarkers to detect immune-tolerising effects in patients requires interaction between clinical investigators for patient samples and EFPIA companies for access to technology and data analysis. SMEs can provide key technologies for biomarker development. These techniques can also be used to monitor the effects of potentially tolerising therapies in a very precise manner. Examples of these techniques are multiplex assays for pathologically relevant autoantibodies and major histocompatibility complex (MHC) class II based tetramer techniques for monitoring of T cell reactivity, including induction of antigen-specific T regulatory cells. Notably, auto-antibodies from RA patients, detectable with these techniques, have been shown to cause direct pathological effects such as bone erosion and pro-inflammatory neutrophil activation.

Scope

The ultimate goal is to develop a translational research project for the induction and monitoring of immune tolerance in RA including the following aspects.

- Development of 'companion diagnostics' that make it possible to recognise specific immune reactions in different subsets of patients with RA and other relevant inflammatory disease including lupus and myositis.
- Development of tools for immuno-monitoring of T and B cell numbers and phenotype (cell surface expressed markers and transcriptome analysis), as well as for other relevant immune and non-immune cell types. These tools should enable the evaluation of immunological effects of potential tolerance-inducing therapies.
- Identification of relevant RA patient cohorts that would be suitable for testing 'tolerising' therapies. Patient selection could be based on genetics, response to therapy, immune phenotype and auto-antibody profiles for example.
- Conduct experimental medicine studies using a small number of carefully selected RA patients to monitor changes in immunity following therapeutic intervention.

In addition to immunotherapy and cell-based approaches, EFPIA partners may have existing immuno-modulating therapeutics that could be assessed in this setting. SMEs with immune-monitoring technology could make a significant contribution.

The safety of tolerance inducing is a key concern. Pre-clinical safety data would be needed in order to progress a novel therapeutic into clinical studies.

Expected key deliverables

Expected key deliverables are likely to include the following.

- Biomarkers for monitoring the development of autoimmunity and status of immune tolerance. This is a pre-requisite step in order to advance novel therapeutics into the clinic and is critical to allow pharmaceutical companies to assess novel therapeutics in early clinical trials.
- Methods to stratify patients for clinical studies of immune tolerance. This is essential to reduce failure rates in early trials and accelerate novel therapies to the correct patient population.
- Methods for T & B-cell phenotype and function and monitoring of autoantibody profiles.
- Experimental medicine studies in RA patients to evaluate novel therapeutics and their effect on biomarkers of immune function and a tolerant immune state. It could be established immunomodulators or novel therapeutics in early clinical development.
- Identification of new drug targets and pathways with the potential to induce immune tolerance, thus expanding the available repertoire of immune-tolerant targets available to treat autoimmune disease;
- A repository for new data will be established to allow mining for new targets and pathways.

Expected impact

The expected impact would be as follows.

- Demonstrating tolerance and an enduring improvement of clinical endpoints in RA requires lengthy clinical studies. Identifying and validating biomarkers that can distinguish between a pathogenic or a quiescent tolerant immune phenotype would enable mechanistic proof of concept for a novel therapy before embarking on lengthy studies.
- Selecting RA patients that are amenable to tolerising approaches improves the chance of success in a small number of patients.
- Investigating the tolerising potential of existing treatments will serve as a benchmark against which novel molecules can be compared.
- If successful, immune tolerance approaches would revolutionise the treatment of existing RA by inducing drug-free remission. Coupled with diagnostic tests and screening initiatives for ‘at-risk’ individuals, treatment of pre-arthritic patients may be able to stop the disease process at the immune phase before inflammation and joint damage can occur. For the healthy but at-risk patient, this would offer a screening and ‘vaccination’ treatment for the prevention of RA.
- This project strongly supports the IMI2 goals for improved therapies and precision medicine.

Potential synergies with existing consortia

Collaboration with other consortia investigating immune tolerance in other disease settings is sought.

- As RA has emerged as a key disease for testing of generic technologies for immune tolerance, the proposed IMI-supported consortium would constitute a very attractive partner for other international initiatives in this area. Building on the outcomes of the existing BT-CURE project and with others such as RA-MAP, TargetIng novel Mechanisms of Resolution in inflammation (Timer), Targeting Src-family tyrosine kinases in chronic autoimmune and inflammatory diseases (TARKINAID), and Tolerance Restoration In Auto-immune Diseases (TRIAD) is desirable.
- The National Institutes of Health (NIH) ‘Tolerance Network’ as well as the recently-started ‘Accelerating Medicines Partnership (AMP)‘ would be key collaborators. Notably, no RA studies are currently ongoing within the NIH tolerance network, and a contribution from European rheumatologists is highly sought after from the NIH networks, in particular as translational research in RA is generally more advanced in Europe than in North America.

Industry consortium

- UCB
- Janssen
- GSK
- Sanofi

Anticipated contribution from EFPIA partners involved:

- Provision of reagents including proteins, antibodies and small molecule tools.
- Provision of clinical samples for analysis.
- Access to cell analysis technology and 'omic' technology.
- Bioinformatic analysis.
- Experimental therapeutics – drug substances.
- Patient samples from ongoing clinical trials.
- Post-doctoral funding for patient sample analysis.
- Other sectors, in particular within the diagnostic area would be able to make very substantial contributions. Novel health informatics tools, in particular tools aimed at providing direct contact between patients and healthcare at early stages of the disease (pre-RA) will be highly beneficial.

Indicative duration of the project

The indicative duration of the project is 60 months.

Indicative budget

The indicative EFPIA in-kind contribution will be EUR 6 000 000.

The IMI2 contribution will be a maximum of EUR 6 000 000.

Applicant consortium

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

The applicant consortium is expected to address the objectives and make key contributions in synergy with the industry consortium which will join the selected applicant consortium in preparation of the full proposal for stage 2. The applicant consortium should summarise their abilities to make assured key contributions in synergy with the industry partners of the consortium (within the framework of the project duration and maximum IMI2 contribution). The applicant consortium should be commensurate with the size of budget and outlined work plan.

They are expected to contribute:

- experienced in the clinical investigation of RA;

- a detailed understanding of immune response in RA and methods for immune monitoring;
- access to patient cohorts and the ability to conduct interventional studies;
- SMEs that can provide relevant immune monitoring technology;
- The involvement of patient groups and regulatory advice from the European Medicines Agency (EMA) and Food and Drug Administration (FDA) as required, particularly for the early treatment of pre-arthritic patient populations.

Suggested architecture of the full proposal

The applicant consortium should include their suggestions for creating the full proposal architecture in their short proposal, taking into consideration the industry contributions and expertise provided.

The applicant consortium is expected to address all the research objectives described in the work packages and make key contributions on the defined deliverables in synergy with the industry consortium. A suggested architecture is provided below. The work packages below are quite broad in outline and different specific project proposals, along with proper justifications, within each work package are expected to be developed by the applicant consortium.

Work package 1: Management, coordination, dissemination and sustainability

- Overall coordination of the scientific work packages, budgets, delivery and dissemination of findings and sustainability planning.

Work package 2: Technologies for monitoring immune state.

- Deep immunophenotyping of patient samples using state of the art technologies such as T cell specificity using tetramers, autoantibody profiling and others.

Work package 3: Patients, cohorts and ethics

- Analysis of retrospective and design and prosecution of prospective clinical trials.

Work package 4: Mechanisms of immune tolerance - basic research

- Detailed analysis of patient tissues and samples to identify novel targets and pathways relevant to immune tolerance.

Work package 5: Bioinformatics and data

- Integration of historic and prospective data for the identification of biomarkers, stratification of patient cohorts and potentially new clinical targets.

In the spirit of the partnership, and to reflect that IMI2 Call topics are built upon identified scientific priorities agreed together with EFPIA beneficiaries/large industrial beneficiaries, it is envisaged that IMI2 proposals and projects may allocate a leading role within the consortium to an EFPIA beneficiary/large industrial beneficiary. Within an applicant consortium discussing the full proposal to be submitted at stage 2, it is expected that one of the EFPIA beneficiaries/large industrial beneficiaries may elect to become the coordinator or the project leader. Therefore to facilitate the formation of the final consortium, all beneficiaries are encouraged to discuss

the weighting of responsibilities and priorities therein. Until the roles are formally appointed through a consortium agreement the proposed project leader shall facilitate an efficient negotiation of project content and required agreements.

Glossary

EMA	European Medicines Agency
FDA	US Food and Drug Administration
MHC	Major Histocompatibility Complex
NIH	National Institutes of Health
RA	Rheumatoid Arthritis
WP	Work package

Topic 3: Data quality in preclinical research and development

Topic details

Topic code	IMI2-2016-09-03
Action type	Research and Innovation Actions (RIA)
Submission & evaluation process	2 Stages

Specific challenges to be addressed

Reproducibility and relevance [1] (e.g. use of models with good predictive and construct validity, proper choice of statistical analysis) of research findings represent the pillars of the scientific method. For drug development, robust data and scientific rigor are key drivers for decision making, determining patent strength, time-to-market and consequently availability of new treatments to patients.

Substantial evidence has accumulated that the robustness, rigor and validity of research data can be problematic [2] [3] [4] [5] [6] [7] [8] [9]. This is of major concern for agencies funding research and the public [10] [11] [12], and has led to major overhauls of data publication guidelines [13] [14] [15] [16]. It also has direct impact on conclusions made regarding the predictability of preclinical models and/or the quality of drug targets for evaluation in clinical proof-of-concept studies. Higher failure rates due to non-reliable scientific data increase the risks and costs associated with R&D [17] and hamper the successful translation of innovation into novel treatments for patients [9] [18] [19].

Clearly, the issues at hand concern all areas of R&D and hamper progression through the drug development pipeline for industry and academics that want to engage in drug development. For the proof of principle, the wish is to make a start with this pilot topic by studying the situation in neuroscience, where a large amount of data is available both from the public and the private sectors and the impact would be very high [1] and comparing this with preclinical safety pharmacology, an area of preclinical R&D also running non-regulated studies, but often under good laboratory practice (GLP)-like conditions, to identify the key factors affecting data quality and develop some solutions.

Need and opportunity for public-private collaborative research

Many factors may contribute to this situation, including technical/methodological, cultural (e.g. publication pressure, funding requirements and biased reporting) [5] [20] [21] [22] and educational (e.g., issues with the experimental design and quality expectations) [8] [23] [24] aspects; there are differences in how researchers in various organisations handle data quality, which hampers rapid and successful innovation and progress in R&D, as well as in academic research.

There is a need for simple, sustainable solutions that facilitate data quality without impacting innovation and freedom of research. Therefore, a joint, collaborative effort is required to facilitate understanding of the different perspectives and to allow exchange of best practices. This mutual understanding between industry and academia is of greater importance than ever before due to the increasing externalisation of research activities by the pharmaceutical industry and the rise in industry-academic collaborations. It fosters the interaction between scientists from different organisations and between quality and research organisations,

and forms the basis to ensure any recommendations to improve the quality of research data will be widely accepted.

To competently address the issues of preclinical data quality, expertise in various fields needs to be combined, such as neuroscience drug discovery and basic research, especially animal model development, as well as in preclinical safety studies, quality assurance, information technology, data management, educational expertise, fundraising, publishing, and regulatory advice. This will require the pooling of resources and can best be achieved by a public-private collaborative effort.

Scope

Starting with a first pilot action focused on some specific areas of neuroscience and safety, the goal is to advance the quality and hence the exploitation potential of the data produced by discovery R&D explorative and hypothesis-testing activities. This action should provide the evidence/data that enable the development of quality criteria for new and/or improved preclinical tests (objective 1). Based on those data, consensus quality management recommendations in non-regulated R&D should be developed to enhance the quality of decisions made based on experimental, explorative or hypothesis-testing data (objective 2). Finally, developing an educational course on data quality would be a major contribution to enhancing the quality culture in preclinical research (objective 3). The action should also contribute to the development of a proficiency test system (ring tests) in preclinical research and to the implementation and testing of the quality principles developed by the consortium in day-to-day research settings, both in academia and industry, to achieve maximal cross-fertilisation.

Objective 1

Objective 1 will be addressed by compiling preclinical research data across industry and academia that help to determine the primary variables in study design and data analysis that affect data quality and levels of robustness. This knowledge will help to design future studies in a manner to minimise variance and enhance reproducibility. The principles, strategies, and research models evolving from this process will be tested and validated in prospective studies.

Objective 2

To achieve objective 2, simple and sustainable best practice solutions have to be agreed upon, based on quality of experimental design principles. A quality system has to be developed that will help researchers to run experiments faster and generate higher quality data. While many quality systems can be generated, they should be lean and fit for purpose, and this is what needs to be developed, including organisational structure, procedures, processes and resources needed. There will be a need for a mechanism to maintain quality principles and have them evolve over time as the scientific landscape evolves, which requires a tool to evaluate whether the principles are being followed, including minimal ‘pass’ criteria for quality systems. There must be a mechanism by which the quality principles can be updated should a sense check reveal valid reasons to do so. Options should be evaluated on how to set up a third party accreditation system.

Objective 3

A cross-sector educational platform needs to be developed that facilitates awareness and sharing of criteria and principles to ensure robustness and quality. Common themes applicable to all fields of research are e.g. accuracy, traceability, reconstructability, an unbiased approach, and open scientific collaborations. Such a training platform will educate a new generation of young scientists familiar with both academic and industrial research environments and enable them to foster a change of the mindset of other scientists and research organisations. This will improve the value and sustainability of the findings from preclinically relevant research

activities as mentioned above. The goal is to develop an effective, positive and engaging, yet informative electronic training course on scientific quality principles.

Expected key deliverables

Based on these objectives, a number of key deliverables have been identified.

- Develop generally applicable, lean and efficacious quality principles for preclinical research in the biomedical field: identify best practices from each partner, arrive at (generally applicable) quality principles for non-regulated preclinical research.
- Review existing guidelines and carry out a white paper exercise to develop key principles for guiding the development of standard assays that can be used by research laboratories (academic, industry, and contract research organisations - CROs) to improve robustness, reproducibility and research efficiency.
- Define a quality assurance system fit for purpose (define appropriate risk levels for different research phases), generate metrics to define success, implement and beta-test that system via an industry/academia young researchers (e.g. PhD) joint exchange scheme; deliver a quality system ready for implementation in industry and academia in non-regulated research.
- Develop cross-site criteria for audit outcomes; combine metrics from different partner companies and universities – feasibility testing by cross-partner auditing. Evaluate the feasibility of a third-party accreditation system so that institutions can apply for a data quality label.
- Establish a database that allows open sharing of information of replication attempts by partners. Consider development of a data sharing platform that would allow storage and sharing of raw data beyond the IMI consortium, e.g. in association with a publisher. Evaluate the quality of metadata through proper integration and sharing [25].
- Collect historical cross-company data and study protocols in that database, run meta-analyses and integrated analyses on these data as part of the industry/academia young (e.g. PhD students) researchers joint exchange scheme, determine the factors that underlie the robustness and generalisability of commonly used assays.
- Test agreed principles of preclinical data generation prospectively in commonly used, harmonised assays as part of the industry/academia young researchers joint exchange scheme; perform ring testing.
- Evaluate existing training modules and develop a comprehensive training platform tailored to young scientists, to be implemented as an industry/academia young researchers joint exchange scheme.

Expected impact

These efforts can be expected to result in an improvement in the data quality of pre-clinical studies via the delivery of reliable and reproducible models with harmonised and standardised protocols and procedures. There will also be a significant contribution to the 3Rs (replacement, reduction and refinement) in the use of experimental animals in preclinical research, to intellectual property (IP) protection and regulatory success by ensuring the validity and traceability of data. Researchers will learn upfront how to consistently generate reliably reproducible preclinical research data that are of sufficient quality to underpin industrial development efforts. This will be directly addressed in the young (e.g. PhD students) researchers exchange scheme jointly run between industry and academia, which will both facilitate usability testing of the newly-developed quality principles and serve as a nucleus from where knowledge of best practice will expand. Through dissemination of the scientific quality principles we expect a cultural change and ripple effect.

The proposed joint public-private project should have a high perceived credibility and will provide scientists, funding agencies, publishers and regulatory bodies with robust guidance for research undertaken in the non-regulated field. It will allow for benchmarking across institutes to exchange best practices and arrive at

common standards for preclinical research. Common quality expectations will foster collaborations among big pharma, start-ups, public and private research organisations and academia. Accreditation, consensus recommendation on quality management and an education module on data quality will facilitate uptake of innovation from academia and SMEs into the R&D process and will obviate the need for duplicate assessment by external partners.

The data producers community should be broadly consulted and involved during the course of the action. This would help establish common understanding and is crucial to ensure impact.

Potential synergies with existing consortia

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

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

Possible synergies could also be developed with activities led by other important organisations active in the field, for example, patient organisations, such as Alzheimer Research UK[8], learned quality societies, such as the Research Quality Association (RQA), UK[9], or scientific networks, such as the European College of Neuropsychopharmacology (ECNP) Preclinical Data Forum Network[10] or the European Infrastructure for Translational Medicine (EATRIS) Network[11]. Synergies could also be developed with IMI consortia where cross-site preclinical data have already been generated that could be used for further retrospective analysis, (e.g., from PharmaCog, NewMeds and EU-AIMS), and other relevant EU-funded and national projects. Applicants are encouraged to approach any initiative with relevant activities in the field for possible integration in the consortium.

Industry consortium

- Janssen (lead)
- Abbvie
- Boehringer-Ingelheim
- Novartis
- Orion
- Pfizer
- Psychogenics
- Roche
- Servier
- UCB

The industry sectors that are expected to contribute to the project are pharmaceutical, quality and information technology (IT), all of which share a common interest to improve the quality of preclinical experimental data.

[8] http://www.alzheimersresearchuk.org/
[9] http://www.therqa.com/
[10] https://www.ecnp.eu/projects-initiatives/ECNP-networks/List-ECNP-Networks/Preclinical-Data-Forum.aspx
[11] http://www.eatris.eu/

Expertise at industry partners ranges from experience in preclinical *in vivo* and *in vitro* neuroscience (focus on psychiatry and neurodegeneration) and drug safety-related discovery activities/experimentation, translational research, strong expertise in quality management, provision of existing data sets (focus on psychiatry and neurodegeneration), statistical expertise, data management and project management, to provision of specific transgenic model organisms and tool compounds.

Indicative duration of the project

The indicative duration of the project is 36 months.

The focus of the action generated from this first topic will be on neuroscience (focus on psychiatry and neurodegeneration) and safety. However, the principles developed in this consortium will be applicable R&D-wide. If validity of the approach can be demonstrated in the areas of neuroscience and safety, expansion into other areas of R&D can be considered for follow up calls for proposals building on outcomes from this pilot initiative.

Indicative budget

The indicative EFPIA in-kind contribution will be EUR 4 500 000.

The IMI2 contribution will be a maximum of EUR 4 500 000.

Due to the global nature of the participating industry partners, and given the scope of the topic, part of these contributions may be provided from non-EU/H2020 associated countries. The contribution includes the financial and in-kind resources to cover half of costs of shared young researchers (e.g. PhD student level) between each industry partner and an academic / SME partner.

Applicant consortium

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

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

This may require mobilising, as appropriate, expertise in: preclinical neuroscience (focus on areas synergistic with those of the industry partners) and safety, capabilities for the analysis of large datasets, neuropharmacology, preclinical safety, systems biology/toxicology, pharmacokinetics, biomarkers, imaging, data management, quality assurance, and the health authorities (the latter in an advisory role to benefit from experience in the regulated space), academic research integrity / ethics / quality groups focusing on non-regulated preclinical research, research intensive SMEs.

The applicant consortium may also need to mobilise, as appropriate, the following resources: old and newly generated data, especially from *in vivo* animal models, including electrophysiological and behavioural data, to the database, synergies with patient, (neuro)science or quality organisations, (as outlined in the synergy section), and ongoing PhD student programmes/schemes to be leveraged: however the students have to have at the start of the action all necessary qualifications for the performance of the tasks attributed to them.

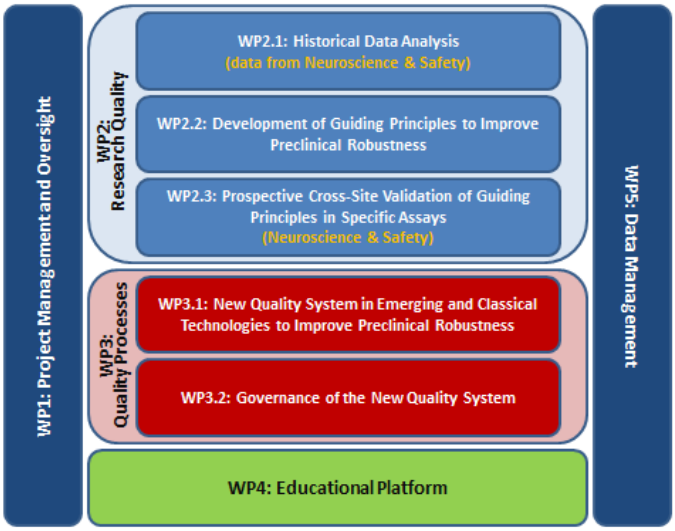
Suggested architecture of the full proposal

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

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

Individual industry partners have already started collecting information on internal efforts that can be mobilised to address some of the issues mentioned in the work packages below, and these will be contributed to the development of the full proposal and later on to the implementation of the action. However, only fragments of the knowledge required are available at individual partners. Only by combining these fragments and linking them with those provided by the applicant consortium will it be possible to generate an overall picture, thereby increasing the value of the collected information.

The work packages below are quite broad in outline and different specific project proposals, along with proper justifications, within each work package are expected to be developed by the applicant consortia.



Work package 1: Project management and oversight

This work package will address the strategy and implementation of the project management. This will encourage regular meetings and interaction between sub-groups and teams to coordinate and follow up on the work effort.

Industry contribution: Assurance of one consortium entity & project management including planning, budgeting, follow-up and tracking, and consolidation of work package reports. Project risk management and comprehensive communication and dissemination of its progress and its milestones are important additional elements of the EFPIA contribution.

Expected applicant consortium contribution: providing detailed follow-up and tracking, via regular work package reports, early reports of any unexpected organisational or structural issues or delays with respect to the project deployment and intermediate objectives.

Work package 2: Research quality

Work package 2.1: Historical data analysis

In this work package data should be compiled across industry and academia to determine the primary variables in study design and data analysis that affect data quality and levels of robustness.

Industry contribution: providing data and study protocols from neuroscience (focus on psychiatry and neurodegeneration) and safety *in vivo* and *in vitro* assays frequently used across different companies so that research methodologies can be catalogued; supervision of shared young researchers (e.g. PhD students).

Expected applicant consortium contribution: meta-analysis and integrated analysis of data; identification of factors determining robustness and generalisability of commonly-used assays; supervision of shared young researchers (e.g. PhD students).

Work package 2.2: Development of guiding principles to improve preclinical robustness

There are no agreed sets of principles across industry, governments, other funders, and academia that guide how to strengthen the robustness of scientific research. The goal of this work package is to increase the success rate to reproduce findings from the literature and to increase the number of valid targets and hence to make preclinical science more efficient.

Joint contributions: review existing guidelines and carry out a white paper exercise to develop key principles for guiding the development of standard assays that can be used by research laboratories (academic, industry, and CROs) to improve robustness, reproducibility and research efficiency. This should start by: development of initial principles based on literature and policy reviews: establish criteria that can be used to guide the development of robust and quality pre-clinical data and define parameters that are important for research robustness depending on the assay. Then in the next phase there should be: refinement of those principles and criteria based on input from work package 2.1 and work package 2.3; establishment of a system that allows systematic evaluation of the reproducibility and validity of published work.

Work package 2.3: Prospective cross-site validation of guiding principles in specific assays

This work package will validate the principles, strategies, and research models that improve robustness and data quality in research, with an initial focus on neuroscience and safety (focus on psychiatry and neurodegeneration). Using input from work package 2.1 and work package 2.2, this work package will test the identified principles, strategies, and models in multiple research settings to determine if the identified variables do indeed lead to increased or decreased robustness.

Joint contributions: define specific, harmonised test protocols for the assays to be used to test the principles developed in work package 2.2, define and implement quality criteria specific to the assays used across sites; validate the robustness of measures in tests focusing on behavioural, electrophysiological and neurochemical studies in rodent models (esp. in transgenic animals) for cognitive dysfunction and synaptic plasticity in neurodegenerative (esp. Alzheimer's disease) and psychiatric disorders, involving studies of memory, attention, cognitive control, basal synaptic transmission, connectivity and translational electroencephalography (EEG) methods. This focus has been chosen to optimally capitalise on the resources and capabilities of the participating EFPIA partners and to ensure generation of sufficient data in comparable assays to address the assumptions related to quality. Develop statistical approaches based on sharing of young researchers working both in industry and academic environments; there should be interest in a joint study of the applications of Bayesian and frequentist methods, including meta-analytic approaches, for example, for analysis of historical data sets, using historical control information for the design, validation and analysis of a large number of sequentially executed discovery research experiments. Development of preclinical proficiency testing for quality and robustness (ring testing); supervision of shared young researchers (e.g. PhD students).

Work package 3: Quality processes

Work package 3.1: New quality system in emerging and classical technologies to improve preclinical robustness

In this work package, generally applicable, lean and efficacious quality principles for biomedical research should be developed. This will involve filtering out best practices from each partner's current approach, development of a common language and understanding, arrival at pharma-wide quality principles for non-regulated research and finally measurement of success by beta-testing.

Joint contributions: define a quality system fit for purpose (phase-appropriate quality), generate metrics to define success (can be cultural/perceptional as well as factual); implement and beta-test the system in the joint young researchers (e.g. PhD students) programme, with a focus on one or two specific emerging technologies from neuroscience and/or safety; measure and combine data from different partners; deliver a quality system ready for implementation innovative/explorative research in industry and academia.

Work package 3.2: Governance of the new quality system

There is a need for a mechanism to maintain quality principles and have them evolve over time as the scientific landscape evolves. Part of this feedback loop consists of a tool to evaluate whether the principles are being followed, including minimal 'pass' criteria for quality systems, and a mechanism by which the quality principles can be updated should a sense check reveal valid reasons to do so. The governance of the new quality system should also oversee and qualify the training measures under work package 4.

Joint contributions: establish minimal acceptability criteria for quality systems; generation of a 'risk assessment' tool to evaluate quality systems with definition of appropriate risk levels for different research phases; cross-site criteria for audit outcomes with exploration of possibilities for informal audits across partners; combination of metrics from different partner companies and universities; establish a governance mechanism for pharma principles.

Investigate whether a third party accreditation system, which would allow institutions to apply for a quality label, is a viable option.

Work package 4: Educational platform

Currently there are limited mechanisms in place to apply the learnings of how to improve robustness and quality across the pharma and academic sectors. A cross-sector strategy needs to be developed to improve awareness and sharing of criteria and principles necessary to address robustness and quality. Common themes applicable to all fields of research are e.g. accuracy, traceability, reconstructability, an unbiased approach, and open scientific collaborations. This education campaign will also improve the sustainability of the findings from the other work packages.

Joint contributions: the goal is to develop a positive, engaging, yet informative electronic training course on scientific quality principles; this should first evaluate existing training modules; then determine the best format; build the platform; incorporate work package 3.1 agreements; apply in an industry/academic young researchers (e.g. PhD students) joint exchange scheme, and eventually disseminate the (pharma) wide principles.

Work package 5: Data management

To support the other work packages, a data management system/database is needed, able to host historical and newly-generated assay/test data, as well as study protocols. Additional properties needed include e.g. document storage / sharing system. The database should allow easy data access and retrieval of data and protocol information as a prerequisite to allow benchmarking of different assays in terms of reproducibility, outcome (specificity, sensitivity) and robustness.

Industry contribution: standard data warehouse for assay data and standard collaboration platform (SharePoint-like) for document storage/sharing to allow fast implementation; development of a common template to optimise transfer of data into the database; data manager.

Joint contribution: pre-processing by participants needed to ensure data fit into the database; consider development of data sharing platform that would allow storage and sharing of raw data beyond IMI consortium, e.g. in association with a publisher. The plan is to make the database publicly available and to build as much as possible on already existing infrastructure, e.g. Mendeley.

Glossary

CRO	Contract Research Organization
GLP	Good Laboratory Practice
EEG	Electroencephalography
EFPIA	European Federation of Pharmaceutical Industries and Associations
EU	European Union
H2020	Horizon 2020 Framework Programme
IP	Intellectual Property
R&D	Research and Development
SMEs	Small Medium Sized Enterprises
Scientific rigour	trustworthiness / credibility; judged by how narrow, concise, and objective the design and analysis techniques are and how scrupulously the rules have been adhered to and applied to all decisions
WP	Work package

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Topic 4: Next generation of electronic translational safety – NexGETS

Topic details

Topic code	IMI2-2016-09-04
Action type	Research and Innovation Actions (RIA)
Submission & evaluation process	2 Stages

Specific challenges to be addressed

Efficient and adequate safety assessment remains one of the main challenges in the drug discovery, development and submission process. Progress in the area demands a larger degree of data sharing across involved actors and along the development pipeline, more accurate prediction methods, streamlined transfer of information to regulatory authorities, and ways of mining and analysing data in safe, flexible and efficient procedures. These should encompass pre-clinical, clinical and post-authorisation studies for a holistic understanding of safety issues that allows optimisation of risk-avoidance strategies, resulting in safer medicines being made available faster to patients.

Recent advances achieved in international initiatives, including the IMI eTOX project initiated several years ago, have shown that sharing of pre-clinical data, both private and public, is achievable through the combination of legal (IP), IT and honest broker concepts. Ontology development has also been fostered in the area, and systems to handle, mine and exploit these data across studies, compounds, pharmacology, side effects and other criteria have been created and partly implemented within industry.

In parallel, the electronic CDISC-SEND format has been chosen for file submission in IND/NDA/ANDA/BLA[12] to the FDA. As well as offering an opportunity for automatic collection of data and data sharing via a common platform for reasons of data transparency, this will make it possible to carry out more powerful predictive data analyses. Existing initiatives in the field offer a relevant basis for an expanded IMI-based effort that leverages databases and data sharing. The intended framework of the proposed project will provide a cost-efficient, ideal environment for incorporating these data, optimising tools and providing linkage to human safety information to support the described regulatory-compliant, holistic perspective. In addition, tools for multivariate and multilevel data analysis and modelling, comparative data display across studies and compounds shall be developed within the proposed project to enable meaningful exploitation of the accrued data.

Beyond data sharing and mining, prediction of potential toxicity events both in preclinical species and in humans is key. The in-depth assessment of the preclinical species predictivity to human can only be achieved by analysing as large an amount of organised data as possible. The linking of pre-clinical databases to chemical and biological knowledge and to human clinical data probably represents the most powerful approach to achieve this endeavour and offers a unique opportunity. Such a translational approach will greatly advance the assessment of the relevance of animal findings for humans. In addition, it will contribute to the public discussion regarding the necessity of animal studies during drug development. Due to the sheer amount of data involved, this preclinical cross-species analysis to human safety data would be the most exhaustive so far. It may therefore, have a very high impact on the 3Rs and animal welfare in the

[12] See glossary for acronyms.

pharmaceutical industry, fitting with Directive 2010/63/EU[13] on the protection of animals used for scientific purposes.

Need and opportunity for public-private collaborative research

To address this challenge, a broad multidisciplinary consortium is required including pharmaceutical companies to provide large datasets on a diverse chemical and pharmaco-toxicological space. While the primary focus will be on pharmaceutical data, the involvement of companies from the agro-chemical and cosmetics sector could also be envisaged. An independent honest data broker is needed to allow all participants to share data comfortably in a secure environment. In addition, experienced software companies are necessary to provide expertise in data analysis, data display and visualisation as well as interfacing with various types of pharmacological, preclinical and clinical databases. In particular, the curation of clinical databases and exploitation of health records for research as well as for the development of new predictive tools will require academic partners and SMEs.

The involvement of health authorities is also needed to guide and advise on activities and acceptance criteria for the predictive models generated as part of the proposed project.

Scope

Development of an internationally accepted guideline for data sharing

Gather the key decision makers to set up general guidelines for data collection, sharing and protection of pre-competitive data. These guidelines could be pushed up to the Organisation for Economic Co-operation and Development (OECD) level for general acceptance for this and further initiatives where pre-competitive data sharing is at the heart of the project.

Accrual of larger sets of data

The participating pharmaceutical companies will share preclinical and high-level clinical safety data on their drugs (small chemical and biological entities) and their applicable targets that were evaluated in good laboratory practice (GLP) and non-GLP animal toxicology studies and progressed into clinical trials (phase 1, 2 and/or 3) or received market approval. Details of safety pharmacology, general toxicity, developmental / reproductive toxicity studies and carcinogenicity data will need to be entered into the database, along with exposure information. *In vitro* safety studies and pharmacological information conducted in the discovery phase should also be entered into the database. Clinical data should include exposure information and adverse events considered to be related to the drug.

All data will be coded and collected anonymously through a third party, leveraging data already collected in other initiatives where possible. Individual animal data will be leveraged when needed from the SEND database that will be developed in work package 4 of NexGETS.

These proprietary data will be first collected as confidential (individual or average data without sharing company origin, chemical structures, compound name, code or CAS number, and pharmacology). The status of these data will evolve to non-confidential (e.g. including all the details mentioned above) upon criteria that have to be agreed between the various industrial partners, however, the data owner (i.e. the company that originally generated the data) will retain the freedom to trigger this status change.

[13] http://eur-lex.europa.eu/legal-content/EN/TXT/?uri=celex%3A32010L0063

Interconnection with human data

A key objective of the proposed project is to conduct a retrospective data analysis to assess translation of preclinical to clinical safety outcomes. This analysis will include quantitative and qualitative endpoints to enable the following:

- Assessment of both general concordance between animal and human toxicities as well as concordance specific to a species and tissue/organ level;
- Assessment of the influence of study type, duration, exposure, and other study parameters on predictivity;
- Identification of false positive/negative results, their contributing factors and consequences for future study design.

Following the outcome of these initial translational assessments, a second key objective will be the achievement of mechanistic understandings for discordance outcomes potentially contributing to adverse outcome pathways (AOP) and the identification of new biomarkers.

It is expected that the results of the project will significantly improve the design of preclinical studies by ascertaining which side effects detected in animal studies will be relevant for humans and which ones would be specific to preclinical species. This knowledge will guide decisions on which preclinical features should be further developed to match clinical needs and improve human safety; but also which animal studies can be avoided because they are not relevant to humans (contribution to 3Rs).

Regulatory readiness (implementing SEND)

With the advent of CDISC-SEND (standards of exchange for nonclinical data), the FDA will rapidly be in the position to query and mine data across projects, companies and indications. The proposed database will ascertain that participating EFPIA (and other pharmaceutical) companies stay at a similar or even greater data access level compared to FDA, thus being able to discuss mining results and related requests on a par with the agency.

Innovative tools for data mining, analysis, data display and prediction

Software solutions shall be developed which let users query and analyse the shared data across studies, species and endpoints. Besides chemical search abilities (various chemico-biological similarity indices, substructure search etc.) these tools shall allow for the analyses of underlying relationship of pharmaco-toxicity, as well as for analysis of mode of action and AOP. The informatics aspect of the proposed action also encompasses data mining tools, statistical tools, and most importantly helper tools to produce proper alignment between preclinical and clinical data.

Expected key deliverables

- Guideline on safe data sharing with acceptance within the ICH (International Conference of Harmonisation[14]) regions.
- Extended preclinical database, able to incorporate individual animal data in SEND format together with structural and pharmacological information. In addition, the database will feature SEND output capabilities for regulatory submission.
- Easy and automated extraction of study reports expert conclusions. This is not in the scope of SEND and would add a great value to the database by capturing the expert data analysis and compound-related event. It would also avoid re-interpretation of data.

[14] www.ich.org

- Interfaces to clinical databases, deeper knowledge on adverse outcomes from clinical studies that are predicted well by animal studies, exploration of mechanisms of toxicity in preclinical data for extrapolation to human risks.
- Extended search tool, allowing for complex multi-parametric search and concomitant searches in clinical databases.
- Advanced tools for data display and visualisation, cross-study and compound analysis and reporting.
- Advanced tools for similarity searches based on both the chemical structure, the pharmacology (target) and the toxicology and corresponding graphical display solutions (e.g. KNN) of the various similarity metrics.
- More reliable *in silico* predictive tools for drug toxicity which incorporate innovative read-across approaches and multi-level, multi-scale modelling methods (multi-level methods: the system should be able to incorporate individual experimental in vitro data points to refine the prediction; multi-scale methods: the system should be able to provide quantitative predictions with respect to the extent of toxicity expected for various doses).
- Tools for correlation analysis of preclinical to clinical safety prediction, including identification of biomarkers.

Expected impact

Up to now, preclinical data have been used for the development of one compound only which will eventually reach the market. The knowledge embedded within these animal data is rarely reused internally within a company and never across companies. The volume of data gathered and shared in the proposed project will allow researchers to compare toxicities to pharmacological targets (improved target safety review), off-targets, chemical structure relationship or *in vivo* events ('read-across'). The accumulation of data enables the extraction of additional knowledge that can be used to avoid repeating similar failures, sometimes even before reaching animal studies. Hence, this approach will have an impact on the 3Rs, whereby the chances of success in animal studies will increase. Therefore, it will reduce the number of animals that are often only used to detect compounds with improper safety margins. The same cause has also an incidence on the attrition rate which should logically improve overall as well. In addition, this approach should reduce the time it takes for drugs to reach patients.

As part of the proposed project, preclinical data will be assessed against human data. The volume of expected preclinical data will allow an unbiased human versus animal cross-analysis to be run for the first time. This has the potential to modify the way preclinical studies are run, and more accurately predict potential human toxicity. The interaction with health authorities within the consortium should ensure a full agreement on how to alter our current way to assess side effects for a better and faster outcome. For example, an important aspect is the questionable relevance of animal carcinogenicity which could ultimately be more accurately assessed.

Finally, the knowledge extracted from the database assembled as part of the proposed project will allow the development of *in silico* predictive algorithms for both preclinical and clinical safety outcomes. This is equally impactful on the 3Rs, the duration of research and development and safety improvement. Also, although more difficult to estimate, these overall improvements may reduce the cost of drug development and therefore could have an impact on various countries' health systems.

The NexGETS project should aim to set world standards and act as the central partner to go to in terms of preclinical data handling, analysis and use for predictive toxicology, either through data mining, *in silico* predictive algorithms and clinical-preclinical analysis and alignment.

Potential synergies with existing consortia

There are currently a number of initiatives which may be relevant to the proposed project, either for their purpose or in their organisation and subject matter. The consortium should explore the potential to build upon the achievements of these initiatives.

- eTOX[15]: An IMI project devoted to large-scale sharing, data-basing and mining of industry legacy tox reports, including predictive models and a central tool for database querying and running of predictive models. It also has developed a series of purpose-fit ontologies. It is expected that the proposed project will negotiate the necessary legal framework with eTOX on fair and reasonable terms in order to be able to utilise the assets developed under eTOX, particularly the preclinical data already collected (see also work package 10). Freely accessible tools can be found in the 'Results' section of the eTOX website.
- iPiE:[16] An IMI project working on environmental tox, akin to eTOX, and with agreement of full compatibility of the two initiatives so that they will result in one single system in the end.
- SAFE-T:[17] An IMI project working on clinical tests to diagnose and monitor drug-induced injury to the kidney, liver and vascular systems in man, relevant to NexGETS work package 7.
- The forthcoming IMI Quantitative Systems Toxicology project.[18].
- EUToxRisk:.[19] A large Horizon 2020-supported collaborative project that aims to become an integrated European 'flagship' programme driving mechanism-based toxicity testing and risk assessment for the 21st century.
- HESS:[20] The Hazard Evaluation Support System represents a collection of about 500 chemicals tested in 4-week rat study data with corresponding metabolism studies.
- Tox21:[21] *In vitro* data of about 10 000 chemicals and pharmaceuticals, including 135 failed drugs, tested on various cell lines mainly for cytotoxicity, caspase activation and nuclear receptor activity.
- IQ: A USA-based not-for-profit organisation of pharmaceutical and biotechnology companies.
- HEVER (USA-based not-for-profit foundation): proposed initiative to collect SEND-formatted preclinical data to deposit in a data warehouse.

It is clear that many additional initiatives will arise in the forthcoming years. The proposed project should be a central vantage point to aggregate these initiatives and get advantageous data and/or know-how from these through collaborations and even perhaps coordination at an international level (e.g. OECD countries).

Industry consortium

- Abbvie
- Bayer
- Boehringer Ingelheim
- Johnson & Johnson
- Merck KGaA
- Novartis
- Roche

[15] http://www.etoxproject.eu/
[16] http://i-pie.org/
[17] http://www.imi-safe-t.eu/
[18] As described in the IMI2 Call 6 topics text:
http://www.imi.europa.eu/sites/default/files/uploads/documents/IMI2Call6/IMI2_Call6_FINAL.pdf
[19] http://www.eu-toxrisk.eu/
[20] http://www.nite.go.jp/en/chem/qsar/hess_update-e.html
[21] http://tox21.org/

- Sanofi
- Servier
- Takeda

Indicative duration of the project

The indicative duration of the project is 60 months.

Indicative budget

The indicative EFPIA in-kind contribution will be EUR 29 000 000. Due to the global nature of the participating industry partners, and given the scope of the topic, it is anticipated that some elements of the contributions will be non-EU in-kind contribution.

The IMI2 contribution will be a maximum of EUR 20 000 000.

The EFPIA in-kind contribution will mainly originate from the new preclinical data generated and structured under the SEND format, within the framework of the consortium of the EFPIA partners. Other significant in-kind contributions may originate from the costs of extraction of legacy preclinical reports, of new preclinical studies designed, the performance of qualification studies for potential new safety biomarkers, and temporary positions created within EFPIA companies for conducting the project and implementing developed IT systems.

Applicant consortium

The applicant consortium is expected to address all the objectives and make key contributions to the defined deliverables in synergy with the industry consortium.

The project requires the selection of applicants that are technically experienced in developing and maintaining searchable databases suitable for conducting meta-analysis. Such partners will be solicited and selected for building, populating and maintaining an anonymised database that is blinded to both the public and private participants and allows for a complex access and user administration. To allow all participants to share data comfortably in a secure environment, the applicant consortium should include an organisation with a proven track record of acting as an independent honest data broker from a legal and historical perspective.

In addition, expertise is required for data visualisation and automated output formats (e.g. tabulated summaries). As the analysis of the database will be a key part of this project, academic members of the consortium should provide statistical and bioinformatics expertise to enable appropriate design and analysis of the database to meet the project objectives, and preclinical and clinical safety expertise to evaluate and interpret the concordance of preclinical data with outcomes and assess the overall prevention or minimisation of adverse events in clinical trials.

Applicant consortia are expected to provide evidence that they have access to advice from health authorities. Such authorities would be needed to advise on the definition of acceptable validation criteria and participate in the overall direction of preclinical-clinical comparative analysis.

In silico models based on complex data integration of preclinical *in vivo* studies and physicochemical properties of small chemical structures (new chemical entities - NCE) will require expertise in predictive

algorithms integrating a large amount of heterogeneous and complex data. The pharmaceutical companies will provide toxicologists able to work closely with such *in silico* experts to achieve relevant models.

Public and private applicants (including academic investigators) should be ready to conduct or support mechanistic work to give insight on areas (compounds, pharmacological class, chemical space) where lack of preclinical-clinical concordance has been demonstrated, and provide a more detailed level of clinical data for endpoints that could provide a better understanding or mechanistic pathway when a finding is not detected in preclinical models.

Suggested architecture of the full proposal

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

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

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

Work package 1: Scientific coordination

- Executive committee (ExCom): Formation of an executive body comprising project leaders (both from the EFPIA consortium and the applicant consortium), the deputy leader of the EFPIA consortium and the project manager with decision-making powers on technical development, work plan updates, and budget assignment within each work package.
- Project management: A management team set up by a partner of the applicant consortium responsible for the daily management of the project, including budget, timing, milestones, meeting preparation, tracking of deliverable, yearly reports etc.
- Work package leaders: leading EFPIA and public participants of each work package, regular reporting to the ExCom.
- Steering committee (general assembly) (SC): A steering committee of all partners participating in the action, with the ultimate decision-making responsibility in matters affecting the overall project strategy, composition of the consortium and budget allocation between work packages.
- Coordination, collaboration and synergies with other initiatives.

Industry contribution

Active participation in the ExCom and other committees as described above.

Expected applicant consortium contribution

Active participation in the ExCom and other committees as described above. Provision of project management expertise with operational responsibilities for day-to-day coordination of the project.

Work package 2 : Overarching policies

- Establishment of general rules for sensitive data management and sharing.
- Proposal of OECD – or ICH-like guidelines for fair data sharing while safeguarding IP requirements.
- Interface with health authorities: Use of the shared data and database, as well as the joint development of predictive tools shall be discussed and aligned with regulatory bodies, particularly with the FDA, EMA and Japan's Pharmaceuticals and Medical Devices Agency (PMDA).
- Health authorities representatives to constitute a Scientific Advisory Board to guide and advise on activities and acceptance criteria for predictive models.

Industry contribution

Establishment of contacts with relevant regulatory bodies.

Expected applicant consortium contribution

Access to health authorities representatives to constitute a Scientific Advisory Board

Work package 3 : Historical data gathering

This work package will coordinate the gathering of data from existing sources from beyond the currently-collected systemic toxicity studies:

- Collaboration with existing initiatives to capture existing curated toxicology data.
- Identification and prioritisation of new preclinical endpoints, development of a roadmap and timelines for data extraction from legacy reports (e.g. safety pharmacology, carcinogenicity, DART, skin sensitisation); identification of preferred providers for data extraction, negotiation of framework agreements).
- Refinement and extension of pre-existing database schemas for new endpoints in close collaboration with IT partner(s) responsible for database.
- Development of automated data curation and quality assurance procedures (workflows and tools).
- Implementation of a harmonised IP strategy for all EFPIA partners to increase the amount of shared non-confidential data.
- Identification of interfaces to other existing databases (e.g. Cosmetics Europe, agro-chemical industry).
- Coordination with work package 4 & work package 5 activities (e.g. aligning the extraction plans, schemas and procedures with forthcoming SEND implementation guides and applying developed ontologies already during extraction procedures).

Industry contribution

Provision of legacy toxicology reports, contacts with adjacent industries.

Expected applicant consortium contribution

Extraction of data from legacy toxicology reports. Development of automated procedures and quality control tools to accelerate such extraction. Expansion of databases to incorporate the data.

Work package 4 : SEND format, data collection & database

- SEND format and SEND data gathering/handling: identification of SEND studies performed among the EFPIA consortium, procedures for harmonised collection and sharing.
- Open source platform for facilitating SEND management (free access): software tools will be developed based on existing ontologies and SEND-CDISC terminologies will convert existing non-SEND data into the SEND format (SEND-in and SEND-out capabilities).
- Establishment a curation and terminology management team for terms currently not covered under SEND. The team will collaborate closely with CDISC on the release of new controlled terms.

- Formatting and migration of existing data into full SEND compatible format: the database will be enhanced to be able to readily incorporate data in SEND format provided from different sources (e.g. LIMS systems, other SEND submission databases); development of tools to facilitate the preparation of SEND-ready submission based on FDA submission guidance.
- Collaboration with the Pharmaceutical Users Software Exchange (PhUSE) and FDA in order to rapidly implement new developments and tools.

Industry contribution

Provision of SEND data files: Preclinical studies eligible for data sharing (i.e. after clearance by companies' legal departments) and performed during the course of the project will be provided in SEND format if possible, and meaningful shared legacy studies will be converted into SEND format.

Expected applicant consortium contribution

Develop IT solutions for importing SEND data from LIMS systems & exporting from databases into submission ready files.

Work package 5: Ontologies

- Collaboration with existing initiatives to maintain ontologies and corresponding curation workflow, completion of unfinished ones.
- Development of preclinical and clinical ontologies' interfaces (e.g. by applying semantic similarity methods).
- Alignment of preclinical with clinical ontologies.
- Grouping and normalising disparate preclinical data sets.

Industry contribution

Verification of applicability of developed tools and interfaces.

Expected Applicant consortium contribution

Alignment and harmonisation of the different ontology sources, assuring their interoperability and the development of appropriate computer tools.

Work package 6 : Translational data analysis

In-depth analysis of the predictivity of animal toxicity studies that would take into account possible improvements in safety evaluation approaches, as well as evolution of portfolios (especially a greater proportion of biologics, compared to new chemical entities) over the last 10-15 years. This analysis will comprise both retrospective and prospective elements that will provide the following.

- A general evaluation of how well preclinical safety studies predict clinical outcome.
- An assessment of the value or lack of value of current testing paradigms, including identification of data gaps, which could help to prioritise innovation and development investments for future projects.
- An identification of target organs, toxicity mechanisms, type of compounds or pharmacology that are not well predicted preclinically.
- A good baseline for future assessments of predictivity of alternative test systems and *in vitro* models.
- An understanding of the mechanistic explanations underlying lack of predictivity, through generation of new experimental data or analyses.
- Depending upon the outcome, results will be used to influence regulatory guidelines and the public on the value of preclinical tests for minimising safety risks to clinical trial subjects and patients; and as a resource for developing/supporting regulatory acceptance of alternative preclinical test strategies (e.g. the need for a second species).

- Establishment of cross-database analysis tools, based on above ontologies (needs hyper-specialists).
- Inter-operability for data mining tools (preclinical, clinical, chemical, environmental, cosmetic).
- Data mining, and translational data analysis, relevance of preclinical species for clinical adverse events.

In addition, it is intended to tap into existing public clinical data bases and proprietary information of the participating companies.

Industry contribution:

Provision of clinical data or access to clinical data sources: EFPIA companies will either provide clinical data (Phase 1, 2 & 3) for corresponding preclinical data packages, establish interfaces with existing databases (in collaboration with IT partners of the project) or provide preclinical and clinical toxicology expertise for the extraction of clinical safety data from various sources.

Expected applicant consortium contribution:

Profound statistical expertise both in the fields of preclinical and clinical data analysis; software tools to automatically interface, exploit and structure existing clinical data sources.

Work package 7 : Safety biomarker data mining

Specific translational and reverse translational analysis of data for the discovery of potential new events relevant for preclinical and clinical safety.

- Explore a potential collaboration with the existing consortia to further qualify biomarker candidates.
- If necessary, run pre-clinical studies to generate new samples and qualification of candidate biomarkers or add new biomarker assays to already planned studies.

This work package will be built on three pillars:

- Data mining from NexGETS databases and any others resources available (especially for clinical data).
  - Assessment of links between biomarkers and histopathology to establish an inventory of fixtures and to discover potential new correlations. Clinical chemical findings, clinical haematological findings, clinical haemostasis findings and urinalysis findings will be queried and compared with histopathological significant findings.
  - Exploration of human biomarkers that are not yet used in preclinical studies (e.g. metabolomics).
  - Querying preclinical and clinical databases to estimate the prediction of non-clinical biomarkers in clinical studies.
- *Ab initio* research of new potential biomarkers and qualification of candidate biomarkers
  - Preclinical studies could be initiated or new biomarkers included in conventional planned *in vivo* studies to confirm or help qualify candidate biomarkers.
  - Additional exploratory arms for the purpose of potential biomarker exploration can be added to clinical studies.
- Qualification of candidate biomarkers.

Industry contribution

Contribute to verification and validation of identified biomarkers in collaboration with regulatory authorities.

Expected Applicant consortium contribution

Performance of data mining, *ab initio* research.

Work package 8 : *In silico* modelling

- Development of automated procedures for enhanced 'read-across approaches' based on preclinical and clinical data. this work package is intended to streamline and standardise search procedures during the early drug discovery phases with regard to similarity queries.
- Enabling the possibility to correlate and validate structural alerts also with EFPIA companies' in-house preclinical and clinical data. Such analysis capabilities will help to improve read-across and grouping approaches used for regulatory risk assessment.
- Development of multi-level and multi-scale tools for the prediction of preclinical *in vivo* toxicity (multi-level methods: the system should be able to incorporate individual experimental *in vitro* data points to refine predictions; multi-scale methods: the system should be able to provide quantitative predictions with respect to the extent of toxicity expected for various doses).
- Development of translational tools and models for the prediction of human toxicity and side effects from poly-pharmacology and deep learning.
- Preclinical safety models: On- and off-target pharmacology of drugs can result in unintended adverse effects (AE). Preclinical data from initiatives (see work package 3) and literature will be compiled and analysed with respect to off-target pharmacology as a reference data set. We intend to implement a computational learning framework that synthesises information from many distinct biological sources, namely compound effects, (off-)target interaction, chemistry and compound descriptors such as interpolated bioactivities originating from predictive *in silico* off target models, ideally with the help of multitask networks.
- Translatability: Better reflection of the mechanistic background of toxicity in preclinical and clinical context is required: An (off-) target is linked to particular adverse effects, if involved in pathways are linked to this effect in a particular species. One objective is to exploit the knowledge available to build a comprehensive set of mechanistic pathways of toxicity. Analysis of species-dependent toxicological relevant pathways will allow to bridge pre-clinical and clinical phenomena, if corresponding data are available as from work package 6, work package 3 and clinical AE. Since a generalised database and access framework is not yet available but a target of work package 6 and the planned 'Quantitative Systems Toxicology' project, this objective shares a strong synergy with both.
- Developing mechanistically-founded computational safety models. Mechanistic pathways of toxicity add toxicological evidence to *in silico* target – ligand associations. Those will be systematically exploited to train *in silico* models for preclinical and clinical endpoints, to detect chemical fragments, target interactions, and pathways that could be limiting for species translatability.

Industry contribution

Prioritise model needs, to test developed models (including tests with proprietary data, to oversee verification and validation procedures in close contact with regulatory authorities).

Expected applicant consortium contribution

Develop the above-mentioned software tools, models and procedures; a particular expertise will be required in the field of exposure assessment (PBPK modelling for risk assessment models).

Work package 9 : Platform and IT integration

- User data access for consortium partners: IT tools will be developed for a sophisticated user and access rights management fulfilling the needs of the different NexGETS partners. In addition, the front end system for access and searches needs to be aligned with the underlying database(s) in an automated way in order to allow rapid access to data collected. In case of local installations behind the firewalls of the different NexGETS partners, technical compatibility with pre-existing databases would be desirable.
- Data search and analysis: software tools will be developed which will enhance the query functions beyond chemical structures and toxicological endpoints. E.g. tools shall be developed to allow the use of different similarity algorithms (beyond Tanimoto and substructure searching, also including searches for target-related similarity).

- Visualisation platform(s) for large data: search results need to be displayed graphically for both individual studies and cross-study analyses (e.g. graphical display of body weight, clinical chemistry data etc. using bar charts, box plots etc.). Chemical and property similarity require interactive graphical visualisation (e.g. 2-D, 3-D property distance visualisation).
- Data export/reporting: Tools will be developed for structured export of tabulated results (e.g. export functions for preparation of submission-ready toxicology summary tables).
- Enabling tools for data harmonisation and sharing.

Industry contribution

Define user requests based on real world application cases, to identify access levels.

Expected applicant consortium contribution

Provide software solutions (both open-source off-the-shelf and tailor-made), to prioritise and implement user requests (visualisation tools, interfaces, export tools etc.).

Work package 10 : Sustainability

- Business plan, dissemination to stakeholders, communication.
- Collaborate with existing initiatives to ensure their results are fully exploited.
- Subsets of the NexGETS database shall be made available to interested third parties, other consortia and regulatory bodies. Contractual prerequisites and guidance shall be developed to fulfil the need of these different customer groups ranging from Memoranda of Understanding (MoUs) to fee-for-service agreements.

Industry contribution

To interact with regulatory agencies (use case development), to develop access rights strategies.

Expected Applicant consortium contribution

To develop a business model and decide on roles (e.g. business broker).

Glossary

ANDA	Abbreviated New Drug Application
AOP	Adverse Outcome Pathways
BLA	Biologic License Application
DART	Developmental and Reproductive Toxicology Database
DMPK	Drug Metabolism and Pharmaco-Kinetics
EFPIA	European Federation of Pharmaceutical Industry and Associated
FDA	Food and Drug Administration (USA)
GLP	Good Laboratory Practice

HESS	Hazard Evaluation Support System (Japan)
ICH	International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use
IND	Investigational New Drug
KNN	k-Nearest Neighbours algorithm
LIMS	Laboratory Information Management System
NBE	New Biological Entity
NCE	New Chemical Entity
NDA	New drug application
OECD	Organisation for Economic Co-operation and Development
Ontology	Defines the vocabulary with which queries and assertions are exchanged, uses the shared vocabulary in a coherent and consistent manner.
PhUSE	Pharmaceutical Users Software Exchange
PMDA	Pharmaceuticals and Medical Devices Agency (Japan)
SEND-CDISC	Standard for Exchange of Nonclinical Data - Clinical Data Interchange Standards Consortium
Tanimoto	An algorithm to calculate similarity between 2 chemical structures
Tox21	In vitro testing of a collection of 10,000 environmental chemicals and approved drugs for toxicity (Federal collaboration among the USA Environmental Protection Agency (EPA), National Institute for Health (NIH) and the FDA).
WP	Work package

Topic 5: Identification and validation of biomarkers for non-alcoholic steatohepatitis (NASH) and across the spectrum of non-alcoholic fatty liver disease (NAFLD)

Topic details

Topic code	IMI2-2016-09-05
Action type	Research and Innovation Actions (RIA)
Submission & evaluation process	2 Stages

Specific challenges to be addressed

The central challenge that we seek to address within this Call topic is to establish non-invasive biomarkers for diagnosing and classifying subjects within the NAFLD spectrum, and in particular identifying those with NASH and predicting those likely to progress to NASH. NASH is a serious liver disease, substantially more serious than earlier stages of NAFLD. NASH can progress to cirrhosis with attendant morbidities of end-stage liver disease (ESLD) and causes heightened risk for hepatocellular carcinoma (HCC). Identifying and validating biomarkers enabling a diagnosis of NASH that can be employed to track disease progression as well as response to intervention will be crucial in furthering advances in clinical care and drug development for NASH and will enable clearer understanding of the heterogeneous outcomes of NAFLD.

NAFLD is not an uncommon disease. The rising prevalence of NAFLD is closely related to the convergent epidemics of obesity, insulin resistance and type 2 diabetes. Many experts regard NAFLD as a hepatic complication of obesity. The estimated worldwide prevalence of NAFLD is approximately 30% and this doubles within a type 2 diabetic population. Not all individuals with NAFLD develop NASH. It is estimated that the prevalence of NASH is approximately 7%, and this too is estimated to be at least two-fold higher among people with type 2 diabetes. It is imperative that those with NASH can be identified within the large population of those with NAFLD. A diagnosis of NASH, its staging and its distinction from NAFLD, is presently based on histological assessment of a liver biopsy. The procedure is invasive, causes discomfort and can be associated with risk, even if it is small. Moreover, while regarded as a gold standard for diagnosis of NASH, a liver biopsy can be subject to sampling variability and variability in scoring. Given these and other challenges, including a paucity of approved therapies, a liver biopsy is performed in only a small proportion of patients with NASH. Despite these acknowledged impediments, NASH is an area of very active drug development. There is clear consensus that a lack of diagnostic, prognostic and treatment response NASH biomarkers hampers clinical practice and seriously impedes drug development.

Need and opportunity for public-private collaborative research

A plethora of candidate biomarkers for diagnosis of NASH have been identified. In nearly all instances, these are the fruit of academic research. Though promising, these biomarkers have been identified in relatively small studies. The findings of any single study have rarely been replicated. None has yet been validated against liver biopsies for either diagnosis or prediction of NASH. Nonetheless, it is quite plausible that one or more of these candidate biomarkers (soluble, imaging and genetic) can be validated if studied systematically

in a sufficiently powered investigation. Or, at least the work done to date offers a solid basis for refinement, for example amongst soluble indicators of hepatic fibrosis. The challenge of constructing a sufficiently-powered investigation, including collation of relevant existing clinical research, and with its central goal being pragmatic and focused upon biomarker validation, is arguably best addressed by a comprehensive public-private collaboration. Without a collaborative public-private research effort, it seems unlikely that these preceding exploratory research efforts to identify NASH and NAFLD biomarkers will be accepted as inclusion criteria for clinical trials, with confidence in tracking disease progression and evaluating efficacy of intervention.

The crucible of a NASH biomarker qualification plan will be to tie this effort to histological assessment of liver biopsy. As noted earlier, liver biopsy is currently the basis for diagnosing and staging the severity of NASH. It is the basis for adjudicating effectiveness of intervention and an on-treatment liver biopsy is a requirement for registration of novel treatment. Thus, validating non-invasive biomarkers for NASH and NAFLD against liver biopsy will not only provide necessary scientific rigour but is needed to bridge to contemporary standards for clinical practice and drug development. The design of the proposed studies, and in particular the inclusion criteria for collating extant clinical research, recognises the necessity of placing carefully-adjudicated liver biopsy data at the core of any biomarker qualification effort. This is not to diminish the value of complementary data, including various liver imaging methodologies and of course clinical case characteristics, but the alpha and omega of validating non-invasive biomarkers for NASH and NAFLD will be against liver biopsy.

The purpose of this ambitious IMI2 initiative is to bring a sufficient level of funding and multi-stakeholder commitment to comprehensively and definitively address biomarker challenges in NAFLD and NASH. The leading edge of this IMI2 initiative is to make use of extant NAFLD and NASH research cohorts and access samples that meet carefully considered criteria, importantly including properly adjudicated liver biopsy samples. The comprehensive public-private collaboration for the qualification of biomarkers will employ standardised laboratory analyses together with bioinformatics to harmonise biomarker data, as well as accompanying clinical and liver imaging data. This unprecedented effort will be transformative for the field and is the type of effort needed to gain consensus acceptance by those carrying out basic research into NAFLD and clinical investigators. It will also instil confidence in the use of biomarkers for decision making by drug developers and, ultimately, lead to regulatory approval of these biomarkers.

Scope

The scope of biomarker collaborative research for NAFLD and NASH can be envisioned to ideally encompass three main objectives, outlined below.

- Develop diagnostic biomarkers that are relatively non-invasive (i.e. blood-based or imaging) for NASH and those that are useful across the spectrum of NAFLD. A NASH diagnostic biomarker, especially relevant to NASH, would be able to identify the severity or stage of hepatic fibrosis and also pertain to the severity of hepato-cellular inflammation. One component of the effort to develop diagnostic biomarkers for NASH and NAFLD will be to include preclinical research directed towards the development, characterisation and validation of novel animal models (including biomarker candidates) which are very close to the human situation with regard to disease mechanisms, phenotype and histological morphology. Novel animal models that bear good concordance with the human pathobiology of NAFLD and NASH are desperately needed to support the development of novel drugs for the treatment of NAFLD and NASH.
- Identify biomarkers that can predict disease progression for NASH. It is generally considered that the course of disease progression in patients with NASH is relatively slow and can be heterogeneous; there are however patients who progress rapidly toward ESLD. And this same principle of indolent yet uneven progression applies to those with NAFLD. There is need therefore to identify biomarkers that can predict disease progression in NASH and across the spectrum of NAFLD. Biomarkers that enable diagnosis could serve equally to predict disease progression for NASH and NAFLD. Alternatively additional biomarkers, more specific for tracking the dynamics of disease progression might need to be identified and qualified. While cross-sectional data can be employed to validate diagnostic biomarkers, within-subject longitudinal data is needed for the qualification of biomarkers that predict progression from NAFLD to NASH, and within NASH, progression across stages of disease severity.

For the identification of NASH and NAFLD biomarkers with adequate rigor and precision, it is envisioned that a key effort will be made by a central laboratory(s) performing standardised assays across the entire cohort. It might be feasible in selected instances to use bioinformatics and related approaches to harmonise previously measured analytes (this will be used for commonly measured clinical laboratory data) but the default for measurement of candidate biomarkers is to conduct these measurements by the project. It is not the goal of the project to perform open platform 'omics' to screen for potential NASH and NAFLD biomarkers. Rather, the intent is to shortlist prime candidates as based on expert review of extant biomarker data together with bioinformatics analyses of these data and then to work forward iteratively using centrally-conducted assays. To clarify, while the broad intent is not to conduct open 'omics' queries, it may prove productive to iterate with targeted 'omics' that stem from promising data; an example might be to explore collagen fragments as an approach to achieving more precise indices of hepatic fibrosis.

- Qualification of preclinical models of NASH. An important component of the work on preclinical model development and qualification will be to test whether identified biomarkers identified to predict clinical progression can be shown to back-translate to the preclinical models. Success in this domain will support the development of novel therapeutics for NASH. The preclinical work in qualifying models of NAFLD and NASH will further seek to increase understanding of the disease mechanisms causing development of NAFLD and its progression to NASH, including the contribution of diabetes to these processes. Another related aspect concerns the establishment and characterisation of a non-rodent model of NASH; one that incorporates a context of the metabolic syndrome (obesity/insulin resistance). Application of various imaging modalities to these models (rodent and non-rodent), especially those approaches that are translatable to humans, will also be perceived as an important adjunctive contribution.

Expected key deliverables

The expected deliverables described concentrate on those to be achieved during the five years of funding described in this Call. The resulting action will encompass Phase 1a and Phase 1b which will cover different aspects of the study.

The key deliverable for Phase 1a is to identify and qualify diagnostic biomarkers for NASH and across the spectrum of NAFLD. It is envisioned that Phase 1a can be fully completed within the five-year funded action. Phase 1a will undertake to access samples and existing biomarker data from extant cohorts of NAFLD and NASH, selected to meet specific criteria. Work packages will be implemented to collate and harmonise the data, including liver biopsy scoring, attendant clinical information, patient reported outcome parameters, and available liver imaging. The work will encompass performing centralised assays on plasma and serum samples, on liver biopsy samples if available, and genotyping (e.g. for PNPLA3). Bioinformatics and biostatistics analyses will drive biomarker qualification. The biomarkers identified and qualified in Phase 1a will then be validated in a separate cohort in Phase 1b.

The two key deliverables for Phase 1b are: 1) to provide validation of the previously-identified diagnostic NASH and NAFLD biomarkers using an independent cohort; and 2) collect and extend longitudinal clinical data to identify biomarkers that predict disease progression. Planning for Phase 1b will take place from the start of this action, but actually starting work on the 'validation cohort' will be contingent on making meaningful progress in Phase 1a. Given the global scope of NAFLD and NASH, a validation cohort (or cohorts) should have broad ethnic and demographic diversity. It may prove feasible to identify pre-existing and available research cohorts that meet criteria for the purposes of independent validation and ethnic and demographic diversity, whether EU-based or non-EU based. And, it may prove necessary to additionally recruit into a validation cohort, at least in part, as a complement to its existing composition.

Delivery of biomarkers that delineate the progression of NASH and NAFLD will require carefully-collected, within-subject longitudinal data and will need to include at least one follow-up liver biopsy. Ideally, and a high priority will be placed upon this, existing study cohorts chosen for Phase 1a will have systematic longitudinal follow-up. The same will apply to cohorts chosen for Phase 1b to provide validation data. More information on selection criteria are presented in a subsequent section of this topic text.

As progress is made in addressing the aims of Phase 1a, it will become clearer what is needed for the size of a validation cohort in Phase 1b. A working assumption at this juncture is that the cohort(s) used in Phase 1b should have broad ethnic and demographic diversity given the global prevalence and rising incidence worldwide of NAFLD and NASH. The same criteria used to select applicant cohorts for Phase 1a will apply to the cohort(s) for Phase 1b. If it is found in the bioinformatics analyses of Phase 1a that a particular hepatic imaging procedure adds unique diagnostic value for NASH, then the feasibility of adding this broadly in Phase 1b will be explored and potentially enabled by support from this action. The same principles will apply to patient reported outcomes. The projected timeline is that sufficient progress will have been made in Phase 1a to warrant beginning Phase 1b and that this can be done as soon as will be feasible, ideally no later than the start of year 3 of this 5 year funding Call.

An identified high priority goal of this five-year funded action will be to make substantial progress in identifying biomarkers that track progression of the NAFLD spectrum including NASH. Establishing these 'dynamic biomarkers' will require empiric validation and will be grounded in a follow-up liver biopsy. It is highly desirable that the applicant cohorts selected for Phase 1a and 1b are longitudinal research efforts with high quality follow-up procedures together with a high level of participant retention. Given contemporary precepts that the courses of NASH and NAFLD are indolent, the interval between the two liver biopsies should be at least two years. Finally, and obviously, plasma and serum samples must be available to this project from more frequent and regular intervals.

If applicant cohorts that meet these criteria can be identified, it is reasonable to postulate that the project will move forward efficiently to achieve the deliverable of a qualified diagnostic biomarker(s) for NASH and across the spectrum of NAFLD. Depending upon when the clock started for these cohorts, it could enable the project to qualify a disease progression biomarker by the end of year 5. But if the duration of follow-up of subjects within applicant cohorts is not sufficient, a more conservative projection of what can be delivered at the end of five years will be validation of diagnostic biomarkers together with establishment of a research infrastructure necessary to track progression in carefully collated cohorts.

In addition, an integral aspect of both action Phases 1a and 1b will be to characterise (and develop where needed) animal models of NAFLD and NASH that manifest sufficient concordance with the pathophysiological data that emerge from this effort and that manifest concordance with patterns for the clinical biomarkers that are qualified by this effort. The anticipated deliverable from such efforts would be to establish a consensus recommendation of animal model(s) suitable to use in support of the development of novel therapeutics for NAFLD/NASH.

Expected impact

Proposals are expected to identify and qualify non-invasive biomarkers for NAFLD and NASH. Thus they will be transformative for the clinical management of patients and profoundly enabling for drug development for the treatment of NASH. Accurate diagnosis, effective treatment and effective tools to monitor disease response are the three pillars essential in support of medical practice. The unmet need that is present with regard to NAFLD and NASH cannot be effectively addressed without the elucidation of validated biomarkers.

Potential synergies with existing consortia

This topic invites applicant consortia to launch a cross-functional research initiative with overall objectives to address the above gaps. A key aspect of achieving the first objective, that of qualifying candidate biomarkers, will be to pool all available information and samples from existing participating clinical databases. There will be a robust and concerted effort to develop synergies with existing consortia, even or perhaps especially if such consortia have as their respective goal the identification of critical pathobiology processes of NAFLD and NASH rather than the identification of candidate biomarkers per se. Indeed, it will be through alignment and collaboration with such existing consortia that synergies valuable to all parties can be achieved.

Industry consortium

- Pfizer
- Merck Sharp Dohme (MSD)
- Boehringer Ingelheim
- Ellegaard
- Eli Lilly
- Novartis
- Novo Nordisk
- Pfizer
- Sanofi
- Somalogic

The industry consortium will bring expertise in methodologies for the merging, harmonisation and meta-analyses of existing biomarker data. This will include expertise in biomarker evaluation, bioinformatics and statistical expertise and possibly technology for measuring specific biomarkers where appropriate. Additional contributions will include NAFLD/NASH clinical trial and regulatory expertise. EFPIA participants have also indicated interest in providing in-kind contributions that will entail efforts at 'back-translation' into preclinical models to help in validating appropriate animal model(s) and biomarkers of NAFLD and NASH. Drug development expertise will also be brought in by the industry consortium.

Indicative duration of the project

The indicative duration of the project is 60 months.

Future project expansion

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

Acceptance of biomarkers by regulatory agencies as surrogates for clinical endpoints is a far horizon aspiration of biomarker research. It will not be feasible to accomplish this within the five year scope of this funding call. Therefore, in the context of the future expansion topic EFPIA companies envision to progress to the clinical validation of the surrogate markers of clinical outcomes in NAFLD and NASH. The ultimate goal would be to deliver further validated surrogate markers that are ready for regulatory acceptance. Part of this effort would be also the construction and maintenance of a longstanding clinical data repository to serve as a future source of biomarker identification and/or validation.

Such further work would be the natural progression of the original project, leveraging its success and maximising the long-term impact. This would enable continued development of new therapeutics, and make more fruitful and efficient their application in the clinic. This proposed project extension would also take advantage of already-established collaborations and networks forged in the overall project, thereby maximising efficiency on time and resources. A restricted Call may allow this to be achieved in the most efficient way. The detailed scope of the Call will be described in the relevant Annual Work Plan.

Indicative budget

The indicative EFPIA in-kind contribution will be EUR 15 828 000.

The IMI2 contribution will be a maximum of EUR 15 828 000.

The budget contribution from the EFPIA participants will be a mixture of cash and in-kind contributions, with a larger proportion of in-kind. Considering the scope of the topic, MSD, Pfizer, Eli-Lilly and Somalogic are expected to contribute to this project a significant proportion as non-EU in-kind contributions because the full time employee equivalents committed to this initiative are based in the US.

Applicant consortium

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

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

To address the ambitious objectives of the topic adequately, the project is expected to establish a multidisciplinary network that will include: scientists and physician-scientists who are recognised experts in liver disease and in NAFLD and NASH more specifically; expertise in developing and maintaining the clinical database for research participants that is relevant to an in-depth characterisation of the presentation of NAFLD; expertise in clinical research recruitment and follow up, including access to needed clinical research facilities.

Such a network will include applicants with the following capabilities to make the following types of contributions.

- Access to clinical cohort that has already been assembled and that meets these criteria for addressing the goals of Phase 1a. Estimated size is 1 500 to 2 500 subjects, who have undergone a liver biopsy, warranted by clinical indication, within 6 months of study entry. It is estimated that within this cohort with liver biopsy establishing NAFLD or NASH, at least one-third must have the latter diagnosis in order to support NASH biomarker qualification. Therefore of interest is a cohort that encompasses subjects with NASH distributed across different stages of severity, but that also includes the full spectrum of NAFLD.
- The clinical data, including liver imaging that led to a decision for liver biopsy, will need to be available and with informed consent to enable these to be entered into the project database. Highly pertinent will be clinical and laboratory data that exclude causes of liver disease other than NAFLD and NASH.
- Liver biopsy performed in a blinded manner by experts experienced with accredited NAFLD and NASH histologic scoring and/or that the histology is still available for such a process to be conducted by the project.
- All liver-related biomarker data will need to be made available. Plasma and serum samples along with documentation of an appropriate chain of custody must be available to the project.

Suggested architecture of the full proposal (optional)

The final architecture of the full proposal will be defined together with the industry consortium and should enable activities designed to achieve all objectives and deliverables as indicated in the previous relevant sections and in collaboration with the EFPIA partners.

The above-described cross-functional project partners are recommended to work together in dedicated work packages addressing the different aspects of the overall topic. It is recommended that each work package team consist of academic and industrial/biotech members with regular interactions to ensure knowledge exchange between the different expertises. Inter-work package knowledge transfer should be ensured at all times via regular management board meetings. A jointly-used data documentation tool is considered a key piece for the success of the overall topic ensuring maximum information gain.

In addition, a plan for interactions with regulatory agencies 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 final architecture of the full proposal will be defined by the participants in compliance with IMI2 rules and with a view to the achievement of the project objectives.

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

Work package 1:

- Overall project co-ordination and integration and dissemination (Phases 1a and 1b).

Work package 2:

- Management and integration of existing databases with a key focus on identification of candidate NAFLD and NASH biomarker(s) using the Phase 1a cohort data.

Work package 3:

- Central laboratory assay development and implementation using samples from the clinical cohorts (Phases 1a and 1b).

Work package 4:

- Clinical replication and validation of the biomarker(s) that have been identified using Phase 1a data in a separate Phase 1b cohort. Collection of patient reported outcomes in the Phase 1b cohort, and if feasible from data obtained in the Phase 1a cohort, is another important goal of this work package.

Work package 5:

- Qualification of clinical imaging modalities of NAFLD and NASH (and stages of NASH) within the context of relationships to liver biopsy data and soluble biomarker data, together with other ancillary data including genetic information.

Work package 6:

- Development and qualification of relevant preclinical disease models (rodent and non-rodent) for NAFLD and NASH that can demonstrate fidelity to clinical pathobiology.

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

Glossary

NAFLD	Non-alcoholic fatty liver disease
NASH	Non-alcoholic steatohepatitis
ESLD	End-stage liver disease
WP	Work package

Topic 6 : Joint influenza vaccine effectiveness studies

Topic details

Topic code	IMI2-2016-09-06
Action type	Research and Innovation Actions (RIA)
Submission & evaluation process	2 Stages

Specific challenges to be addressed

Influenza is one of the top 10 infectious diseases worldwide and among the leading causes of hospitalisation and death due to infectious diseases in developed nations.

Vaccination is considered to be the most effective measure against the influenza disease and, as such, it is recommended by the European Council and included in all of the EU/European Economic Area (EEA) Member State national immunisation programmes, through yearly national influenza vaccination campaigns[22][23].The circulating influenza virus strains constantly evolve as a result of antigenic drift and/or shift. The production of seasonal influenza vaccines follows the yearly World Health Organization (WHO) recommendations on the influenza vaccine strain composition[24]. In case of a mismatch between the recommended influenza vaccine strain composition and the actually circulating strains, lower influenza vaccine effectiveness is commonly observed. Recently this was observed for the 2014-15 influenza season with regards to the H3N2 strain which raised concerns among experts and the public on the overall benefit of the vaccine[25].

Measurement of influenza vaccine effectiveness is a particularly complex endeavour, as the effectiveness of the vaccine depends on a number of intertwined factors in addition to the circulating strains, such as the population coverage reached, as well as differences between age and risk groups due to differences in immunological response. Since the recommended strain composition generally differs from season to season, vaccine effectiveness cannot be inferred from estimates from previous seasons and hence must be conducted on an annual basis.

National public health bodies have a role in assessing national vaccination programmes, and therefore are the holders of national programme-level vaccine exposure and effectiveness data. Vaccine manufacturers on the other hand are accountable for the quality and integrity of vaccine product-specific data presented to regulatory authorities. Changes in the regulatory requirements for marketing authorisation holders are

[22] European Council recommendation of 22 December 2009 on seasonal influenza vaccination; http://eur-ex.europa.eu/LexUriServ/LexUriServ.do?uri=OJ:L:2009:348:0071:0072:EN:PDF

[23] Venice report 'Seasonal influenza vaccination in Europe - Overview of vaccination recommendations and coverage rates in the EU Member States for the 2012–13 influenza season'; http://ecdc.europa.eu/en/publications/Publications/Seasonal-influenza-vaccination-Europe-2012-13.pdf

[24] See strain selection mechanism in place since 1973 : http://www.who.int/influenza/vaccines/virus/recommendations/consultation201602/en/

[25] Valenciano, M., Kissling, E., Reuss, A., Rizzo, C., Gherasim, A., Horváth, J. K., Domegan, L., Pitigoi, D, D., Machado, A., Paradowska-Stankiewicz, I. A., Bella, A., Larrauri, A., Ferenczi, A., O´Donell, J., Lazar, M., Pechirra, P., Korczyńska, M. R., Pozo, F., Moren, A., on behalf of the I-MOVE multicentre case–control team. Vaccine effectiveness in preventing laboratory-confirmed influenza in primary care patients in a season of co-circulation of influenza A(H1N1)pdm09, B and drifted A(H3N2), I-MOVE Multicentre Case–Control Study, Europe 2014/15. Euro Surveill. 2016;21(7):pii=30139. DOI: http://dx.doi.org/10.2807/1560-7917.ES.2016.21.7.30139

anticipated to take effect in 2016[26]. These include that the immunogenicity criterion to evaluate seasonal influenza vaccines (due to the absence of clear correlates of protection) should be replaced by strengthened and sustainable surveillance and monitoring of vaccine performance that will provide product-specific (type/brand)[27] influenza vaccine effectiveness and safety data.

A strengthened capacity in Europe to monitor the effectiveness of the yearly seasonal influenza vaccines to generate effectiveness data across age, risk groups and vaccines would provide clear benefits for manufacturers, the public health sector, and ultimately Europe's citizens. Influenza vaccine effectiveness measurement will become an important tool for regulators to assess the balance of benefit and risk of influenza vaccines available on the market. It will be the responsibility of the vaccine manufacturers, as marketing authorisation holders, to submit the relevant data to regulatory authorities following the new regulatory requirements in this regard. Importantly, a strong influenza effectiveness study platform in Europe should allow for a better evaluation of the performance of influenza immunisation programmes. This is expected to allow Member States to better evaluate the public health return on vaccinations. It should also improve the level of information about different vaccines that is available for the public and healthcare professionals with the goal of building trust and confidence in influenza vaccines. The findings are also expected to result in enhanced knowledge to guide the development of new influenza vaccines.

Given the complexity and the need to respond to the regulatory changes, it is evident that a higher level of collaboration and partnership amongst public health institutes, regulatory bodies and vaccine manufacturers will be necessary. The purpose of this topic is therefore to create a platform under a public-private partnership with the capacity to perform influenza effectiveness assessments. This platform would assemble all of the key stakeholders and develop a jointly acceptable governance structure.

Need and opportunity for public-private collaborative research

Under the new requirements, brand-specific data will need to be collected and this will necessitate appropriate infrastructure at country level that enables the capture of sufficient programme level data to measure brand-specific vaccine effectiveness, which is at present missing in the majority of Member States. Furthermore, where this brand-specific data is available it is often challenging to set up the appropriate governance model to ease collaboration between vaccine manufacturers and public health institutes to enable the latter to conduct the studies.

Both public health institutes and vaccine manufacturers have a joint interest in improving the availability of vaccine effectiveness data across Members States; the first in order to appropriately evaluate the public health benefits accrued by their influenza immunisation programmes, and the second to meet regulatory requirements, to closely and continuously report on the benefit/risk of marketed vaccines (risk management plans, periodic safety update report, etc.) and to inform future seasonal vaccines development. This synergy can best be achieved through the development of a transparent collaboration between public and private actors which is an important objective of this topic. Discussions on how to best achieve such a collaboration through involvement of all relevant stakeholders at the EU and national levels (public health institutes, regulatory agencies, and vaccine manufacturers) have been ongoing for several years.

The operational research elements of this project under IMI aim to put in place and pilot governance approaches involving all stakeholders and reach a model acceptable for all considering EU/national data protection laws, scientific guidance from EMA and any other specific constraints by the different stakeholders in order to achieve the intended objective of setting up a mechanism for strengthened and sustainable yearly monitoring of the effectiveness of influenza vaccines.

With IMI being an established public-private partnership, it provides a ready and transparent mechanism for assembling the key stakeholders for developing the platform and a jointly acceptable governance approach for the data collection and analysis framework.

[26] Guideline on influenza vaccines – Non-clinical and clinical module, http://www.ema.europa.eu/docs/en_GB/document_library/Scientific_guideline/2014/07/WC500170300.pdf

[27] By type it is intended for example Trivalent (TIV), Quadrivalent (QIV), Adjuvanted, etc. influenza vaccines.

Scope

This action will cover four influenza seasons; 2017-2018 to pilot tools and 2018-2019, 2019-2020, 2020-2021 to progressively scale up the platform.

The action should do the following.

- Develop and validate a sustainable governance model for the evaluation of type/brand-specific seasonal influenza vaccine effectiveness in Europe, through collaboration between public and private partners.
- Build an EU/EEA-wide recognised and accepted platform for influenza vaccine effectiveness studies. To be successful, the action should work towards a pan-European network well beyond past or existing initiatives also including Member State organisations not previously involved in such activities in order to build European capacity and improved generalisability of the results through a large representation of EU/EEA Member States.
- Develop communication tools and guidance for dissemination of the results obtained from the influenza vaccine effectiveness studies so as to better inform healthcare professionals and the general public about the performance of the influenza vaccines in use and their respective implementation programmes. It is expected that such information will contribute to improving understanding of the benefits of influenza vaccination, as well as pave the way for the R&D of new generation influenza vaccines through better understanding of the factors that impact influenza vaccine effectiveness.

The specific objectives of the action are the following:

1. **Develop, refine and validate a governance model for influenza vaccine effectiveness studies in Europe.**

   Reaching consensus on the governance model for influenza vaccine effectiveness studies and ensuring its acceptability constitutes one of the most challenging and critical objectives of the action.

   This activity of discussing, refining, and validating a governance model should be carried out in collaboration with all stakeholders at EU/EEA and national level, i.e. the European Centre for Disease Prevention and Control (ECDC), the European Medicines Agency (EMA), national public health institutes (NPHIs), national regulatory agencies (NRAs) and vaccine manufacturers. In doing so, the needs and concerns of all stakeholders should be taken into account, and a transparent process with the roles and responsibilities of the different stakeholders carefully defined for each step ranging from the study design to implementation, analysis and finally communication of the results should be developed.

   In particular, the present concern of many public health bodies throughout Europe and ECDC with regards to the independence of the scientific results and transparency of the processes should be met. In that context, industry should not have a decision-making role in the design, conduct, analysis, and primary publication of results of vaccine effectiveness studies[28].

   On the other hand, the needs of industry in view of the new regulatory requirements should be taken into account to ensure that vaccine manufacturers can fulfil their obligations and responsibilities in the role of marketing authorisation holder as set by EU/EEA regulators. This includes for example the need to contribute to the study design, have access to the final study results and an independent system to perform cross-validation of the data analysis for audit purposes.

   Solutions should be explored to satisfy the above needs and requirements. For example, the following components could be included: (a) validation of protocols and analysis plans by an independent organisation, e.g. the EMA; (b) an independent auditing body in charge of auditing the study conduct, conducting data quality checks and quality control of the data analysis; (c) a transparent process by which, in the event of disagreement between partners in the interpretation of study results, differing views will be published in the final report/publication.

[28] In accordance with the position of the ECDC Advisory Forum from 14 September 2015 put forward as a prerequisite for ECDC's engagement in this action.

The final governance model should be established following an iterative process supported by the experience developed by all stakeholders during the course of the project.

2. Carry out pilot studies for determining type/brand-specific influenza vaccine effectiveness

Evaluate the sample sizes needed for brand-specific seasonal influenza vaccine effectiveness and develop selection criteria for sites (e.g. country/region, inpatient/outpatient setting) and sampling schemes to capture populations vaccinated with all authorised influenza vaccines/brands.

Develop agreed tools and protocols for influenza vaccine effectiveness studies to ensure homogeneity in the methodology between sites in order to allow for data pooling if needed and to get reliable results. This activity will aim to expand and build on the scientific tools produced since 2008 under the leadership of ECDC.

Establish systems for documenting vaccination status and identifying vaccine/brand used. Where relevant and agreed, share experience acquired in EU/EEA Member States that have initiated immunisation registries and use data mining tools. Provide training and technical support for the development of new immunisation registries or use of data mining tools.

Set up a system for independent study site audits to monitor the conduct of studies. Pilot data collection and quality control at sites. Explore whether data collection could be integrated into strengthened routine surveillance activities to ensure sustainability.

3. Develop options for the sustainability of the proposed model for influenza vaccine effectiveness studies in Europe, including sustainability of tools, in synergy with other EU/EEA projects and with relevant EU/EEA-level institutions.

This action should build on results that have been and are being obtained by other initiatives and efforts. The action should lead towards a structure and model that is sustainable and that will fit into a larger model of vaccine effectiveness studies in Europe.

4. Produce, communicate and disseminate results

Establish rules and methods for data pooling, EU-level analyses and control for confounding factors.

Work towards acceptance of the proposed and validated governance model for influenza vaccine effectiveness studies in Europe by engaging the relevant stakeholders, by disseminating and communicating clear messages in particular with regards to avoidance of conflicts of interest and ensuring maximum transparency and credibility of the results.

Define elements to be taken into account to effectively communicate the obtained results (explanations of results and potential bias, assessment of the reliability of the results, set up channels of communication for programme performance reporting to national regulatory and public health institutes, EMA, WHO, healthcare professionals and the general public). The appropriate involvement of civil society and patient organisations is considered of major relevance in this regard.

Identify gaps in vaccine performance for future R&D. Effectiveness data will facilitate the identification of populations/circumstances where current seasonal vaccines have underperformed. This will provide insight into suitable targeted approaches that would support the validation of potentially improved new vaccine candidates or programme implementation approaches.

Expected key deliverables

Sustainable platform for influenza vaccine effectiveness studies involving all relevant stakeholders

- A validated governance model for influenza vaccine effectiveness studies in Europe developed with the involvement of all relevant stakeholders.
- A plan for sustaining the results of this action and integrating them into a larger and more generally applicable model for vaccine effectiveness studies in the EU/EEA.

Conduct of pilot studies for determining type/brand-specific effectiveness

- Tools for study site selection based on the expected use of influenza vaccine brands by region/country in the EU/EEA.
- Updated protocol for type- and brand- specific influenza vaccine effectiveness studies.
- Methodology guidelines to identify vaccine status and brands used in study participants from different age/risk groups (e.g. the introduction of barcodes on influenza vaccines).
- Evaluation of the feasibility of using existing electronic immunisation registries to collect information including vaccine status and brands used in all age/risk groups and, if no registries exist, sharing of best practices or technical support to support the development of such registries.
- Standard operating manual identifying factors that influence the site implementation of the core protocol including audit checklist for site oversight.
- Evaluation report based on the operational research experience during this project with a focus on governance, sample size and feasibility of conducting brand-specific seasonal influenza vaccine effectiveness yearly.
- Recommendation on the use of study outputs to feed the WHO vaccine strain selection mechanism, the European Influenza Surveillance Network (EISN) and WHO Global Influenza Surveillance and Response System (GISRS).
- Exploring the feasibility of whether representative samples from unvaccinated and vaccinated individuals with breakthrough infections obtained for diagnostics in the studies could be further analysed (genetic, perhaps even whole genome, and antigenic analysis) and feed into the yearly European influenza surveillance and WHO vaccine strain selection.

Guidelines and recommendations on the production of influenza vaccine effectiveness data, and on the communication and dissemination of results from influenza vaccine effectiveness studies

- Methodology guidelines for concerted analysis of data and control of confounding factors.
- Analysis plan and guidelines to be endorsed by regulators for interpretation of obtained study data using a multi-stakeholder approach.
- Four timely seasonal reports (2017-2018, 2018-2019, 2019-2020, 2020-2021); these reports do not intend to be fully-fledged pan-European vaccine effectiveness estimations, but they will be considered as proof of concept of what can be achieved through the platform. It is expected that the scope and size of the data will increase with each report . The initial focus will be on type of vaccines, such as trivalent, quadrivalent and adjuvanted vaccines, and then move into brand-specific effectiveness data.
- Evaluation of how the vaccine effectiveness results could fulfil the new regulatory requirements.
- Communication guideline and tools including lessons learnt from the actual dissemination of the seasonal study results.
- R&D recommendations based on the identified gaps in the vaccine performance.

Expected impact

A validated governance model for influenza vaccine effectiveness studies in Europe established in public-private partnership will constitute an important building block towards a larger platform for vaccine effectiveness studies in Europe.

The action should achieve a European network that is of sufficient scope and sustainability to deliver robust estimates of effectiveness at a product-specific level for all influenza vaccines used in the EU/EEA over a prolonged period.

Through the development of a sustainable platform, tools, standards and approaches agreed by all key stakeholders, this action will set a model for the yearly evaluation of seasonal influenza vaccine effectiveness and the documentation of type/brand coverage. These are essential components of influenza vaccine benefit/risk assessments. If successful, the same model could be expanded to evaluation of all other vaccines used in national/sub-national immunisation programmes.

Together with an appropriate communication strategy targeting public health, medical professionals, policymakers and the general public, this enhanced vaccine programme evaluation will likely lead to a better societal acceptance of influenza vaccines, improved vaccine coverage in the EU and ultimately reduced disease burden.

Besides providing a platform for real life evaluation of seasonal influenza vaccines, the outcome of this project will also help define features of the next influenza vaccine candidates and provide an evaluation platform when they are being rolled out.

Potential synergies with existing consortia

This action is expected to build on the experiences and best practices of existing initiatives, develop synergies and avoid duplication of efforts with existing consortia and other relevant initiatives. The details of these interactions will have to be defined at the full proposal stage, however the application should include considerations as to how the interactions with ongoing consortia and other initiatives, such as the following, are envisaged to ensure maximising the value of the different projects.

- The IMI project 'ADVANCE': applicants should consider the ADVANCE good practice guidelines on governance and code of conduct in a public-private collaboration model[29]. Furthermore, ways should be explored on how to make studies conducted under this action of use to the ADVANCE project. ADVANCE started in 2013 and is a 5-year project.
- The H2020 action 'I-MOVE+': this 3-year project funded in 2015 by an EC H2020 grant aims to measure and compare the effectiveness and impact of influenza and pneumococcal vaccines and vaccination strategies in the elderly (>65 yrs). Applicants should take into account activities and results published by I-MOVE+ and explore synergies with I-MOVE+ so that it can focus the effort under this action on brand data documentation, age groups not covered, the development of models of public-private collaboration for vaccine effectiveness studies and communication.
- The IMI project 'FLUCOP': Synergies should be explored with the IMI project FLUCOP, a 5-year project launched in 2015 that is looking into serological assay standardisation for influenza vaccines. For example, it could be envisaged that data and findings from this action could facilitate further definition of the typology of non-respondents in FLUCOP. This could help to define a correlate of protection for influenza vaccines.

[29] The ADVANCE Code of Conduct: A tool for vaccine benefit-risk monitoring in Europe http://www.advance-vaccines.eu/app/archivos/publicacion/10/ICPE_2015_Poster_ADVANCE-CoC.pdf

Industry consortium

- Sanofi Pasteur
- Sanofi Pasteur MSD
- Abbott
- Seqirus (former Novartis and bioCSL)
- GSK

Indicative duration of the project

The indicative duration of the project is 60 months.

Indicative budget

The indicative contribution from EFPIA companies is EUR 1 000 000[30].

The IMI2 contribution will be a maximum of EUR 9 000 000.

Applicant consortium

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

The applicant consortium should include a limited number of public and/or private partners with the necessary expertise to facilitate and coordinate the development of a governance model for joint influenza vaccine effectiveness studies and to operationally manage and facilitate the conduct of pilot studies. Specifically, the applicant consortium should combine expertise in the following areas:

- conduct of prospective observational studies
- epidemiology
- public-private partnership
- governance principles, transparency, auditing
- large international project coordination
- regulatory processes
- negotiation and consensus building
- pooled data analysis and interpretation
- communication of complex notions to professional and lay audiences.

The pan-European network, expertise and access to data from national immunisation programmes that is required for the successful implementation of the effectiveness studies should not be part of the applicant consortium, but is expected to be added during stage 2 (see next page, section 'The role of ECDC and national public health and regulatory bodies').

[30] EFPIA companies part of the industry consortium are making a EUR 4 000 000 financial contribution to the IMI2 JU in support of this action.

In their short proposal, the applicant consortium should address all the objectives of this topic and describe their suggested approach to reaching the defined deliverables in synergy with the organisations (i.e. the industry consortium, ECDC, national public health and regulatory bodies) that will join the selected applicant consortium in stage 2 for the preparation of the full proposal.

In addition to addressing all the objectives of this topic, applicants should demonstrate in their short proposal a good understanding of:

- the EU/EEA current landscape regarding influenza vaccination and influenza programme evaluation and the key gaps in relation to this project;
- the expectations and needs of both public and private partners and how they will be taken into account in the development and validation of a consensus governance model for an influenza vaccine effectiveness platform;
- potential organisational models for an EU/EEA level influenza vaccine effectiveness study platform including use of in- and outpatient care settings and how they can be evaluated during the project;
- the tools that need to be developed to support the project, such as for example methods, protocols, analysis plans, agreements for data pooling, plans for audits;
- methods for communication and dissemination of obtained results and how they can be evaluated and optimised during the project;
- how to engage with regulators and ensure regulatory acceptance.

The role of ECDC and national public health and regulatory bodies

To ensure a fair competition at stage 1, applicants should note that the partners providing the unique expertise and data from national immunisation programmes, and that are required to establish the pan-European network for implementation of the effectiveness platform, including ECDC, NPHIs, and - to the extent needed – NRAs (referred to below as PHRBs[31]), will join their consortium in stage 2, as do the EFPIA companies listed under the section 'Industry consortium'. The first-ranked consortium from stage 1, the EFPIA consortium and PHRBs will together develop the full proposal during stage 2.

The participation of PHRBs is required due to the nature and objective of the action and because of the specific mandate of such organisations given to them by the Member States and the EU, respectively.

The applicant consortium should note that ECDC in cooperation with NPHIs will take the lead on the scientific elements of the project, and will have a key role in defining the governance model acceptable by the public sector and in the discussion on the sustainability of the influenza vaccine effectiveness platform.

In addition of their contribution to the overall project, NPHIs will also facilitate access to national programme data and infrastructures.

In their resource allocation planning, the applicant consortium should set aside an appropriate budget for PHRBs and other possible study sites to cover their activities (mostly data collection). It is anticipated that this budget could be in the range of EUR 5 000 000 to EUR 7 000 000, but importantly it should be aligned with the activities and overall strategy proposed. The appropriateness of the allocation of tasks and resources will be one aspect that is evaluated during the evaluation. The final detailed resource allocation plan will be set in collaboration with all partners during the full proposal development in stage 2.

[31] ECDC, national public health institutes and national regulatory agencies are defined in the context of this call text as Public Health and Regulatory Bodies (PHRBs).

Interaction with regulatory agencies

The applicant consortium should demonstrate good knowledge of existing opportunities for interaction with regulatory agencies such as dialogue with the Vaccine Working Party, broad or product-specific scientific advice, or qualification procedures.

EMA will offer assistance in putting scientific advice or procedural advice requests together through pre-submission meetings. In addition, the scientific advice office will be able to provide informal guidance to the consortium regarding the best route to take at the various stages of the project. Any other opportunities for exchange of information will be welcomed by EMA.

Suggested architecture of the full proposal

Applicants should include in their short proposal their suggestion for creating the full proposal architecture, taking into consideration the contribution and expertise of the partners joining during Stage 2, i.e. industry and PHRBs.

For example, the project might be divided into the following 6 work packages :

Work package 1:

- Development of a governance model for joint influenza vaccine effectiveness studies in Europe

Work package 2:

- Tools and protocols development

Work package 3:

- Pilot study conduct

Work package 4:

- Generation of result reports

Work package 5:

- Communication and dissemination of results

Work package 6:

- Project coordination

The final architecture of the project will be defined in detail together with all partners during stage 2 (i.e. including the industry consortium and PHRBs) when the full proposal is developed, and should enable activities designed to achieve all objectives and deliverables as indicated in the previous relevant sections.

Industry contribution

Vaccine manufacturers will contribute extensive experience in conducting / analysing influenza vaccine efficacy and effectiveness studies following rigorous standards and protocols agreed by regulators. They will further contribute with expert knowledge on their vaccines and with expertise in epidemiology / pharmacoepidemiology, pharmacovigilance, biostatistics, data management and regulatory interactions. Industry will also contribute with their experience in governance, legal and communication. They are also part of other existing consortia and will contribute to the identification of potential synergies (ADVANCE,

FLUCOP…). Apart from a financial contribution to IMI2 JU, the industry contributions to the project are based on qualified staff full time equivalents (FTEs) to support it.

Glossary

ECDC	European Centre for Disease Prevention and Control
EEA	European Economic Area
EISN	European Influenza Surveillance Network
EMA	European Medicines Agency
EU	European Union
FTE	Full-time equivalent
GISRS	Global Influenza Surveillance and Response System
NPHIs	National public health institutes
NRAs	National regulatory agencies
MS	Member State
PHRBs	Public Health and Regulatory Bodies, defined in the context of this call for proposals as ECDC, national public health institutes and national regulatory agencies
WHO	World Health Organization
WP	Work package

Conditions for this Call for proposals

All proposals must conform to the conditions set out in the H2020 Rules for Participation (https://ec.europa.eu/research/participants/portal/doc/call/h2020/common/1595113-h2020-rules-participation_oj_en.pdf) and the Commission Delegated Regulation with regard to IMI2 JU http://eur-lex.europa.eu/legal-content/EN/TXT/PDF/?uri=CELEX:32014R0622&from=EN.

The following general conditions shall apply to this IMI2 Call for Proposals:

Applicants intending to submit a Short proposal in response to the IMI2 Call 9 should read this topics text, the IMI2 Manual for submission, evaluation and grant award and other relevant documents (e.g. IMI2 model Grant Agreement).

Call Identifier	**H2020-JTI-IMI2-2016-09-two-stage**
Type of action	**Research and Innovation Actions (RIA)**
Publication Date	**27 April 2016**
Stage 1 Submission start date	**27 April 2016**
Stage 1 Submission deadline	**26 July 2016 (17:00:00 Brussels time)**
Stage 2 Submission deadline	**10 January 2017 (17:00:00 Brussels time)**
Indicative Budget	
From Industry consortia (EFPIA companies)	EUR 59 328 000
From the IMI2 JU	EUR 58 328 000

Call Topics

IMI2-2016-09-01	The indicative contribution from EFPIA companies is EUR 3 000 000 The financial contribution from IMI2 is a maximum of EUR 3 000 000	Research and Innovation Actions. Two-stage submission and evaluation process. Only the applicant consortium whose proposal is ranked first at the first stage is invited for the second stage.
IMI2-2016-09-02	The indicative contribution from EFPIA companies is EUR 6 000 000 The financial contribution from IMI2 is a maximum of EUR 6 000 000	Research and Innovation Actions. Two-stage submission and evaluation process. Only the applicant consortium whose proposal is ranked first at the first stage is invited for the second stage.

IMI2-2016-09-03	The indicative contribution from EFPIA companies is EUR 4 500 000 The financial contribution from IMI2 is a maximum of EUR 4 500 000	Research and Innovation Actions. Two-stage submission and evaluation process. Only the applicant consortium whose proposal is ranked first at the first stage is invited for the second stage.
IMI2-2016-09-04	The indicative contribution from EFPIA companies is EUR 29 000 000 The financial contribution from IMI2 is a maximum of EUR 20 000 000	Research and Innovation Actions. Two-stage submission and evaluation process. Only the applicant consortium whose proposal is ranked first at the first stage is invited for the second stage.
IMI2-2016-09-05	The indicative contribution from EFPIA companies is EUR 15 828 000 The financial contribution from IMI2 is a maximum of EUR 15 828 000	Research and Innovation Actions. Two-stage submission and evaluation process. Only the applicant consortium whose proposal is ranked first at the first stage is invited for the second stage.
IMI2-2016-09-06	The indicative contribution from EFPIA companies is EUR 1 000 000[32] The financial contribution from IMI2 is a maximum of EUR 9 000 000	Research and Innovation Actions. 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.

[32] EFPIA companies part of the industry consortium are making a EUR 4 000 000 financial contribution to the IMI2 JU in support of this action.

List of countries and applicable rules for funding

By way of derogation[33] from Article 10(1) of Regulation (EU) No 1290/2013, only the following participants shall be eligible for funding from the Innovative Medicines Initiative 2 Joint Undertaking:

a) legal entities established in a Member State or an associated country, or created under Union law; and

b) which fall within one of the following categories:

   i. micro, small and medium-sized enterprises and other companies with an annual turnover of EUR 500 million or less, the latter not being affiliated entities of companies with an annual turnover of more than 500 million; the definition of 'affiliated entities' within the meaning of Article 2(1)(2) of Regulation (EU) No 1290/2013 shall apply *mutatis mutandis*;

   ii. secondary and higher education establishments;

   iii. non-profit organisations, including those carrying out research or technological development as one of their main objectives or those that are patient organisations.

c) the Joint Research Centre;

d) international European interest organisations;

In accordance with Article 10(2) point (a) of the Regulation (EU) No 1290/2013, in case of participating legal entity established in a third country, that is not eligible for funding according to point (a) above, funding from the IMI2 JU may be granted provided the participation is deemed essential for carrying out the action by the IMI2 JU.

Admissibility conditions for grant proposals, and related requirements

Part B of the General Annexes[34] to the H2020 Work Programme shall apply *mutatis mutandis* for the actions covered by this Call for proposals.

For this call, the page limit for a stage 1 – short proposal is 30 pages. The page limit for a stage 2 – full proposal is 70 pages.

Eligibility criteria

Part C of the General Annexes to the H2020 Work Programme shall apply *mutatis mutandis* for the actions covered by this Call for proposals.

Additionally, under the two-stage submission procedure of this Call for proposals the following additional condition applies:

- The participants from EFPIA constituent entities and affiliated entities, and other Associated Partners if any, which are pre-defined in the topics of a Call for proposals do not apply at the stage 1 of the call. The applicant consortium selected from the stage 1 of the Call for proposals is merged at the stage 2 with the EFPIA constituent entities or their affiliated entities and other Associated Partners.

Furthermore, in the context of topic 6 of this Call for proposals under the scientific priority 'Infection control including vaccines, Innovation in vaccines', the following additional condition applies:

[33] Pursuant to the Commission Delegated Regulation (EU) No 622/2014 of 14 February 2014 establishing a derogation from Regulation (EU) No 1290/2013 of the European Parliament and of the Council laying down the rules for participation and dissemination in 'Horizon 2020 — the Framework Programme for Research and Innovation (2014-2020)' with regard to the Innovative Medicines Initiative 2 Joint Undertaking

[34] http://ec.europa.eu/research/participants/data/ref/h2020/other/wp/2016-2017/annexes/h2020-wp1617-annex-ga_en.pdf

- The European Centre of Disease Prevention and Control (ECDC), the National Public Health Institutes (NPHIs) and National Regulatory Agencies (NRA) will join the applicant consortium selected from the stage 1 only during stage 2, together with the participants from EFPIA constituent entities and affiliated entities. This condition is justified in consideration of the nature and objective of the action.

Types of action: specific provisions and funding rates

Part D of the General Annexes to the H2020 Work Programme shall apply *mutatis mutandis* for the actions covered by this Call for proposals.

Technology Readiness Levels (TRL)

Part G of the General Annexes to the H2020 Work Programme shall apply *mutatis mutandis* for the actions covered by this Call for proposals.

Evaluation

Part H of the General Annexes to the H2020 Work Programme shall apply *mutatis mutandis* for the actions covered by this Work Plan with the following additions:

Experts will evaluate the proposals on the basis of "Excellence", "Impact" and "Quality and efficiency of the implementation" according to the stage of the evaluation procedure

Type of action ***Evaluation stage***	**Excellence**	**Impact**	**Quality and efficiency of the implementation***
RIA and IA ***1st stage evaluation***	The following aspects will be taken into account, to the extent that the proposed work corresponds to the topic description in the call for proposals and referred to in the IMI2 annual work plan: ▪ Clarity and pertinence of the proposal to meet all key objectives of the topic; ▪ Credibility of the proposed approach; ▪ Soundness of the concept, including trans-disciplinary considerations, where relevant; ▪ Extent that proposed	The following aspects will be taken into account, to the extent to which the outputs of the project should contribute at the European and/or International level: ▪ The expected impacts of the proposed approach as mentioned in the call for proposals ▪ Added value from the public private partnership approach on R&D, regulatory, clinical and healthcare practice as relevant; ▪ Strengthening the competitiveness and industrial leadership and/or	The following aspects will be taken into account: ▪ Coherence and effectiveness of the outline of the project work plan, including appropriateness of the roles and allocation of tasks, resources, timelines and approximate budget; ▪ Complementarity of the participants within the consortium (where relevant) and strategy to create a successful partnership with the industry consortium as mentioned in the topic description in the Call for

	work is ambitious, has innovation potential, and is beyond the state of the art; ▪ Mobilisation of the necessary expertise to achieve the objectives of the topic, ensure engagement of all relevant key stakeholders	addressing specific societal challenges; ▪ Improving European citizens' health and wellbeing and contribute to the IMI2 objectives[35].	proposal. ▪ Appropriateness of the proposed management structures and procedures, including manageability of the consortium.
RIA and IA ***2nd stage evaluation***	The following aspects will be taken into account, to the extent that the proposed work corresponds to the topic description in the call for proposals and referred to in the IMI2 annual work plan and is consistent with the stage 1 proposal: ▪ Clarity and pertinence of the proposal to meet all key objectives of the topic; ▪ Credibility of the proposed approach; ▪ Soundness of the concept, including trans-disciplinary considerations, where relevant; ▪ Extent that proposed work is ambitious, has innovation potential, and is beyond the state of the art; ▪ Mobilisation of the necessary expertise to achieve the objectives of the topic, ensure engagement of all relevant key stakeholders.	The following aspects will be taken into account, to the extent to which the outputs of the project should contribute at the European and/or International level: ▪ The expected impacts of the proposed approach as mentioned in the call for proposals; ▪ Added value from the public private partnership approach on R&D, regulatory, clinical and healthcare practice as relevant; ▪ Enhancing innovation capacity and integration of new knowledge; ▪ Strengthening the competitiveness and industrial leadership and/or addressing specific societal challenges; ▪ Improving European citizens' health and wellbeing and contribute to the IMI2 objectives;[35] ▪ Any other environmental and socially important impacts; ▪ Effectiveness of the proposed measures to exploit and disseminate the project results (including management of IPR), to communicate the project, and to manage research data where relevant.	The following aspects will be taken into account: ▪ Coherence and effectiveness of the project work plan, including appropriateness of the roles and allocation of tasks, resources, timelines and budget; ▪ Complementarity of the participants within the consortium (where relevant); ▪ Clearly defined contribution to the project plan of the industrial partners (where relevant); ▪ Appropriateness of the management structures and procedures, including manageability of the consortium, risk and innovation management and sustainability plan.

[35] Article 2 of the Council Regulation (EU) No 557/2014 of 6 May 2014 establishing the Innovative Medicines Initiative 2 Joint Undertaking (O.J. L169 of 7.6.2014)

The scheme above is applicable to a two-stage submission procedure. At each evaluation stage of the two-stage submission procedure, the relevant evaluation criteria and threshold apply.

These evaluation criteria include scores and thresholds. Evaluation scores will be awarded for the criteria, and not for the different aspects listed in the above table. For all evaluated proposals, each criterion will be scored out of 5. Half marks may be given.

For the evaluation of first-stage proposals under a two-stage submission procedure, the threshold for the two first criteria 'excellence' and 'impact' is 3. The proposals will also be evaluated for the 'quality and efficiency of the implementation' criterion but with no threshold. There is no overall threshold.

For the evaluation of second-stage proposals under a two-stage submission procedure the threshold for individual criteria is 3. The overall threshold, applying to the sum of the three individual scores, is 10.

Following each evaluation stage, applicants will receive an ESR (Evaluation Summary Report) regarding the respective evaluated proposal.

The full evaluation procedure is described in the IMI2 Manual for submission, evaluation and grant award in line with the H2020 Rules for Participation[36].

Under the two-stage evaluation procedure, and on the basis of the outcome of the stage 1 evaluation, the applicant consortium of the highest ranked short proposal (stage 1) for each topic will be invited to discuss with the relevant industry consortium the feasibility of jointly developing a full proposal (stage 2). The applicant consortia of the second and third-ranked short proposals (stage 1) for each topic may be invited for preliminary discussions with the industry consortium if the preliminary discussions with the higher ranked proposal and the industry consortium fail. In such case, the applicant consortium and the industry consortium shall be responsible for jointly notifying the IMI2 JU if the preparation of a joint full proposal is not feasible. This notification must be accompanied by a joint report clearly stating the reasons why a joint full proposal is considered not feasible. Upon acknowledgement and after consideration of the specific circumstances, the IMI2 JU may decide to invite the next-ranked applicant consortium in priority order, i.e. the second ranked proposal is contacted only after failure of preliminary discussions with the first ranked, and the third ranked after the second ranked.

Under the two-stage evaluation procedure, contacts or discussions about a given topic between potential applicant consortia (or any of their members) and any member of the relevant industry consortium are prohibited throughout the procedure until the results of the stage 1 evaluation are communicated to the applicants.

As part of the panel deliberations, the IMI2 JU may organise hearings with the applicants to:

- clarify the proposals and help the panel establish their final assessment and scores, or
- improve the experts' understanding of the proposal.

Indicative timetable for evaluation and grant agreement

	Information on the outcome of the evaluation (single stage, or first stage of two stages)	Information on the outcome of the evaluation (second stage of a two stages)	Indicative date for the signing of grant agreement

[36] http://www.imi.europa.eu/sites/default/files/uploads/documents/IMI2_CallDocs/IMI2_Manual_submission_evaluation_grant_v1.3_April2016.pdf

Two stages	Maximum 5 months from the submission deadline at the first stage.	Maximum 5 months from the submission deadline at the second stage.	Maximum 8 months from the submission deadline at the second stage

Budget flexibility

Part I of the General Annexes to the H2020 Work Programme shall apply *mutatis mutandis* for the actions covered by this Call for proposals.

Financial support to third parties

Part K of the General Annexes to the H2020 Work Programme shall apply *mutatis mutandis* for the actions covered by this Call for proposals.

Submission tool

The IMI electronic submission tool **SOFIA** (Submission OF Information Application) is to be used for submitting a proposal in response to a topic of this Call; no other means of submission will be accepted. Proposals may be finalised and re-opened online until the 'Submit' button is pressed. To trigger the admissibility check, eligibility check and the evaluation, firstly the 'Finalise' button and secondly the 'Submit' button must be pressed in SOFIA by the Call submission deadline.

Access to the IMI electronic submission tool SOFIA for the first time requires a request to access the tool.

Others

For proposals including clinical trials/studies/investigations, a specific template to help applicants to provide essential information on clinical studies in a standardised format is available under:

http://www.imi.europa.eu/sites/default/files/uploads/documents/IMI2_CallDocs/ClinicalTrialInfoTemplateIMI_v201602.docx

In the first stage of a two-stage evaluation procedure, this template should not be submitted. However, applicants may integrate relevant aspects of this information in their short proposal (within the page limit). In the second stage of a two-stage evaluation procedure involving clinical studies, the use of this template is mandatory in order to provide experts with the necessary information to evaluate the proposals. The template may be submitted as a separate document.

Ethical issues should be duly addressed in each submitted proposal to ensure that the proposed activities comply with ethical principles and relevant national, Union and international legislation. Any proposal that

contravenes ethical principles or which does not fulfil the conditions set out in the H2020 Rules for Participation, or in the IMI2 JU Call for proposals shall not be selected. [37]

In order to ensure excellence in data and knowledge management consortia will be requested to do the following:

1) disseminate scientific publications on the basis of open access[38].(see 'Guidelines on Open Access to Scientific Publications and Research Data in Horizon 2020');
2) include a data management plan outlining how research data will be handled during a research project, and after it is completed, as part of the full proposal. (see Guidelines on Data Management in Horizon 2020 providing guidance for the collection, processing and generation of research data). In order to ensure adherence to the legislation concerning protection of personal data, controlled access digital repositories and data governance will need to be considered;
3) use well-established data format and content standards in order to ensure interoperability to quality standards. Preferably existing standards should be adopted. Should no such standards exist, consideration should be given to adapt or develop novel standards in collaboration with a data standards organisation (e.g. CDISC);
4) disseminate a description of resources[39] according to well-established metadata standards such as the Dublin Core (ISO15836) in order to make the resources included and generated by the IMI actions discoverable for metrics and re-use.

Full proposals shall contain a draft plan for the exploitation and dissemination of the results.

Consortium agreements

In line with the Rules for Participation and Dissemination applicable to IMI2 actions[40] and the IMI2 model grant agreement, participants in IMI2 actions are required to conclude a consortium agreement prior to grant agreement.

[37] Article 19 of *Horizon 2020 Framework Programme*, and Articles 13 and 14 of the *Horizon 2020* Rules for Participation
[38] Article 43.2 of Regulation (EU) No 1290/2013 of the European Parliament and of the Council laying down the rules for participation and dissemination in *Horizon 2020 - the Framework Programme for Research and Innovation (2014-2020)* and repealing Regulation (EC) No 1906/2006
[39] Examples of resources are (a collection of) biosamples, datasets, images, publications etc.
[40] Regulation (EU) No 1290/2013 of 11 December 2013 and Commission Delegated Regulation (EU) No 622/2014 of 14 February 2014.