

# IMI2

## 12th Call for proposals

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## Introduction

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

The Innovative Medicines Initiative 2 Joint Undertaking (IMI2 JU) has been created<sup>1</sup> 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<sup>2</sup>.

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

The initiative should therefore seek to involve a broader range of partners, including mid-sized companies<sup>3</sup>, 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)<sup>4</sup> is the main reference for the implementation of research priorities for IMI2 JU. The scientific priorities for 2017 for IMI2 JU have been prepared based on the SRA.

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

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

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

Applicant consortia shall ensure that where relevant their proposals abide by the EU legal framework on data protection<sup>5</sup>.

Before submitting a proposal, applicant consortia should familiarise themselves with all Call documents such as the IMI2 Manual for evaluation, submission and grant award<sup>6</sup>, 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), Coordination and Support Action (CSA).

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<sup>1</sup> Council Regulation (EU) No 557/2014 of 6 May 2014 establishing the Innovative Medicines Initiative 2 Joint Undertaking (IMI2 JU).

<sup>2</sup> [http://www.who.int/medicines/areas/priority\\_medicines/en/](http://www.who.int/medicines/areas/priority_medicines/en/)

<sup>3</sup> Under IMI2 JU, mid-sized companies having an annual turnover of EUR 500 million or less not being affiliated entities of companies with an annual turnover of more than 500 million; the definition of 'affiliated entities' within the meaning of Article 2(1)(2) of Regulation (EU) No 1290/2013 applies mutatis mutandis. Where established in an EU Member State or an associated country, are eligible for funding.

<sup>4</sup> [http://www.imi.europa.eu/sites/default/files/uploads/documents/IMI2\\_SRA\\_March2014.pdf](http://www.imi.europa.eu/sites/default/files/uploads/documents/IMI2_SRA_March2014.pdf)

<sup>5</sup> 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>

<sup>6</sup> [http://www.imi.europa.eu/sites/default/files/uploads/documents/IMI2\\_CallDocs/IMI2\\_ManualForSubmission\\_v1.5\\_July2017.pdf](http://www.imi.europa.eu/sites/default/files/uploads/documents/IMI2_CallDocs/IMI2_ManualForSubmission_v1.5_July2017.pdf)

## Topic 1 : Development and validation of technology enabled, quantitative and sensitive measures of functional decline in people with early stage Alzheimer's disease (RADAR-AD)

### Topic details

|                                 |                                       |
|---------------------------------|---------------------------------------|
| Topic code                      | IMI2-2017-12-01                       |
| Action type                     | Research and Innovation Actions (RIA) |
| Submission & evaluation process | 2 Stages                              |

### Part of the Remote Assessment of Disease and Relapse Programme (RADAR)

#### Introduction to the RADAR programme and problem statement

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

Measuring physiological and activity-based parameters remotely and continuously via unobtrusive on-body sensors or smartphones has the potential to revolutionise our ability to predict and pre-empt harmful changes in disease trajectory. Developing methods for real-time identification of behavioural and physiological patterns (bio-signatures) that culminate in relapse is of great importance; early detection and communication of 'red flags' to patients, caregivers and care providers can prompt help-seeking behaviour and deployment of just-in-time interventions that may prevent relapse episodes, effectively altering one's clinical trajectory. A platform to acquire data in a real world setting would also enable the development of measures of real world effectiveness of medicines.

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

- 1) a lack of fundamental disease understanding into the signals and fluctuations in disease state;
- 2) the lack of clear policy, guidelines and pathways to develop and license 'pre-emptive' therapeutic strategies that use such digital monitoring and remote assessment technology;
- 3) the immaturity of the technology platforms, including sensor technology, data exchange standards, continuous sensor data access and stream processing technology, as well as the analytical methodology, where today research is hampered by ad-hoc solutions that are not suitable to develop healthcare products in the longer term.

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

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

Scientific feasibility will be performed via the individual topics of the RADAR programme to focus on the specifics of different disease areas. The first topic of the RADAR platform was published as part of IMI2 JU - Call 3, and the action that it generated studies the fluctuation of the chronic diseases of depression, multiple sclerosis and epilepsy, using remote monitoring technology, to provide a foundation for developing a novel paradigm based on prediction and pre-emption. The current topic, launched as part of IMI2 – Call 12 will study the development and validation of technology-enabled, quantitative and sensitive measures of functional decline in people with early stage Alzheimer’s disease.

Research in these areas needs to bring together physicians, patient groups, sensor manufactures, ICT (information and communication technology) providers, data management and analyst specialists with the pharmaceutical industry.

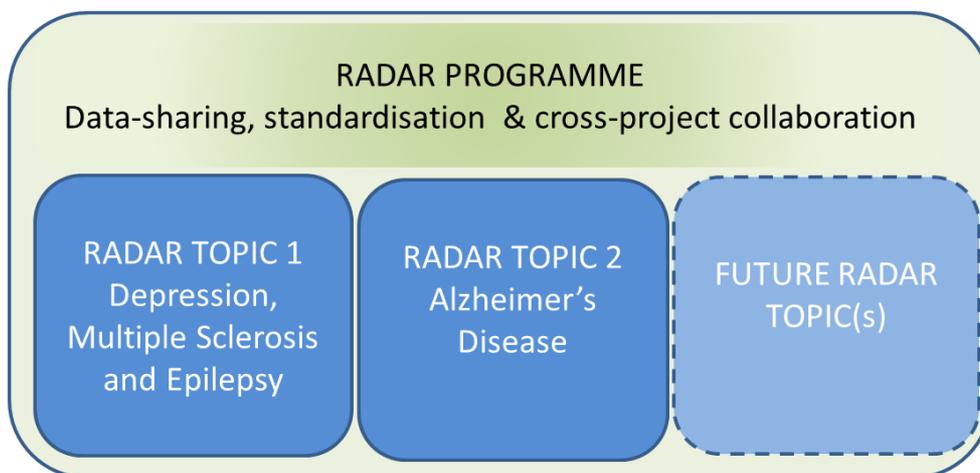
Introducing a drug development and a clinical care strategy based on such science and technology requires a second type of public-private research to be undertaken to: 1) develop policy for the regulatory and licensing pathways to deliver a digital intervention; 2) understand and develop a framework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

### Overall objectives of the RADAR programme

The key objective of the RADAR programme is to develop the foundational components of a digital platform to improve patient outcomes through remote assessment. These components will be split into several topics, with some cross-cutting themes co-ordinated across all topics. Considering the overall objective of the RADAR programme, the actions stemming from the different topics will be deemed to be complementary to each other.

### RADAR programme architecture

The full RADAR programme will consist of several topics that are resourced and managed independently but will join forces in key areas such as technological approach and data sharing. The RADAR-CNS action covering depression, MS and epilepsy was generated from the topic launched under IMI2 - Call 3. It has developed a key part of the core platform for the collection, transmission, storage, analysis and visualisation of the relevant functional measures for the whole RADAR platform, which can act as the basis for the integration of further modules provided by other RADAR initiatives. The core platform will be extended with new or enhanced capabilities wherever identified as beneficial for the topics at the core of the present project on patients with dementia, hence beyond RADAR-CNS, to make sure the platform can evolve with the state-of-the-art in the field. Applicants must reserve some resources to facilitate these cross-projects activities and consider this key aspect when developing their solutions to ensure interoperability through the horizontal platform. Under IMI2 - Call 12, one additional topic will be launched in Alzheimer’s disease (AD).



### Future RADAR topics

At a later stage, IMI2 JU may publish additional topics which will become part of the RADAR programme.

In that respect, potential applicants must be aware that all or some of these RADAR topics, if exceptionally needed and so foreseen in the applicable IMI2 JU Annual Work Plan, may be restricted to those consortia already selected under the relevant Calls in order to enhance their results and achievements by extending their duration and funding.

Consortia will be entitled to open to other beneficiaries as they see fit to fill critical skills gaps in the consortia that reflected the extensions in these work plans.

In the case of the RADAR-AD topic, a restricted Call may be launched as part of a future IMI2 JU Annual Work Plan, for further detail see below under 'Future Project Expansion'.

## **General Principles for all Projects Conducted under the RADAR Programme:**

### **Data Sharing and interoperability**

Data sharing and interoperability is paramount to the success of the RADAR programme. The framework supporting this data sharing (i.e., the type of data to be shared and the rules governing the access, (use/ re-use and informed consent) to data as well as the data sharing) must be established prior to the submission of the full proposal in line with IMI2 Intellectual Property (IP) policy and considering the overall approach agreed upon in the other RADAR projects. EFPIA members and consortia partners will be committed to sharing all data (clinical, bio-sensor, etc.) available to, or generated by the RADAR program amongst all members of a RADAR topic, and across topics as required. In addition to data, RADAR constituents will also share, among others, domain practices and expertise developed with respect to data management procedures, usability, regulatory and policy pathways etc. across the RADAR program and externally as required by IMI policy and procedures. Please, also see the expectations with regard to data standards, compatibility and interoperability in the impact section of the topic description. It is to be noted that the digital platform in development should be able to interface to different kind of sensors and devices, which, some of them, will be tested in the frame of the present project.

### **Specific challenges to be addressed**

Alzheimer's disease (AD) is today the leading cause of dementia and one of the most common causes of disability and loss of independence among the elderly. The World Health Organization (WHO) estimates the cost of dementia disorders in the European Union alone to be more than € 160 billion per annum. This cost will continue to rise dramatically as the numbers of people with dementia in the European Union are projected to nearly double every 20 years, due to Europe's aging demographic.

The early stages of AD are associated with cognitive decline, overlapping with increasing functional decline (impairments in the ability to perform daily activities), leading to progressive loss of independence and escalation of caregiver burden and medical costs. While much effort has gone into developing sensitive measures of cognition, today there are no similar measures of subtle functional changes in early AD subjects which have a direct impact on disease burden.

Recent data from long-term longitudinal cohorts have begun to delineate cognitive domains and functional tasks that are most affected by AD pathology. These include cognitive domains related to episodic memory, spatial orientation, processing speed and functional read-outs such as changes in ability to perform simple financial calculations, ability to use a phone/computer, gait speed, driving performance, and ability to adhere to medications, among other things. In addition, AD and related co-morbidities also have an effect on stress, mood and sleep. Impairment of these cognitive domains, functional capabilities and mood and sleep can be captured by new technology methods such as wearables, mobile devices and home-based sensor technologies.

The overall goal of the action generated from the RADAR-AD topic would be to measure functional status and some key underlying cognitive abilities of AD patients in order to identify meaningful differences compared to normal status, using a robust, scalable technology-enabled system that can be deployed in real world settings to monitor and improve real world outcomes that are relevant to patients and their caregivers. While the main focus of the topic is to understand functional decline in subjects with mild cognitive impairment (MCI) and in the early stages of AD, nevertheless late-stage AD monitoring should also be considered in order to validate the results and show the relationship of functional measures with all stages of AD.

## Need and opportunity for public-private collaborative research

The ability to track and measure functional decline in AD populations to shorten clinical development and generate payer-relevant evidence of real world impact of therapeutic interventions is a precompetitive need in the field of Alzheimer's drug development. The development and validation of technology-enabled functional endpoints in AD will require public-private collaboration between AD clinical sites, home-based caregivers, sensor manufacturers, analytics experts and software developers. In addition, successful implementation will also require a collaborative partnership with AD patient advocacy groups, the caregiver community and privacy and bioethics experts to ensure that the technology solutions developed in the project can be adopted in the real world. The implementation of the project involving all these stakeholders will ensure the sustainability of the results. These stakeholders need to have expertise from diverse fields and different industries, and they need to align with patients and regulators; all these requirements imply that the goals of the RADAR-AD topic are best accomplished in a public-private consortium setting.

## Scope

The main goal of the action to be created from this topic is to develop a digital platform to measure a valid and meaningful combination of smartphone, wearable and/or home sensor based parameters that can detect subtle functional deficits in early Alzheimer's patients (mild AD, MCI or earlier), in the context of AD progression. Risk factors and other biomarkers that could identify pre-symptomatic prodromal AD will be also considered as exploratory assessment. Even though the system developed should be suitable for longitudinal assessment of function, in their proposal applicants should come with their suggestions on how the digital platform will generate validity data from a cross-sectional study to demonstrate that function can be measured at baseline in a reliable and sensitive manner. Considering the limited budget and project duration, the solution to be built will have to rely upon already available technology platforms and on available longitudinal datasets. In case of a successful outcome, the results should be discussed with regulatory agencies in order to obtain guidance about how to develop a path for formal qualification as outcome measurements to be used in the real world for assessing future therapeutic intervention.

The following activities will be within the scope of proposals to achieve the topic goals:

- Analysis of existing longitudinal AD datasets and disease model(s) to identify functional domains or markers that are specific and sensitive to early stages of Alzheimer's progression and most predictive of deleterious long-term outcomes such as loss of independence and nursing home entry. Such functional domains should include real world activities such as the ability to perform financial calculations, utilise the phone, navigate around the house/neighbourhood, adhere to a medication schedule, interact socially with appropriate behaviour and perform other everyday tasks that require episodic memory and executive function. The applicants should identify and gain access to the appropriate longitudinal datasets that allow retrospective analysis of cognition, function and caregiver / payer relevant long-term outcomes.
- Obtain and incorporate feedback from regulators (i.e. scientific advice) regarding the potential use of technology-enabled functional end-points to be possibly considered in future for registration studies of drugs.
- Obtain and incorporate feedback from patients, caregivers and payers to ensure that the functional domains being measured are relevant and meaningful.
- Implement a platform technology-enabled system of sensors and devices to continuously analyse data from identified functional domains, including smartphones, wearable and/or fixed home-based sensors. This can concern measures that are passive (e.g. ability to use phone or computer keyboard, gait speed etc.), or active (a challenge task requiring financial calculations etc.) with respect to patient interaction.
- Validate the platform technology-enabled function assessment system in a real world clinical setting. This cross-sectional validation study will require a short-term (approximately 3 months) baseline assessment of function to establish a reliable cross-sectional measure of function using the built sensor-based system in cognitively normal, MCI and mild AD cohorts. In addition, moderate AD and some severe AD patients will be also included.

The functional measures will be optimised for the following.

- Ability to best differentiate different stages of Alzheimer's disease (i.e. cognitively normal vs. MCI vs. mild AD vs. moderate AD ). The main focus will be to identify functional measures that best separate cognitively normal from early MCI patients.
- Ability to show sensitivity to changes using appropriate modelling-based approaches.
- Correlation with cognitive domains known to be effected in AD (e.g. episodic memory).
- Correlation with established paper and pencil (self-reported) scales to measure function and cognition in AD.
- Correlations with known risk factors for AD (body mass index (BMI), physical exercise, sleep, etc.) for the possible identification of a putative pre-symptomatic cohort.
- Correlation with known biomarkers of pathology, such as positron emission tomography (PET) and cerebro-spinal fluid (CSF) markers, or clinical scales (ADAS-Cog) if available.
- Correlation with caregiver burden and healthcare utilisation costs.
- Ease of use and adherence by technology users in real world clinical settings.

## Collaboration agreements

The key objective of the RADAR programme is to develop the foundational components of a digital platform to improve patient outcomes through remote assessment. To ensure the interactions between the projects under the RADAR programme, which are paramount for its overall success, and the necessary data sharing and interoperability, the funded actions are expected to share data and collaborate in domain practices and expertise developed with respect to, among other things, data management procedures, usability, regulatory and policy pathways. Therefore all grants awarded under the RADAR programme will be complementary Grant Agreements. The respective options under Article 2, Article 31.5 and Article 41.4 of the IMI2 Model Grant Agreement will be applied to the relevant Grant Agreements.

## Expected key deliverables

- Prioritised list of functional domains relevant to early Alzheimer's disease progression (based on analysis of existing datasets and input from experts, payers, patient and caregiver advocacy groups).
- Prioritisation of pre-existing wearable/home-based sensors & devices and computerised functional tasks that would best measure the target functional domains in early AD populations.
- Development of continuous data-sensing solutions as shown to be needed for the monitoring of the identified relevant parameters in the AD functional domains. The members of the industry consortium of the RADAR-AD topic will make available facilitating tooling and horizontal platform assets to support such development, assuming the integration of pre-existing and newly added components to the evolving platform infrastructure. In this way, the interoperability of all solutions developed on the platform inside and outside the action will be ensured. The solutions developed, irrespective of whether they leverage the planned facilitating common platform infrastructure or are built independently from it, should in any case allow for cross-analysis, data stream sharing and aggregated visualisation both across all solutions developed by the action generated by this topic, and in combination with pre-existing solutions such as those being elaborated under the RADAR CNS action (see what is specified in the introduction to the RADAR programme). It is indeed paramount to the value of the project deliverables that they do not result in vertical, ad-hoc solutions as often seen in today's practice.
- Cross-sectional validation of the developed system/digital platform and ad hoc sensors and devices in clinical cohorts (normal, at risk, MCI, AD) in order to gather cross-sectional validation data from normal, at risk, MCI, mild AD and moderate AD cohorts, and further refinement of the system through optimisation studies: baseline cross-sectional assessment is proposed to last 2-3 months.
- Finalised version of the system ready for deployment in exploratory clinical trials and for real world evidence gathering studies at home settings or in elder/dementia care facilities.

## Expected impact

The development of objective and sensitive functional measures will enable potential dementia therapies to demonstrate functional impact and clinical meaningfulness of early intervention without requiring long follow-on studies, thus reducing the time and cost required to bring Alzheimer's disease modifying drugs to market.

An objective, scalable, platform technology-enabled functional assessment system will also allow the measurement of the real world impact of disease trajectory on individual patients in home and caregiver settings and help direct scalable and customised interventions that target specific functional deficits that promote independent living, thus reducing the cost and care-giving burden. Another valuable impact would be given by integrating organisations, e.g. small and medium-sized enterprises (SMEs) with expertise in developing sensors and also in the area of processing and analysing the data from sensors/ devices related to the scope of measuring the functional decline due to Alzheimer disease, as well as addressing the specific problem of the digital platform/user interface for these populations. This approach will allow the SME community to build up their skills and increase competitiveness within this area.

Furthermore, adding AD to the RADAR programme will make the entire system more attractive to professionals involved in dementia care, thus helping with the dissemination and adoption of the entire RADAR platform, ensuring interoperability and technology evolution without disrupting the continuous build-up and extension of the knowledge collection and research practices across the whole RADAR scope (i.e. without having to resort to ad-hoc, un-reusable solutions for specific research topics, with their own visualisation etc.).

To maximise impact, it is expected that the system built within the action generated from the RADAR-AD topic will adhere to well-accepted data standards, where applicable, to ensure compatibility with other systems both within the RADAR programme and more widely. For example, many patients with Alzheimer's disease also have depression as a co-morbidity. The facility to deal with many diseases will make the entire system more attractive to professionals involved in elder care, thus helping with the dissemination and adoption of the entire RADAR platform.

The system created via the RADAR-AD topic has the potential to become a widely used tool to measure and help improve quality of life in elder care homes and assisted-living facilities that focus on dementia and other age-related causes of functional decline. The platform developed to measure function in AD patients by the action will be made available for further refinement and validation in longitudinal clinical studies to each of the industry members of the consortium. Consequent incorporation in any controlled clinical trials will help gain regulatory acceptance of the platform as a valid efficacy endpoint. The platform will also be made available to a broader set of clinical studies that may be ongoing in various IMI-funded projects. Opportunities to deploy the platform will also be explored in more real world settings such as elder care and dementia care facilities. In the long term it is expected that the platform created by the action will be used both in AD clinical trials, as a valid and sensitive efficacy measure, as well as in real world settings, such as homes and senior care facilities, to track functional decline in patients with AD in a way which will lead to better interventions that improve the quality of life.

## Potential synergies with existing consortia

Applicants should take into consideration, while preparing their short proposal, relevant national, European (both research projects and 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.

As indicated in the introduction to the RADAR programme, the action generated from this topic is expected to actively synergise with the already generated RADAR-CNS action (<http://www.radar-cns.org/>), as well as with future actions that will be generated under the programme. Thus applicants must plan for resources to facilitate these cross-projects activities and consider this key aspect when developing their solutions to ensure interoperability through the horizontal platform.

In addition, synergies should be considered with existing IMI projects in the AD field.

- **EMIF** (<http://www.emif.eu/>): The applicants should explore collaborations with EMIF to access the datasets required to evaluate functional domains in AD patients. The applicant consortium should seek to

utilise the output of IMI EMIF to acquire longitudinal datasets for the evaluation of functional changes in AD subjects.

- **BD4BO ROADMAP** (<http://roadmap-alzheimer.org/>) the action generated from this topic should strive to form a collaboration with the ROADMAP consortium to obtain input from regulators and payers which will be important in developing valid and meaningful functional measures and can be obtained via mechanisms developed in ROADMAP.

Other initiatives to be considered for synergy activities are mentioned below.

- Several initiatives on assessing ageing are taking place in various European countries, as summarised in the SHARE project ([www.share-project.org](http://www.share-project.org)) addressing topics relevant for the Call, .i.e. computerised functional tasks, functional domains of the ageing brain, biomarker/data analysis especially in healthy, ageing or early affected patients. See as example of a national initiative in Germany: <http://www.gesundheitsforschung-bmbf.de/de/5765.php>
- There are substantial activities on Ambient Assisted Living (AAL) in various European countries under the umbrella of the AALIANCE2 consortium (see [www.aal-europe.eu](http://www.aal-europe.eu)). For more information on single initiatives, see CORAL ([www.coral-europe.eu](http://www.coral-europe.eu)) and ECHAlliance ([www.echalliance.com](http://www.echalliance.com)).

Synergies with other relevant initiatives/projects should also be explored in order to consider learnings as well as the potential for future combination, once the digital platform generated via the RADAR-AD topic has been successfully implemented and validated. These can be initiatives focussed on early risk detection and intervention in the area of active and healthy ageing in relevant EU funded projects, such as those supported by Horizon 2020 Societal Challenge 1: Health, Demographic Change and Well-being, as well as European platforms and infrastructures as relevant. Examples here include:

- **NC3:** <http://www.bioshare.eu/content/nc3>
- **BBMRI-ERIC Work Programme 2017:** [http://www.bbmri-eric.eu/wp-content/uploads/2016/07/BBMRI-ERIC\\_Work\\_Programme\\_2017\\_online.pdf](http://www.bbmri-eric.eu/wp-content/uploads/2016/07/BBMRI-ERIC_Work_Programme_2017_online.pdf)
- **ELIXIR:** <https://www.elixir-europe.org/about-us>
- **Human Brain Project (HBP)** ‘Medical Informatics Platform: searching real patient data to understand similarities and differences among brain diseases’, released in March 2016, see: <https://www.humanbrainproject.eu/en/>
- **AgedBrainSYSBio:** <http://www.agedbrainsysbio.eu/>
- **SENSECog:** <http://www.sense-cog.eu/>.

Applicants should also consider how the results of the action could contribute and align with the policy of the European Commission’s Directorate-General for Health and Food Safety (DG SANTE) on Alzheimer’s and other dementias ([http://ec.europa.eu/health/major\\_chronic\\_diseases/diseases/dementia\\_en#fragment2](http://ec.europa.eu/health/major_chronic_diseases/diseases/dementia_en#fragment2)).

Finally, interesting activities on the validation of digital biomarkers in patients with neurodegenerative disorders are sponsored in the US by the Critical Path Institute’s Coalition Against Major Diseases (CAMD) (<https://c-path.org/>).

## Industry consortium

The industry consortium is composed of the following EFPIA companies:

- Janssen (lead)
- Takeda
- Eli Lilly
- Novartis
- Nokia

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

- Software AG

The industry consortium will contribute the following expertise and assets:

- programme leadership, project management, financial management;
- expertise in longitudinal analysis of AD cognition, function, biomarker and clinical data;
- expertise in payer and regulatory perspectives;
- expertise in data analysis, biosensor evaluations;
- clinical study design, biostatistics, expertise in clinical assessment of AD patients, including cognitive and functional endpoints;
- expertise in patient association and ethical aspects;
- biosensor evaluations;
- clinical study design, biostatistics, data management expertise and monitoring/data review tools, especially with data on demand approaches for visualisation and monitoring of studies utilising smartphone apps;
- expertise in functional assessments, such as activities of daily living (ADL) gained through clinical studies in AD and eventually clinical datasets that may be made available;
- AD therapeutic area expertise and data analysis along with years of digital and clinical endpoint strategy knowledge;
- Nokia will bring IMPACT SW platform licence and support;
- Software AG will bring Apama, Universal Messaging, MashZone, Terracotta, Apama Predictive Analytics add-on, and Device Integration Platform software licences.

## Indicative duration of the action

The indicative duration of the action 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 the results and achievements by extending the duration and funding. The consortium will be entitled to open to other beneficiaries as it sees fit.

A restricted Call may be launched as part of a future IMI2 JU Annual Work Plan to enable the validation of the biomarkers that have been found promising, following positive regulatory scientific advice, and / or to perform the necessary longitudinal clinical studies to determine the utility of the digital platform, as to being able to detect AD specific change in function, and the feasibility for its integration in clinical trials.

## Indicative budget

The indicative in-kind contribution is EUR 3 555 000. This contribution comprises an indicative EFPIA in-kind contribution of EUR 2 830 000 and an indicative IMI2 Associated Partners in-kind contribution of EUR 725 000.

Due to the global nature of the participating industry partners it is anticipated that some elements of the contributions will be non-EU in-kind contribution<sup>7</sup>.

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<sup>7</sup> Note: This does not however constitute the justification referred to in Article 4(2) of the IMI 2 JU regulation.

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

## 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. Therefore, the applicant consortium should be able to demonstrate the full scope of experience and expertise needed in order to address effectively and meet all goals outlined in this topic.

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

- AD clinical research and trials and disease area expertise, regulatory science, patients and patient organisations, data and knowledge management;
- project management and professional communication expertise, design and conduct of clinical studies (end-points, inclusion criteria etc.);
- expertise in clinical data management and clinical statistics;
- expertise in device and sensor development (including SMEs); IT / analytics expertise (including SMEs);
- expertise in data privacy and security;
- regulatory expertise and experience in development and qualification of novel end-points using digital technologies; clinical and general project management.

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

- access to patient cohorts in all stages of Alzheimer's disease (preclinical, MCI, mild to moderate AD), possibly with a biomarker characterisation, and non-affected control subjects sharing a similar environment;
- data management architecture, hardware / software platform, state-of-the-art algorithms to process and analyse data from sensors / devices; device, data and connectivity management;
- architecture, hosted semantic web (SW) platform, allowing the on-boarding and life cycle management of medical equipment in a communication secure environment (including SMEs) that could be further developed or modified for use in assessing functional decline due to AD.

## Suggested architecture of the full proposal

The applicants 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 EFPIA and the Associated Partner.

In the spirit of the partnership, and to reflect how IMI 2 JU call topics are built on identified scientific priorities agreed together with EFPIA beneficiaries/large industrial beneficiaries, these beneficiaries intend to significantly contribute to the programme leadership and project and financial management.

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

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

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

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

### **Work package 1 – Management, coordination, dissemination and sustainability**

- 1.1. Set-up of project management boards: governing, steering, communication, intellectual properties.
- 1.2. Development and implementation of a dissemination programme.
- 1.3. Development and implementation of internal and external communication tools.
- 1.4. Financial management, monitoring and project management support and implementation.
- 1.5. Development of a sustainability plan facilitating continuation beyond the duration of the action.

Industry contribution: shared programme leadership with the action coordinator, project management, financial management; development and implementation of a data management plan and correlated activities; contribution to communication and information diffusion.

Expected applicant consortium contribution: it is expected that the applicant consortium has the necessary skillsets to contribute effectively to all the tasks foreseen in the WP description and in a manner compatible with contributions of the industry consortium.

### **Work package 2 – Assessment of functional domains relevant to early Alzheimer’s disease progression**

- 2.1. Assessment of existing clinical, functional, cognitive, digital data regarding AD patients at different stages; collect input from patients and caregivers so as to identify functional domains that are amenable to digital data collection and that are specific and sensitive to the early stages of AD progression and most predictive of deleterious long-term outcomes.
- 2.2. Identification and use of appropriate longitudinal datasets that will allow a modelling-driven interpretation of the cross-sectional data collected in the clinical study described in WP5; progression and most predictive of deleterious long-term outcomes.
- 2.3. Prioritisation of functional domains relevant to early Alzheimer’s disease progression.

Industry contribution:

- expertise in clinical, functional, behavioural and biomarker measurement mostly gained through clinical studies in AD patients;
- expertise in biomedical statistical analysis;
- expertise in disease modelling , identifying and accessing appropriate datasets, interpreting analyses of longitudinal datasets and prioritisation of functional domains relevant to early Alzheimer’s disease progression;
- opportunity to connect with other IMI programmes regarding tools and knowhow that could be transferred into the current project so as to maximise the probability of success.

Expected applicant consortium contribution: the applicant consortium should have the necessary skillsets and the capacity to engage with institutions where they can access patients in all stages of Alzheimer’s disease (preclinical, MCI, mild to moderate AD) and their caregivers. They should have a clear understanding of their need and the opportunity to engage with patients for technology pilot testing and eventually for a proper clinical trial. They should have analytical and statistical competence for contributing to the existing data analysis and inclusion in a model-based assessment of the data that will be collected in the project.

### **Work package 3 – Communication with regulatory authorities, patient associations, payers and Ethical Boards**

- 3.1 Connect with patient associations, caregivers and payers of some European countries to understand the ethics and relevance of the functional domains chosen to be measured, the acceptability of technology and the overall feasibility of the project, so as to adaptively define the progression of the project. Furthermore, activities should be considered to ensure, where relevant, alignment with DG SANTE's policy on Alzheimer's and other dementias.
- 3.2 Align with the regulatory requirements for approaching a possible future qualification of the use for digital technology to monitor AD patients.
- 3.3 Progress the preparation of the documents required for a European Medicines Agency (EMA) Scientific Advice to lay down a plan regarding the future potential use of technology and related functional endpoints and biomarkers, when appropriate, in order to streamline the project progression into a clear deliverable.

Industry contribution: Expertise in payer and regulatory perspectives and processes for obtaining Scientific Advice; expertise in policy, regulatory affairs, patient associations and payers.

Expected Applicant consortium contribution: engaging patient associations or advocacy groups; competences on data privacy and data security. Applicants should also be able to support the industry partners in the process for obtaining a scientific advice from the regulatory agency to lay the foundations for future qualification of the medical device.

### **Work package 4 – Development of a technology-enabled system to measure identified functional domains via smartphone, wearable and fixed home-based sensors**

- 1.1 Prioritisation of pre-existing wearable/home-based sensors and computerised functional tasks that would best measure the target functional domains in early AD populations.
- 1.2 Development of plug-in solutions for monitoring the parameters relevant to AD in order to be fully interoperable with a pre-existing platform.
- 1.3 Extension of the assets of the already-existing continuous monitoring and remote assessment platform in order to permit the connection of the plug-in solutions developed.

Industry contribution:

- expertise in data analysis, biosensor evaluations; software licences (Apama, Universal Messaging, MashZone, Terracotta, Apama Predictive Analytics add-on, and Device Integration Platform software licences);
- software licenses (IMPACT CDP device and subscription management, IMPACT secure data gateway, IMPACT connectivity management), related application hosting services;
- experience with digital biomarkers collected through smartphone apps and other wearables for continuous monitoring and data analysis;
- expertise in both the Activities of Daily Living (ADL) and digital biomarkers collected through smartphone apps for continuous monitoring from previous studies;
- prioritisation of pre-existing digital tools that would best measure the target functional domain in early AD;
- scientific search of technologies used in studies to measure functional domains of AD;
- market research of technologies commercially available, and proposed prioritisation along pre-defined criteria;
- identification of gaps / functional domains that cannot be covered by adequate technology (or are not satisfactorily understood).

Expected Applicant consortium contribution: it is expected that the applicant consortium will be able to utilise relevant hardware / software and extend any relevant pre-existing platform for digital data collected in patients with neurologic or psychiatric disorders in order to meet the needs of the action selected under this topic. The applicant consortium is expected to on-board devices (hardware) as seen needed for the specific AD studies at hand and specify data management and analytics procedures (software) with the same aim, on top of the

industry-provided and pre-existing platform infrastructure, as such realising the technical environment for validation in WP5. The solution should be modifiable and extendable and able to benefit from technology assets brought forward by the industry (Nokia will bring IMPACT SW platform licence and support; Software AG will bring Apama, Universal Messaging). They should also be able to engage in bench tests, simulations and empirical pilot experiments with patients and caregivers in order to effectively select the sensors / devices that will be used for the actual proof-of-concept study.

### **Work package 5 – Validation of the technology-enabled function assessment system in a real world clinical setting**

- 5.1 Deployment of the digital platform developed by the action in a cross-sectional clinical study to establish correlation to disease stages (normal, MCI, AD), to cognition, to traditional ‘paper-pencil self-reported measures’ of function and other biomarkers.
- 5.2 Optimisation work of the developed system of sensors and devices in order to establish a reliable cross-sectional measure of function in cognitively normal, MCI, mild AD and moderate AD cohorts.
- 5.3. Implementation of the results obtained into a model based on longitudinal data, in order to propose a possible progress of the dataset produced into a future longitudinal cohort study, and thus providing a starting point for a process of regulatory validation of this approach.

Industry contribution: To provide qualified support to the definition of the clinical study design and the preparation of the study protocol and the statistical analysis package by implementing expertise and know-how in clinical science, clinical operation, regulatory, biostatistics and data management, report preparation to support a scientific publication.

Expected applicant consortium contribution: it is expected that the applicant consortium will contribute to the clinical trial design, to identify and engage the recruitment centres, to manage the implementation aspects of clinical operation required for the actualisation of the study, to manage appropriately the relationship with patients and caregivers that will volunteer in the study, to coordinate the implementation of the digital technology selected for the trial, to ascertain that data are collected and safely stored in the platform in line with the pilot study results, and to contribute to the definition of the statistical analysis plan and to data analysis, data representation and support for a scientific publication.

## **Glossary**

|       |   |
|-------|---|
| AAL   | Ambient Assisted Living   |
| AD    | Alzheimer’s disease   |
| ADL   | Activities of Daily Living  |
| CAMD  | Coalition Against Major Diseases                                  |
| CNS   | Central Nervous system  |
| COPD  | Chronic Obstructive Pulmonary Disease                             |
| CSF   | Cerebrospinal Fluid   |
| EFPIA | European Federation of Pharmaceutical Industries and Associations |
| EMA   | European Medicines Agency   |
| EMIF  | European Medical Information Framework                            |
| EPAD  | European prevention of Alzheimer’s dementia consortium            |
| EU    | European Union  |
| H2020 | Horison 2020 Framework Programme                                  |

|           |  |
|-----------|--|
| ICT       | Information and Communication Technology   |
| IP        | Intellectual property  |
| MCI       | Mild Cognitive Impairment  |
| MS        | Multiple Sclerosis   |
| PET       | Positron Emission Tomography   |
| RADAR     | Remote Assessment of Disease and Relapse   |
| RADAR CNS | Remote Assessment of Disease and Relapse in Central Nervous System Disorders                 |
| ROADMAP   | Real World outcomes across the AD spectrum for better care: Multi-Modal data Access Platform |
| SME       | Small and medium-sized enterprises   |
| SW        | Semantic Web   |
| WHO       | World Health Organisation  |
| WP        | Work package   |

## Topic 2: FAIRification of IMI and EFPIA data

### Topic details

|                                 |                                      |
|---------------------------------|--------------------------------------|
| Topic code                      | IMI2-2017-12-02                      |
| Action type                     | Research and Innovation Action (RIA) |
| Submission & evaluation process | 2 Stages                             |

### Specific challenges to be addressed

Since 2008, numerous IMI consortia have been generating results in a diverse set of biomedical domains ([www.imi.europa.eu/content/ongoing-projects](http://www.imi.europa.eu/content/ongoing-projects)). In many projects these results have been stored in a custom database, sufficient for the project itself but difficult to access by scientists outside the project. In addition, relatively little attention has been paid to making the data from different projects interoperable, i.e. making the databases 'talk to each other'. The same is true for many internal industry research and development databases, including databases that store chemical compounds, proteins, pharmacological activities, Absorption, Distribution, Metabolism, Excretion, Toxicity (ADMET) data, gene and protein expression data, high content image data, phenotypic assay data, video, etc. In addition, clinical data are often stored in separate databases, complicating their analysis in the context of preclinical data. Making a significant portion of the data from IMI projects accessible and interoperable with other datasets and databases will greatly improve the use and impact of the data for translational biomedical research.

The concept of FAIR data principles (Findable, Accessible, Interoperable, Reusable)<sup>8</sup> [1] is perfectly suited for this task. There is a strong and growing acceptance of the necessity of these data principles in ongoing database organisations such as ELIXIR<sup>9</sup>, but also in global organisations such as the G20 countries<sup>10</sup>. Very similar principles for data stewardship are described in the H2020 Guideline for data management<sup>11</sup> as part of the H2020 Open Research Data Pilot (ORDP, Art. 29.3 of the MGA) and the IMI2 Data Management Plan template<sup>12</sup>.

ICT, legal and contextual interoperability of databases opens up exciting opportunities for data mining and hypothesis generation by using information from multiple domains simultaneously. The linked data can be explored with advanced analytical methods such as computer reasoning and inferencing, making the value of the collection of linked databases much greater than its constituent parts. For clinical data this will open opportunities in bench-to-bedside translational research, by connecting preclinical with clinical information. Corporate databases usually contain proprietary data that is not publicly shared, but significant value will be obtained if their scientists can perform data exploration and mining across all the datasets available to them, including public, licensed/commercial, along with their own companies' private databases. For academia and SMEs this project will facilitate working with pharmaceutical companies, as they will have a much better understanding of the content and format of the industry's internal data and the industry's specific needs and future directions.

### Need and opportunity for public-private collaborative research

The expertise in this field is highly complementary between academia, SMEs, and industry, and a collaborative approach on this topic is necessary for the following reasons:

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<sup>8</sup> <https://www.force11.org/group/fairgroup/fairprinciples>

<sup>9</sup> <https://www.elixir-europe.org>

<sup>10</sup> [http://europa.eu/rapid/press-release\\_STATEMENT-16-2967\\_en.htm](http://europa.eu/rapid/press-release_STATEMENT-16-2967_en.htm)

<sup>11</sup> [http://ec.europa.eu/research/participants/data/ref/h2020/grants\\_manual/hi/oa\\_pilot/h2020-hi-oa-data-mgt\\_en.pdf](http://ec.europa.eu/research/participants/data/ref/h2020/grants_manual/hi/oa_pilot/h2020-hi-oa-data-mgt_en.pdf)

<sup>12</sup> [http://www.imi.europa.eu/sites/default/files/uploads/documents/New\\_Folder/DataManagementPlanTemplate.docx](http://www.imi.europa.eu/sites/default/files/uploads/documents/New_Folder/DataManagementPlanTemplate.docx)

- SME and academic expertise on implementation of FAIR principles in databases has evolved significantly, and this expertise is highly needed for executing the FAIRification of public and private databases. Good examples of this are the FAIR data creation and conversion projects that are organised by ELIXIR<sup>13</sup> and its member national nodes, in which SMEs and academic groups are essential participants.
- The pharmaceutical industry is well placed to define what data sources are most relevant to drug discovery research, and which ones will give most added value when they can be queried in an interoperable way.
- Joint public-private development of FAIR databases will create a broad acceptance and usability of the data produced in IMI projects, and will allow all scientists in public and private organisations to analyse their internal data in the context of all databases that they have access to.

## Scope

The project will focus on IMI projects that have data that is scientifically valuable and amenable to being made FAIR. It is expected that the databases of more than 20 IMI projects will be made FAIR in this project. All IMI projects will be assessed for the presence of data that requires FAIRification, though it should be noted that IMI2 projects are already required to manage their data according to similar protocols.<sup>14</sup>

Three main issues need to be addressed to allow the scientists in academia and industry to maximally use all databases that they can access:

- Use of standard vocabularies, taxonomies, and ontologies to describe the entries in all databases. The objective is not to generate or modify elaborate vocabularies and ontologies, but to define a consensus for minimum metadata information standards in EFPIA-relevant scientific domains.
- Placing the data in a database that is accessible through a user interface and a computer interface (a documented API - application programming interface), while taking into account personal data protection and confidentiality aspects as well as the intellectual property (IP) conditions for access rights to results that are specific to each IMI project, as laid out in the respective project or consortium agreement.
- The project will identify sustainable solutions for hosting the data to help ensure the long term sustainability of the data by developing a strategy for hosting, curation, maintenance, and integration of the databases. Sustainable storage options for the EFPIA databases will also be evaluated but implementation is the responsibility of EFPIA companies themselves. The actual EFPIA databases will not be shared with or made accessible to the consortium, but the process of their FAIRification, including the minimum information standards and the metadata, will be made publicly available. Thus, by making the EFPIA databases FAIR, specific scientific questions can be more easily addressed, and this in turn will speed up the process of drug discovery and development for the benefit of patients and other stakeholders.

It should be noted that FAIR data is not identical to open access data. The 'Accessible' part of FAIR implies computer and human accessible data, and applies to parties who are authorised to access specific data under the conditions of established IMI project or consortium agreements, falling under the guidelines and rules of IMI and respecting also general data protection legislation as well as confidentiality issues, if applicable. In the same way that many IMI data have restricted access, the same is true for most internal pharmaceutical industry data. As this project will not own the data being made FAIR, full open access to the data cannot be mandated. However this project will strongly encourage making the IMI data as broadly accessible as possible to maximise the public value of the data through prioritising datasets with open public access. Selected projects for FAIRification that need to keep data access restricted for IP or confidentiality reasons will also be strongly encouraged to make metadata available so the broader public can at least identify if data of interest is present. Access to the data itself can then be requested to the data owners.

## Expected key deliverables

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<sup>13</sup> <https://www.elixir-europe.org>

<sup>14</sup> See the IMI2 data management plan template:

[http://www.imi.europa.eu/sites/default/files/uploads/documents/New\\_Folder/DataManagementPlanTemplate.docx](http://www.imi.europa.eu/sites/default/files/uploads/documents/New_Folder/DataManagementPlanTemplate.docx)

- Development of transparent criteria for the selection of data sources within completed and ongoing IMI projects for FAIRification. The results of this analysis and the rankings based on expected scientific value will be shared.
- Development of transparent criteria for the selection of data sources within pharmaceutical industry participants that will enable relevant questions in pharmaceutical research to be addressed when the data is made interoperable with existing public and other internal databases.
- Development of minimum metadata information standards for data from industry and IMI relevant scientific domains.
- FAIR transformation of databases from at least 20 IMI projects to make them compliant with FAIR principles. Access to the databases for permitted scientists and computers will be provided via an API (application programming interface).
- Multiple FAIR databases per EFPIA company available internally within the company.
- Identification and publication of barriers to making IMI project data fully open, and publication of proposed solutions to reduce those barriers.
- Publication and dissemination of guidelines, advice, and detailed processes (workflows and specific technical details) that can be used by other projects, pharmaceutical companies and their partners to make databases compliant with FAIR principles and able to be integrated with their internal data systems and public databases.<sup>15</sup>
- Dissemination of a data catalogue that lists all FAIRified databases handled by the consortium. Metadata on individual databases will provide information on content, access, and use. Metadata detail level depends on the accessibility of the databases themselves. In some cases, access to the actual FAIRified data may require contacting the data owners. This deliverable is optional for selected internal EFPIA databases.<sup>16</sup>

## Expected impact

- Making existing scientific data from completed and ongoing IMI programmes broadly usable and sustainable will allow the scientific community to maximally leverage data from legacy and current IMI projects. Increasing the usability of corporate databases by integration with fast-growing public databases and with other licensed or internal databases will enable future research.
- Strong increase of expertise in the creation, curation, and stewardship of FAIR databases within IT communities.
- Building skills and increasing competitiveness for SMEs in Europe.
- Better understanding of the complexity, structure, and breadth of pharmaceutical data; minimum metadata standards will allow the SME community to make their data, analysis tools and services better connected and aligned to pharma data and facilitate future collaboration. Better understanding on the storage and usage of emerging data types, such as images.
- Interoperability of the databases will allow sophisticated data analysis in all phases of drug discovery, including advanced analytical methods such as computer reasoning and inferencing.
- The project will have a significant impact on the scientific community regarding the broad adaptation of FAIR data stewardship. This in itself will have a long-lasting value-adding impact on effective scientific data usage.

## Potential synergies with existing consortia

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<sup>15</sup> Grant Agreement option 28.2a will apply

<sup>16</sup> Grant Agreement options 29.1a and 29.1b will apply

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

Applicants should consider any relevant related projects from IMI, FP7, H2020 and other relevant initiatives outside the EU.

This FAIRification project will build on the achievements of the **Open PHACTS** ([www.openphacts.org](http://www.openphacts.org)) project, which has shown that making a large number of public databases interoperable creates unique opportunities for answering scientific questions that were very hard or impossible to tackle previously. Moreover, the **eTRIKS** project ([www.etriks.org](http://www.etriks.org)) has focused on making data from multiple IMI cohort study projects available on a common platform.

Since this project focuses on data generated in other IMI projects, there is a very high level of synergy with a broad list of existing consortia, see [www.imi.europa.eu/content/ongoing-projects](http://www.imi.europa.eu/content/ongoing-projects) for details.

## Industry consortium

The industry consortium is composed of the following EFPIA companies:

- Janssen (lead)
- Bayer
- GlaxoSmithKline
- Eli Lilly
- AstraZeneca
- Novartis
- Boehringer Ingelheim

Due to the nature of the participation of industry partners, it is anticipated that some elements of the contributions will be non-EU/H2020 Associated Countries in-kind contributions.<sup>17</sup>

The industry consortium will provide expertise in scientific domains, ontologies and vocabularies, database management as well as contributing to all work packages as indicated below.

## Indicative duration of the action

The indicative duration of the action is 36 months.

## Indicative budget

The indicative EFPIA in-kind contribution is EUR 3 730 000.

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

## Applicant consortium

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

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

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<sup>17</sup> Note: This does not however constitute the justification referred to in Article 4(2) of the IMI 2 JU regulation.

preparation of the full proposal for stage 2. This may require mobilising appropriate expertise, in particular from SMEs, as follows: pharmaceutical research scientific subject matter, scientific data vocabularies and ontologies, the existing database landscape, legal expertise in database access, FAIR data principles, data stewardship, database management, computer programming, data hosting organisations and solutions.

## Suggested architecture of the full proposal

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

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

In the spirit of the partnership, and to reflect how IMI 2 JU call topics are built on identified scientific priorities agreed together with EFPIA beneficiaries/large industrial beneficiaries, these beneficiaries intend to significantly contribute to the programme leadership and project and financial management.

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

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

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

### **Work package 1 – Identification of project data sources for FAIRification and sustainable data hosting platforms.**

*Work package 1.1 – Identification of closed and ongoing IMI projects with data most suitable for FAIRification.*

This WP will prioritise datasets within IMI projects for FAIRification. Criteria that should be taken into account include relevance of the data today and in the future, access to the data (higher priority will be given to open access data), the value of using this data in an integrated way with other databases, and the technical feasibility of FAIRifying the data. For databases that need to maintain restricted access, priority will be given to projects that allow sharing of metadata, allowing a broad audience to identify what data is available. In these cases access to the data itself would still require contacting the data owners. The exact, transparent criteria will need to be defined and communicated. It is recommended that selected partners from the IMI projects and other scientific domain experts be consulted (data owners, domain experts, legal experts, and data interoperability experts).

*Work package 1.2 – Identification of industry data sources at industry partners most suitable for FAIRification*

As above, but for industry databases. Internal EFPIA experts and public scientific domain experts will need to be consulted (data owners, domain experts, legal experts, and data interoperability experts).

- Industry contribution:

Pharmaceutical research scientific domain experts, legal experts, database content experts, data interoperability experts.

- Expected applicant consortium contribution:

Scientific domain experts, legal experts, database content experts, data interoperability experts, FAIRification process experts.

### **Work package 2 – Development of FAIRification process for selected data sources and implementation**

### *Work package 2.1*

For the selected data sources, a detailed analysis of the data and how the data will be used is needed. Decisions on what ontology and vocabulary to use need to be made. Minimum metadata information standards will have to be defined, as much as possible by consensus (see for instance the Minimum Information About a Microarray Experiment (MIAME) standards [2]). The development of a level of standardisation for databases from related domains would be highly desired.

### *Work package 2.2:*

Organisation of BYOD (bring your own data) sessions where all relevant experts and data owners come together to develop the details of FAIRification of selected data sources<sup>18</sup>. Deliverables are detailed FAIRification processes that will allow data in the selected data sources to be transformed into the required format.

- Industry contribution:

Pharmaceutical research scientific domain experts, vocabulary and ontology experts, database content experts, data interoperability experts.

- Expected applicant consortium contribution:

Ontology/vocabulary experts, data interoperability experts, IT experts, and scientific domain experts, FAIRification process experts.

## **Work package 3 – Identification of and implementation of data on sustainable data hosting platforms**

### *Work package 3.1:*

A sustainable database hosting platform/organisation should be identified for every IMI FAIR database. Selection criteria will include domain expertise, connectivity with the scientific community, cost, and long-term stability of the host.

### *Work package 3.2:*

Transfer of the IMI FAIR databases to the identified sustainable hosting platform.

### *Work package 3.3:*

Identification of sustainable solution options for the industry FAIR databases will be identified. Solutions can be internal EFPIA hosting, external (private cloud) based solutions, and combinations of the two.

- Industry contribution:

Database technology experts, IT experts, legal experts.

- Expected applicant consortium contribution:

Database technology experts, IT experts, database hosting experts.

## **Work package 4 – Communication and outreach to FAIR data user community**

To maximise the use and impact of the publically available FAIR databases, academia and SMEs need to be made fully aware of the availability of this data and encouraged to develop analysis tools, incorporate the data into interoperable data systems, and use the data in biomedical data analysis.

- Industry contribution:

Pharmaceutical research scientific domain experts, database content experts.

- Expected applicant consortium contribution:

Scientific domain experts, communication experts.

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<sup>18</sup> <http://www.dtls.nl/fair-data/byod/>

## Work package 5 – Project management, coordination, dissemination and sustainability

This work package will establish effective governance and internal communication procedures to allow for the flow of information within the project. It will also fulfil the administrative tasks associated with management of this project:

*Work package 5.1: Setting-up of project management boards: governing, steering, communication, IP*

*Work package 5.2: Development and implementation of data management plan and correlated activities*

*Work package 5.3: Development and implementation of dissemination programme*

*Work package 5.4: Development and implementation of internal and external communication tools*

*Work package 5.5: Financial management, monitoring and project management support and implementation*

*Work package 5.6: Development of a sustainability plan facilitating continuation beyond the duration of the action*

- Industry contribution:

Project management expertise.

- Expected applicant consortium contribution:

Project management expertise.

## References

- [1] Wilkinson et al. The FAIR Guiding Principles for scientific data management and stewardship Scientific Data 3. 2016. Available at <http://dx.doi.org/10.1038/sdata.2016.18>
- [2] Brazma, A Minimum Information About a Microarray Experiment (MIAME) – Successes, Failures, Challenges, The Scientific World Journal 2009, 9, 420. Available at <http://dx.doi.org/10.1100/tsw.2009.57>

## Glossary

|       |   |
|-------|---|
| ADMET | Absorption, Distribution, Metabolism, Excretion, Toxicity         |
| API   | Application Programming Interface                                 |
| BYOD  | Bring Your Own Data   |
| EFPIA | European Federation of Pharmaceutical Industries and Associations |
| FAIR  | Findable, Accessible, Interoperable, Reusable                     |
| IP    | Intellectual Property   |
| MIAME | A Minimum Information About a Microarray Experiment               |
| SME   | Small and medium-sized enterprises                                |
| WP    | Work package  |

## Topic 3: Development of sensitive and validated clinical endpoints in primary Sjögren's Syndrome (pSS)

### Topic details

|                                 |                                       |
|---------------------------------|---------------------------------------|
| Topic code                      | IMI2-2017-12-03                       |
| Action type                     | Research and Innovation Actions (RIA) |
| Submission & evaluation process | 2 Stages                              |

### Specific challenges to be addressed

**Unmet medical need:** Primary Sjögren's syndrome (pSS) is a common systemic autoimmune disease affecting as a hallmark exocrine glands leading to sicca symptoms of the eyes and the mouth [1]. Systemic and extra-glandular manifestations can often develop as well. A negative impact on quality of life (QOL) is prominent, mainly due to the disabling fatigue as the most important factor in loss of work productivity [2]. Moreover, pSS patients have 9-fold higher risk of developing B cell lymphomas [2]. Only symptomatic treatments are available for commercial use. Given the significant heterogeneity in the clinical presentation and course of patients with pSS, success in therapeutic trials will depend on a better understanding of disease phenotypes to drive patient selection and stratification [3]. There are no treatments for systemic correlates of the disease and there have been no industry sponsored studies that have been able to show a disease modifying effect.

**Challenges for medicines development:** Currently, published data from placebo-controlled and adequately powered clinical trials in pSS are scarce [3]. Although specific novel, validated treatment outcome measures have been developed recently, e.g. European League against Rheumatism (EULAR) Sjögren's syndrome disease activity index (ESSDAI) and EULAR Sjögren's syndrome patient reported index (ESSPRI) [4] [5], their recent use in clinical trials has yielded mixed results [6] [7]. Important features of pSS such as swallowing difficulties, dietary problems, mental health challenges, sexual dysfunction, dental problems (including tooth loss and decay) are not (adequately) captured. Overall, the utility of the currently available measures (including sensitivity to change in Patient Reported Outcomes (PROs) and in various ESSDAI domains) in assessing the efficacy and disease-modifying potential of an investigational drug is still to be determined. Moreover, no objective validated measure or functional marker of disease activity for assessing therapeutic benefits of improvement is currently available. Sensitive and validated endpoints including objective measures/biomarkers of improvement are needed to increase the likelihood of success of drug development in pSS [8].

**Scientific opportunities to address the challenge:** With the growing number of clinical trials testing different treatment modalities, there is an emerging opportunity for comprehensive, integrated analysis of the data generated in the past combined with data analysis of future results from pSS clinical trials. Such a two-tiered approach offers an unprecedented opportunity to identify additional or improved outcome measures that are sensitive, reflect the disease biology, and are most suitable as endpoints for clinical trials of new drug development or may confirm the utility of the currently-available pSS endpoints.

### Need and opportunity for public-private collaborative research

The ability to measure and monitor clinically relevant endpoints in pSS populations is an early need in the field of drug development in pSS prior to the existence of proven disease-modifying therapies. Furthermore, enhancing clinical development and generating payer-relevant evidence of real world impact of therapeutic interventions will be important. This effort is well suited for a public-private consortium.

The identification, development and validation of clinical endpoints in pSS will benefit most from public-private collaboration between pSS clinical sites / centres, academic and industry experts and regulatory authorities. In

addition, the value and impact of the proposed project will be further enhanced by a collaborative partnership with patient advocacy groups, the caregiver community, and privacy and bioethics experts to ensure that the solutions developed can be adopted in the real world.

While outcome measures have been recently proposed and introduced into clinical trials by efforts of the academic community, large, randomised placebo-controlled clinical trials applying and validating these endpoints are lacking. There are regulatory uncertainties with respect to the best registration endpoints for pSS. Involvement of health authorities, patient groups and the pharmaceutical industry can help cover further aspects of and needs for these outcome measures, and generate larger datasets –those can be a challenge if handled by the academia alone. This is why this project may relevantly complement the HarmonicSS H2020 project which shares similar objectives. Therefore it is envisioned that the project funded under this topic will be conducted in close collaboration with this ongoing H2020 project to enhance both efforts in delineating such key scientific questions.

Clinical parameters as well as novel biomarkers (including laboratory and imaging tools) would help better characterise this heterogeneous population, making it possible to link the mechanisms of the disease with clinical manifestations, disease severity and progression. A better patient phenotyping will also be beneficial in the understanding of the clinical endpoints' behaviour and response to therapy.

## Scope

The overarching objective of this proposal is to develop sensitive and validated clinical endpoints for use in future clinical trials of pSS. The goal is to identify and eventually propose a single composite endpoint that could provide evidence of disease-modifying and symptomatic efficacy.

The major scope of this effort will be the identification, development and validation of pSS-related outcome measures including clinical, PRO, laboratory, bio-behavioural activity and imaging parameters (biomarkers), applying the following step-wise approach:

- Data generation and review: Existing data including published epidemiology data, results from interventional and non-interventional studies, and from pSS registries will be reviewed and analysed. As a key contribution to this step, data from prospective, randomised, controlled clinical trials comprising baseline data and longitudinal data from the anonymised control (placebo) groups in Phase 2 (or Phase3 if available) trials from the participating industry partners will be made available.
- Development of new outcome measures based on the review and analysis activities.
- Application and validation by prospectively testing these proposed new pSS outcome measures, as well as existing ones, in (at least one) dedicated, prospective clinical trial. It is anticipated that this future clinical study will be an interventional clinical trial adequately designed to determine if the endpoint model is sensitive to detect treatment differences for use in registration trials.
- Analysis of the outcome of the validation trial and validation of the new endpoint(s). The performance of the new outcome measures or scoring systems will be compared to that of the existing ones, with the purpose to select the most promising outcome measures for future validation.

It is anticipated that the scoring system(s) will require a combination of objective and subjective outcome measures to improve upon existing scoring systems (e.g. selected, core set of ESSDAI domains combined with ESSPRI fatigue or other key PRO items).

If industry sponsored, large e.g. Phase 3 trial(s) are conducted for novel therapies in parallel with (but independently of) the validation trial during the project, the proposed new endpoint(s) may be included as exploratory endpoints in the Phase 3 trials to increase the power and robustness of the validation. The analysis of these trials may, however, occur after this IMI project.

Health technology Assessment (HTA) and payer views and expectations will be integrated in determining the endpoints for regulatory approval and market access requirements. Input from patient groups will also be sought and considered in the analyses to capture relevant and currently underestimated or ignored disease aspects.

While the development of the new sensitive and validated clinical endpoints are primarily intended for use in future clinical trials of adult pSS, feasibility in paediatric SS will also be cautiously evaluated for which further validation would be required as part of the project sustainability plan.

## Expected key deliverables

Expected deliverables will be a set of sensitive and validated pSS outcome measures with potential regulatory and market access consensus.

The project is also expected to provide evidence for the characterization and usefulness of the currently-available outcome measures (e.g. ESSDAI or ESSPRI).

The following deliverables are anticipated from the project:

- (i) Identification and characterisation, (ii) prospective qualification, and (iii) regulatory acceptance of disease scoring tools to assess key features of pSS including disease activity, organ specific improvement and reduced damage under therapy.
- Identification and validation of a biomarker or sets of prognostic markers that could be used as a surrogate endpoint(s) in Phase II trials, and which would be early predictors of long-term organ specific changes or adverse systemic outcomes, for example lymphoma development.
- Development of an endpoint model to determine what the patient- (and payer-) relevant endpoint measures are, independent of where treatments have an effect. The endpoint model will be used to develop a relevant patient reported outcome measure that can be deployed in future clinical trials.
- Development of a suitable methodology to capture semi-continuous bio-behavioural activity data in pSS patients by exploring activity patterns and features which are specific to pSS fatigue symptomatology.
- Patient phenotyping to characterise different subgroups of pSS (being a heterogeneous disease). For this, clinical data as well as established and novel biomarker data will be used that could identify commonalities and differences across subgroups as well as response to therapies.

## Expected impact

This project is expected to enhance the development of new systemic treatments in pSS and to generate evidence for a potential new alternative for consideration by the health authorities. It is expected to result in more efficient clinical trial designs that will minimise the number of subjects required to be able to detect statistically significant and clinically meaningful differences between treatments. The optimal duration of clinical studies required to demonstrate these differences will also be characterised. Furthermore, new relevant outcomes will have potential to optimise pSS patients' management, and large data sets about the natural history of the disease will provide information about the clinical utility of new and innovative diagnostic and treatment interventions in pSS. Engagement of important stakeholders including regulators, payers and patient advocacy groups will help capture all aspects of pSS.

Consequently, improved and innovative therapies are expected to emerge and be available to pSS patients whose health-related quality of life and productivity will eventually improve. Selection of the optimal treatment for the right patient in a clinically and molecularly heterogeneous disease will be made possible in pSS.

Overall, the project goals and expected impact are in line with the predefined IMI2 JU objectives<sup>19</sup>) in the following aspects:

- the success rate in clinical trials for pSS is expected to increase;
- time to reach clinical proof of concept in medicine development is expected to be reduced for pSS;
- new therapies for pSS for which there is a high unmet need would be developed;
- diagnostic and treatment biomarkers would be developed for pSS.

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<sup>19</sup> Article 2 (from (i) through (iv)) 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): [http://eur-lex.europa.eu/legal-content/EN/TXT/?uri=uriserv:OJ.L\\_.2014.169.01.0054.01.ENG](http://eur-lex.europa.eu/legal-content/EN/TXT/?uri=uriserv:OJ.L_.2014.169.01.0054.01.ENG)

## 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 .

Projects and initiatives that may be considered for collaboration by the applicants are:

**HarmonicSS** ([http://cordis.europa.eu/project/rcn/207205\\_en.html](http://cordis.europa.eu/project/rcn/207205_en.html) ), an ongoing Horizon 2020 project. One of the goals of HarmonicSS is the 'data generation and review', that is very similar to the scope of this topic. Thus, collaboration with this project would allow a more rapid progression and a more thorough and extensive data analysis. The synergy of the two initiatives would therefore be of mutual benefit. The prospective validation trial may also be done in collaboration.

**PRECISESADS** ([www.precisesads.eu](http://www.precisesads.eu)), an ongoing IMI project that aims to molecularly reclassify systemic autoimmune diseases. The expected outcomes of this project that will end in Q1 2019 are the generation of clusters of patients defined according to their molecular taxonomy. Such data could provide relevant insights to define patient subpopulations and biomarkers. Therefore collaboration with this project will enhance the scientific impact of this new project as well as of the PRECISESADS project.

**EULAR** ([www.eular.org](http://www.eular.org)) task force responsible for classification guidelines and EULAR sponsored EU pSS registries, e.g. Big Data Sjögren Project (EULAR-SS Task Force International Network) and Systemic Involvement at Diagnosis Evaluated by the ESSDAI in 3314 Patients with Primary Sjögren Syndrome [9].

In addition, collaborations with transatlantic projects and initiatives such as ones by the American College of Rheumatology ([www.rheumatology.org](http://www.rheumatology.org)) and/or by the Sjögren's Syndrome Foundation (<https://www.sjogrens.org>) may also be considered.

## Industry consortium

The industry consortium is composed of the following EFPIA companies:

- Novartis (lead)
- GlaxoSmithKline
- Bristol-Myers Squibb
- Servier
- Eli Lilly

The industry consortium will contribute the following expertise and assets:

- programme management to oversee budgets, timelines, and administration of all uniform processes and procedures including confidentiality agreements, master contracts, budget templates, and institutional review board/ethics committee processes;
- clinical trial design including adaptive design and the use of modelling/simulation and predictive analytics for determination of dose selection, sample size, and other parameters;
- a clinician, clinical pharmacologist, statistician or clinical scientist from each company to act as a company network champion and facilitate company communication and participation with the network;
- clinicians for communication, on-site visits, and other interactions with academic medical centres, investigators, and advisory boards;
- biostatistical / data management expertise to co-lead the central network data coordinating centre, co-maintain the central organisation website, and co-lead the installation of performance monitoring tools and procedures needed at all participating sites;
- regulatory expertise in interacting with the European Medicines Agency (EMA), and other regulatory health authorities;

- clinical operations including feasibility assessment, informed consent forms and assents, recruitment and retention of subjects, clinical trial monitoring, and assessment of trial performance metrics;
- business planning and development; contractual agreements;
- financial planning and implementation;
- legal counselling;
- industry-sponsored clinical trials and the data generated from such clinical trials to test the viability of the network.

## Indicative duration of the action

The indicative duration of the action is 72 months.

## Indicative budget

The indicative EFPIA in-kind contribution is EUR 8 200 000.

Due to the global nature of the participating industry partners it is anticipated that some elements of the contributions will be non-EU/H2020 Associated Countries in-kind contributions<sup>20</sup>.

The financial contribution from IMI2 is a maximum of EUR 8 200 000.

## Applicant consortium

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

- experience and know-how in conducting clinical trials in Sjögren's;
- expertise in the science of drug development including all aspects of clinical pharmacology and study design and conduct;
- access to a large representative pSS population(s);
- expertise in patient reported outcomes, development and validation;
- physicians and other health care providers covering the spectrum of clinical manifestations of pSS (rheumatologists, dental care etc.);
- patient advocacy organisations able to actively contribute to development and standardisation of study procedures and processes, to assess feasibility, clinically meaningful endpoints, and risk-benefit;
- regulatory expertise, including in interacting with EMA or national regulatory authorities;
- expertise in interacting with national payers (e.g. the National Institute for Health and Care Excellence) will be also important to success;
- information technology / data management;
- expertise in legal and clinical compliance aspects (International Conference of Harmonization) and Good Clinical Practice;
- strong project management and communication expertise;

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<sup>20</sup> Note: This does not however constitute the justification referred to in Article 4(2) of the IMI 2 JU regulation.

- office administration and website management.

Efforts should be made to include organisations in as many European countries as possible from the outset as part of the applicant consortium. Small to medium-sized enterprises (SMEs) are also welcome to join this consortium to bring value from a complementary perspective to the academic organisations. Such SMEs may include (but are not limited to) biostatistics and pharmacometrics specialty groups, healthcare research and analysis groups or clinical research organisations (CROs).

## Suggested architecture of the full proposal

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

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

In the spirit of the partnership, and to reflect how IMI 2 JU call topics are built on identified scientific priorities agreed together with EFPIA beneficiaries/large industrial beneficiaries, these beneficiaries intend to significantly contribute to the programme leadership and project and financial management.

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

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

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

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

### Sustainability

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

### Work package 1 – Project management and oversight of IMI project

#### Objectives:

- to establish a framework for collaboration and ensure minimisation of duplicative work and maximisation of sharing across the various work packages as well as to ensure strategic alignment of efforts;
- to define the goals that would benefit from synergistic collaboration with other identified consortia in view and to establish working procedures and a Global Steering Committee to oversee the work progression;
- to coordinate contacts with health authorities between all projects.

Specific activities include:

- project design and charters with clear accountabilities;
- set-up of joint governance structure;
- provide coordination and support to work package teams;

- define work expectations of different work streams, deliverables, dates, activities and review progress regarding adherence to budget, timelines and quality;
- ensure key cross-functional partners are engaged;
- define project interdependencies, stakeholders and risks;
- ensure meetings and interactions between work packages, sub-groups, and consortium governance bodies to coordinate and follow-up on work effort.

**Industry contribution:**

- project management support with project design and day-to-day operation;
- legal expertise, clinical operations, data management, and clinical expertise to support regular review of deliverables regarding quality and operational ability;
- ensuring the implementation and maintenance of ethical requirements, e.g. patient informed consent forms, data anonymisation etc.

**Expected applicant consortium contribution:**

- ensuring the implementation of the coordinating tasks and running the day-to-day operation, such as project tracking and reporting, meetings, internal communication, budget management, etc.;
- ensuring the implementation and maintenance of ethical requirements, e.g. patient informed consent forms, data anonymisation etc.

Co-leads from industry partners and applicants will jointly decide on the consortium governance structure and meetings.

**Work package 2 – Understanding of pSS disease mechanisms and outcomes**

**Objective:** to evaluate currently available evidence as well as prospective clinical trial including clinical as well as biomarker data to set up the scientific consensus necessary to support designing for outcome measures.

**Industry contribution:**

- clinical trial data (prospective clinical trials considered from the start of the project as well as existing data from clinical industry sponsored clinical trials);
- clinical, medical and drug safety expertise;
- expertise in health economics and outcomes research (HEOR), statistical modelling, epidemiology, and translational science;
- medical writing and medical communication expertise;
- biomarkers operational deployment and analysis;
- specific expertise, investigational/diagnostic products, related centralised bioanalytical facilities, operations to deliver results and reports;
- work package co-chairs.

**Expected applicant consortium contribution:**

- expertise in conducting literature reviews and on determining relevant outcomes in collaboration with multiple stakeholders including academic environment, regulatory agencies, HTAs, payers, clinical research organisations, patient organisations and advocacy, and cooperative international groups;
- expertise in developing and validating new patient reported outcome measures;
- data management and statistical modelling expertise;
- expertise in medical research;
- scientific clinical expertise in biomarkers including collection, banking and analysis;
- biomarker assay implementation per protocol;

- elaboration of a strategy to liaise I with HarmonicSS or other existing relevant initiatives.

### **Work package 3 – Generation of novel endpoints, design and execution of clinical trial to validate pSS endpoints**

**Objective:** to plan and conduct dedicated clinical trial(s) including novel as well as conventional endpoints based on data generated in WP2.

#### **Industry contribution:**

- providing expertise in randomised clinical trial initiation and conduct;
- oversight over the study management, and the accomplishment of overall objectives;
- technical and logistic assistance for the meetings of the study committees, etc.

#### **Expected applicant consortium contribution:**

- experience and expertise in conducting clinical trials including clinical and care facilities and adequate trained physicians and specialised personnel to implement the clinical trial protocol;
- state-of-the-art expertise in the field of primary Sjögren’s syndrome; own patient cohort data including long-term clinical and biomarker follow-up data;
- efficient patient recruitment capacity by using territorial network.

### **Work package 4 – Evaluation of validation trial results**

**Objective:** To evaluate clinical trial data, with special attention to the outcome measures in order to draw the necessary clinical and regulatory conclusions regarding their future use in trials (with potential regulatory and market access consensus).

#### **Industry contribution:**

- data analysis;
- planning, hosting and organising workshop(s) with regulators;
- contributing to results discussion via its experts (including biostatisticians);
- technical support (translations, etc.); (co-)authoring of reviews and white paper(s).

#### **Expected applicant consortium contribution:**

- data analysis;
- active contribution to constructive discussion with regulators and payers to achieve scientific and regulatory agreement over the interpretation of study results;
- consolidation of the scientific consensus to support sound operational definitions in terms of use of clinical trial;
- (co-)authoring of reviews and white paper(s);
- Elaboration of a strategy to liaise with HarmonicSS or other existing relevant initiatives .

### **Work package 5 – Biomarkers**

**Objective:** to manage in synergy with other projects the identification of relevant biomarkers able to relevantly separate patient subtypes in relation e.g. to prediction of disease evolution or disease severity.

#### **Industry contribution:**

- clinical and scientific expertise;
- expertise in biomarker analyses and development of biomarker identification tools;
- ensuring the preparation of communication with health authorities including scientific advice preparation;

- work package co-chairs.

**Expected applicant consortium contribution:**

- knowledge of the available or expected outcomes from the other consortia;
- biomarker datasets and analyses from academic groups or consortia;
- expertise in biomarker assays.

**Work package 6 – Engagement with health authorities, payers and patients’ groups**

**Objective:** consensus with health authorities, payers and patients’ groups as key stakeholders regarding the use of new endpoints for regulatory approvals and reimbursement, respectively, in the management of primary Sjögren’s syndrome.

**Industry contribution:**

- expertise in developing proposals and recommendations to gain regulatory acceptance, including writing of briefing books as well as presentations of positions and supporting arguments;
- regulatory and reimbursement expertise;
- editorial support.

**Expected applicant consortium contribution:**

- medical / scientific community: establish link between clinical outcomes and value creation (for individuals and society); insights on future developments in diagnostics and therapeutics;.
- the applicants can help define, interpret and evaluate the value of a new outcome measure; it would be welcome if the applicant consortium can support establishing the link across different perspectives for the new endpoint;
- regulatory, reimbursement, HTA bodies and patient organisations: healthcare delivery needs, gaps and opportunities; insight into policy evolution and potential changes;
- patient advocacy and representative groups: provide point of view of patients in terms of relevant outcomes and current challenges within healthcare delivery.

**Work package 7 – Legal and ethical compliance**

**Objective:** Develop and maintain ethical and legal framework to provide guidance on patient confidentiality and data sharing and ownership throughout the project,

**Industry contribution:**

- expertise in legal, ethical, compliance, communication.

**Expected applicant consortium contribution:**

- expertise in legal, ethical, compliance; patient advocacy, and technical writing support.

**Work Package 8 – Communication**

**Objective:** to define and execute the overall communication strategy for the project including internal as well as external publications, dissemination of results, web postings, repository of key documents, and quality assessment of documents.

**Industry contribution:**

- medical communication;
- media interactions;
- medical writing;
- contact with healthcare provider professional organisations and their communication groups;

- contact with patient organisations.

**Expected applicant consortium contribution:**

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

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## Glossary

|        |   |
|--------|---|
| CRO    | Clinical Research Organisation                                    |
| EFPIA  | European Federation of Pharmaceutical Industries and Associations |
| EMA    | European Medicines Agency   |
| ESSDAI | EULAR Sjögren's syndrome disease activity index                   |

|        |   |
|--------|---|
| ESSPRI | EULAR Sjogren's Syndrome Patient Reported Index       |
| EULAR  | European League against Rheumatism                    |
| HEOR   | Health Economics and Outcomes Research                |
| HTA    | Health Technology Assessment                          |
| NICE   | The National Institute for Health and Care Excellence |
| PRO    | Patient reported outcome                              |
| pSS    | primary Sjögren`s syndrome                            |
| RCT    | Randomized controlled trial                           |
| QOL    | quality of life                                       |
| WP     | Work package  |

## Topic 4: European Health Data Network (EHDN)

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

### Introduction to the BD4BO programme and problem statement

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

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

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

The following topic (the European Health Data Network) sits within the BD4BO programme.

### BD4BO Programme structure

The BD4BO programme is composed of several projects which will be key enablers for the transition of healthcare systems towards more outcomes transparency. These include an over-arching coordination structure (through a Coordination and Support Action (CSA)) implemented by the **DO-> IT** consortium (<http://www.bd4bo.eu/>), several disease/therapeutic area (TA) topics focusing on a specific disease, population, therapeutic area or technology: **HARMONY** (<http://www.imi.europa.eu/content/harmony>), **ROADMAP** (<http://roadmap-alzheimer.org/>), and **BigData@Heart** and this **European Health Data Network (EHDN)** topic. Future topics may be added to the programme as indicated below.

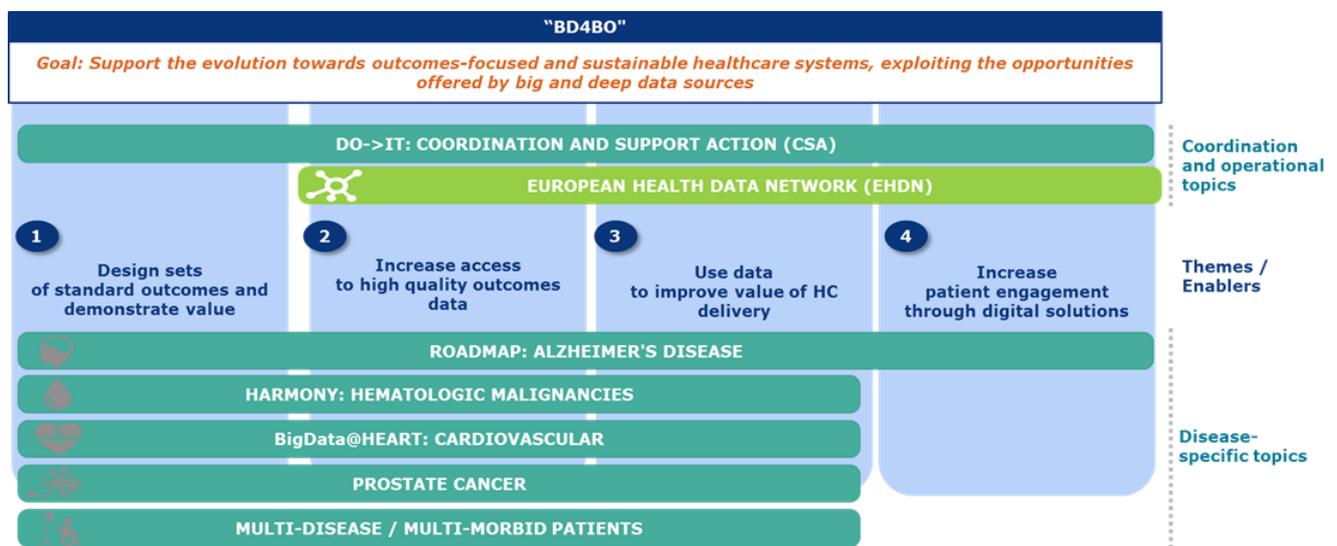


Figure 1: Programme structure, themes / enablers and CSA

The success of the overall BD4BO programme will rely on a coordinated approach across projects to ensure strategic alignment and consistency and to define new business and health funding models (including incentive models) that will allow for healthcare systems transformation. In addition, integration of areas of expertise which are common to most projects (such as legal, ethics, data privacy, sustainability or collaboration with payers/HTAs) will yield higher quality results, consistency and increased efficiency by avoiding duplication of work.

## Expected impact of the BD4BO programme

The expected result of the overall BD4BO programme will be a network of different health data sources to support the growing requirement for evidence to support expanding value-based and outcomes-focused healthcare delivery in Europe. Technological development will accompany the network based on prior programmes to support the relationship between data users and data providers, but a key driver for success will be active collaboration within the network (see below). The programme will also enable the evolution and management of R&D portfolios and the prioritisation of research methodologies in line with outcomes focused healthcare services in Europe. It must be recognised that the growing use of multi-centre observational studies, with their increasing complexity, requires organisation and a broader Europe-wide strategy.

## Collaboration agreements

It is the absolute objective of EHDN project to fully collaborate with (and support) other projects in the IMI2 BD4BO programme, therefore, the grant awarded for the EHDN will be complementary to the Grant Agreements already awarded under the BD4BO programme<sup>21</sup> and also to future BD4BO Grant Agreements. The respective options of Article 2, Article 31.6 and Article 41.4 of the [IMI2 Model Grant Agreement](#) will be applied.

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<sup>21</sup> The ROADMAP, HARMONY, DO->IT, BigData@Heart projects

## European Health Data Network (EHDN)

### Topic details

|                                 |                                       |
|---------------------------------|---------------------------------------|
| Topic code                      | IMI2-2017-12-04                       |
| Action type                     | Research and Innovation Actions (RIA) |
| Submission & evaluation process | 2 Stages                              |

### Specific challenges to be addressed

The central theme for the BD4BO programme is the prospect of outcomes-driven, sustainable healthcare systems. At the same time, it is recognised that reuse and analysis of healthcare data holds the key to the transition to these systems, under the maxim that, ‘you cannot change, what you do not measure’.

The EHDN initiative seeks to address this critical challenge by converting a large number of relevant datasets across Europe to a common format and standard so that they can be more efficiently used to their full potential within a federated network to achieve the objectives as mentioned above, while respecting patient privacy, local data provenance, governance and applicable regulations. Achieving this is pivotal and implies addressing the following challenges:

1. **Technical:** Healthcare data are very fragmented. Even data within one healthcare centre are typically spread across different repositories. Across entities, different standards are used to code diagnosis, lab results, drugs or procedures. In most healthcare systems, a majority of the core clinical data is buried in unstructured (text) notes, making data analysis even more challenging. The EHDN will provide a harmonised model to address the structural heterogeneity and the use of different coding standards, expediting efficiencies in the research process
2. **Socio-ethical:** Besides the technical heterogeneity amongst data sources, a similar diversity in governance processes to perform studies using data collected by healthcare providers, can be seen. The project will specifically seek to provide a pragmatic governance framework that can be used to accommodate cross-centre studies, within the confines of societal parameters that manage data use in the EU.

It must be stressed that the EHDN aims at a federated network approach. There is no intention of creating a centralised repository of patient level data. The data will remain local, on the premises of the data owner / custodian, and under their clear control and governance. However, by implementing a harmonised, standardised version of their data set, research and reuse of data can be executed much more efficiently. In essence, the “analysis is brought to the data” and only aggregated results are returned, therefore, no patient data leaves the premises. Reuse of data in a full study can also only happen after approval of local governance bodies. This federated network approach has been used successfully in other initiatives such as the EMIF project (<http://www.emif.eu>) or in the OHDSI community ([www.ohdsi.org/](http://www.ohdsi.org/)).

To obtain concrete results, it is important to note that the EHDN project's ambition will need to be sharply focused on providing pragmatic solutions thereby reusing results and solutions from prior IMI and other projects as much as possible. To achieve this focus EHDN will focus on facilitating three “Application Domains”.

**Application domain 1: Research:** This initiative will shape and lead a community of interested data sources and data scientist and engage with broader (global) community (e.g the OHDSI community). Topics can range from e.g. discovery, pharmacovigilance, ongoing monitoring of effectiveness / safety of compounds, outcomes research, identification of variability in care delivery, disease background related info or epidemiology of disease.

**Application domain 2: Health services efficiency:** This application domain will focus on how best to deliver real world data that is relevant to evaluating real world outcomes for therapeutic interventions. Activities could cover e.g. outcomes based contracting, optimizing patient pathways, quality improvement of health services

(dashboard driven / financial incentives / driving changes to health care systems). Regulatory applications will also be covered within this domain. Recent experience in projects such as GetReal ( <https://www.imi-getreal.eu/> ) and EMIF ( <http://www.emif.eu/> ) point to the growing interest and support for real world data (RWD) by the European Medicines Agency (EMA) and the Health Technology Assessment (HTA) bodies.

**Application domain 3: Individual patient care:** This domain is focused on the application of the federated data network to support patient level decision-making in clinical care. Aspects to cover could be e.g. providing an interoperable data standard to facilitate and stimulate a market in digital health solutions, expert systems, predictive algorithms, etc., integration with mobile health.

## Need and opportunity for public-private collaborative research

To achieve the objectives mentioned, health care systems are challenged with

- 1) lack of definition and alignment on outcomes that are relevant to all stakeholders and patients;
- 2) policy makers having limited benchmark data to evaluate the risk/benefit ratio and value;
- 3) personalised medicine allowing for more focused treatment options thus increasing the difficulty of demonstrating the risk/benefit in the real world, driven by rapid technological and biological innovation;
- 4) clinicians having to make treatment choices based on short-term, surrogate and often not comparable data;
- 5) patients not having access to the right treatment at the right time;
- 6) payers having to make reimbursement decisions on life prolonging options with limited data and finite budgets.

Collaboration among healthcare systems and relevant stakeholders is necessary to capture and aggregate data, analyse it and extract relevant insights. Engagement of payers, providers and regulators will ensure these outcomes and clinical endpoints are measured and used in healthcare systems (e.g. for reimbursement or assessments). A critical element in achieving a more outcomes based healthcare system is the adoption of well-suited standards. EHDN will apply two important standards, the Observational Medical Outcomes Partnership Common Data Model (OMOP CDM) and the International Consortium for Health Outcomes Measurement (ICHOM) standards<sup>22</sup>.

The OMOP CDM is the result of a public-private collaboration, currently under the umbrella of the Observational Health Data Sciences and Informatics project (OHDSI, pronounced 'Odyssey', <https://ohdsi.org/>) project [1]. OHDSI is an international collaboration of more than 120 researchers (public and private) from 12 countries that contributes expertise at all levels, from infrastructure to clinical research, ensuring that the developed infrastructure meets clinical research needs. OHDSI's Common Data Model [2], originally developed as part of the Observational Medical Outcomes Partnership (OMOP) [3], is a deep information model that specifies how to encode and store clinical data at a fine-grained level, ensuring that the same query can be applied consistently to databases around the world. OHDSI has chosen data standards that dovetail with those of the United States government and the international community, and it also supplies tools and mapping tables for converting data from other standards. At the last count, 52 databases, with a total of 682 million patient records, had been created using the Common Data Model [1]; this number may include duplicate records for databases with overlapping populations. As such the OHDSI suite of standards and tools is rapidly becoming a de facto international standard for working with real world data.

The ICHOM standards<sup>22</sup> identify specific outcomes metrics for a number of diseases. Where possible, the BD4BO programme is reusing the metrics. For some disease areas, no such metrics have been proposed and hence, the first step for a number of the BD4BO projects is to define relevant disease specific outcomes metrics. Whereas the OMOP CDM provides a common model (and controlled vocabulary) for data, ICHOM

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<sup>22</sup> <http://www.ichom.org/>

standards provide metrics. Both are complementary and many of the ICHOM metrics (or other outcomes metrics) can be informed by the OMOP CDM. In cases where data elements are lacking (e.g. patient reported outcomes) novel approaches can be developed to capture data.

Besides standardisation and technical aspects, there is also a paramount need for further shaping a trusted environment for data sharing in Europe. To move the data sharing agenda forward, creating benefits for all stakeholders in the eco-system, several non-technical dimensions are of critical importance. These are, for example legislative aspects, data security and privacy or data quality improvement.

## Scope

The EHDN project is a critical enabling component of the IMI BD4BO programme and is responsible for supporting the research aspects of the other BD4BO projects in delivering the vision of large scale medical outcomes research. Therefore, the *EHDN should focus on being an enabling project* with the aim of developing a data network to allow other researchers to ‘find’ and safely ‘reuse’ data.

The European landscape for the secondary use of medical data is fragmented across different nations and providers. The resulting paucity of common standards makes outcomes based research difficult to perform in Europe. Several initiatives such as the FP7 projects EU-ADR ([www.euadr-project.org/](http://www.euadr-project.org/)) and TRANSFORM ([cordis.europa.eu/project/rcn/93775\\_en.html](http://cordis.europa.eu/project/rcn/93775_en.html)), the IMI projects EH4CR (<http://www.ehr4cr.eu/>) and EMIF (<http://www.emif.eu/>) and the US-based OHDSI project (<https://ohdsi.org/>) have demonstrated methodologies that can be used to perform such research.

*The first goal of the EHDN is to ‘reduce to practice’ the approaches pioneered in these earlier research projects and develop a standard methodology.*

The European ‘market’ for health outcomes research is limited to commercial providers and a limited number of academic health science centres with funds available to develop secondary use platforms for research. This both biases the research that can be undertaken as only data collected by these providers can be used and in some cases, creates a monopolistic environment that prevents health outcomes research from gaining more traction. It would likely be true to say that not one data source provides the whole truth in the real world, and as such collaboration is critical to supporting quality evidence.

*The second goal of EHDN is to help mature both the supply side and the demand side of this ‘health data eco-system’ in compliance with robust privacy and ethics governance.*

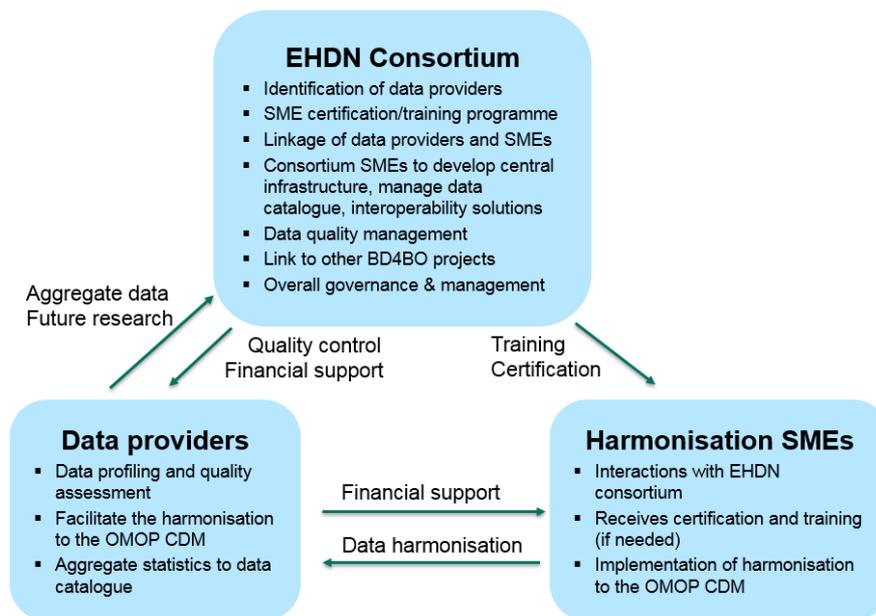
The adoption of common enabling technology across all nodes in the EHDN will stimulate a new generation of (digital) providers to develop and deliver services in data transformation, data semantics and analytical capabilities. This will be achieved through the implementation of a certification process for SMEs and other providers. This has the halo effect of creating a second generation of practitioners and services who can further reap the benefits of health outcomes research, ensuring a common stewardship to the use of health data.

*The third goal of EHDN is to stimulate development of new and augmented health services through available and expanded technologies, in the interest of health outcomes.*

The EHDN will implement a federated data network, the implementation of which is based on the OMOP Common Data Model and will utilise existing solutions and methodology approaches as such, no further development or research is needed: the use of the OHDSI toolsets and EMIF contributions have already validated this approach and method. By doing this, EHDN will fully adhere to the FAIR principles of data networks. Via technical and governance solutions, data will be made Findable, Accessible, Interoperable and Reusable. For more information on the FAIR principles, see [http://ec.europa.eu/research/participants/data/ref/h2020/grants\\_manual/hi/oa\\_pilot/h2020-hi-oa-data-mgt\\_en.pdf](http://ec.europa.eu/research/participants/data/ref/h2020/grants_manual/hi/oa_pilot/h2020-hi-oa-data-mgt_en.pdf)

Through the EHDN, a business ecosystem will be stimulated by matching data consumers with data providers (via a data set catalogue) under a standardised governance process, with an upfront agreed and transparent business model. This ecosystem will facilitate the provision of additional services through a platform being built on open source components with public standards. Small and Medium-sized Enterprises (SMEs), both within and outside the consortium, can develop and offer commercial services to data providers or consumers (see section on Applicant Consortium for the distinction of SMEs in- and outside of the consortium).

The process is summarised as follows:



## Collaboration agreements

The grant awarded for the EHDN will be complementary to the Grant Agreements already awarded under the BD4BO programme as described in the introduction, above. Therefore, the respective options of Article 2, Article 31.6 and Article 41.4 of the [IMI2 Model Grant Agreement](#) will be applied.

## Expected key deliverables

The EHDN project executive will administer an open, transparent call process where third party data providers (e.g. hospitals, regional data sets, disease registries) that can provide data for the selected priorities (disease areas, type of data, data quality requirements etc) will be identified. These third party data providers can apply for financial support to have the OMOP common data model constructed and deployed within their firewall, and also ensure their staff receive the necessary training.

It is envisaged that the technical IT services to perform the data harmonisation will be provided by a number of EU based SMEs. These SMEs will normally not be part of the applicant consortium but will be identified once the project is underway in through an open, transparent, objective process.

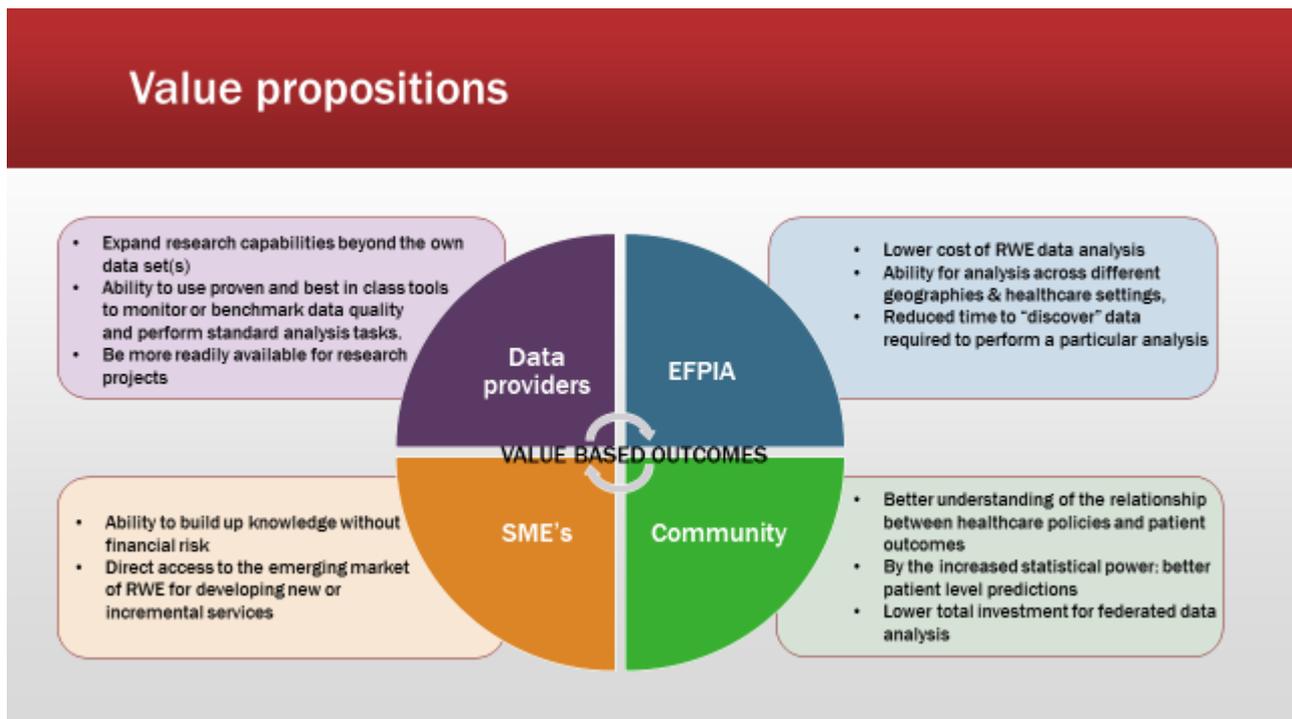
By linking the third party data providers to suitable data harmonisation SMEs, the ultimate outcome of the project will be a set of harmonised data sets that will remain within the firewalls of the respective data owners' organisations. The data sets will be compliant with the EHDN suite of tools for reusing data. This will enable the data providers to carry out outcomes focused research projects through the BD4BO programme and elsewhere.

Overall the EHDN project will support:

- The implementation of the OMOP common data model within data provider firewalls to deliver an operational network of data sets covering up to 20% of the EU population or approximately 100 million people (estimated to be around 200 data sets) in support of existing and new BD4BO or other health outcome related initiatives. Key performance indicators will be developed to monitor the progress in terms of the absolute number of data sources covered, diversity across different disease areas, geographical coverage and breadth of coverage across different types of data sets.
- The validation of harmonised data sets as compliant with the EHDN suite of tools for accessing data thereby providing the opportunity for the data owners to participate in BD4BO and other research projects. This will imply the existence of an operational data quality management framework for real world data. This data quality management framework (definition of criteria, applicable procedures, technical implementation) will be operational by the end of year 1.

- European SMEs experienced in building innovative services for data providers and/or consumers. This will be further facilitated by organising hackathons and targeted competitions.
- Certification of the IT technical services of EU SMEs where the technical services relate to the preparation, execution, testing, deployment and documentation of the transformation from source to harmonised data sets.
- EHDN project governance with a focused approach to manage the recruitment and approval of third party datasets, to oversee the data harmonisation and to interact with other BD4BO projects.

## Expected impact



The EHDN project aims to improve Europe's (technical) capabilities to undertake systematic health outcomes research at an unprecedented scale across the entire region. It will achieve this by taking advantage of, and implementing the validated and robust OHDSI collaboration tools and common data model; supporting data providers with the transition to the common data model for easier reuse of data, and consistency across data platforms; ensuring full compliance and governance is in place to protect integrity of the data; and offering the BD4BO projects a platform for successful and compliant data reuse and analysis.

The aim of the EHDN is to not just create a network of data providers that are making data available, but also to facilitate further research that will allow these data providers to gain additional value while working towards a value based outcome mandate. This additional research will be carried out through collaboration with other initiatives such as the existing and future IMI2 BD4BO projects.

By implementing a common data model, the data providers should find it easier to also participate in other future research studies.

For the community at large, the research enabled through this platform will contribute to the BD4BO objective of an outcomes-driven and sustainable healthcare. This project should therefore also result in an increased use of outcomes based models in actual healthcare delivery and regulatory/HTA decision making.

## Potential synergies with existing consortia

Applicants should consider incorporating technologies, experience and insights from previous/ongoing projects including:

- **EMIF** (<http://www.emif.eu/>)
- **EHR4CR** (<http://www.ehr4cr.eu/>)
- **GetReal** (<https://www.imi-getreal.eu/>)
- **ENABLE** (<http://nd4bb-enable.eu/>)
- **eTRIKS** (<https://www.etriks.org/>)
- **OHDSI** (<https://ohdsi.org/>)

## Industry consortium

The industry consortium is composed of the following EFPIA companies:

- Janssen Pharmaceutica (lead)
- Pfizer
- AbbVie
- Servier
- Sanofi
- Bayer
- Eli Lilly
- Ipsen
- AstraZeneca
- Novartis
- UCB

The industry in-kind contributions will be dedicated to project governance, communication, and general and project management.

## Indicative duration of the action

The indicative duration of the action is 60 months.

Following an initial two-year period, a project review will be held to ensure the project is on track to deliver the expected impacts within the five year period.

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 could include, but is not limited to, additional extension of the data network and further development and refinement of tools. The decision for this will be based on progress of the project and decision envisioned to be made in the sustainability work stream of the project.

## Indicative budget

The indicative EFPIA contribution is EUR 14 127 000<sup>23</sup>.

The financial contribution from IMI2 JU is a maximum of EUR 14 127 000.

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<sup>23</sup> This figure includes both in-kind and financial contributions.

The overall objective of the EHDN project is to significantly extend the volume of ‘readily available’ data sets for outcomes research through the harmonisation of data on approximately 100 million people. These data harmonisation activities are estimated to cost approximately EUR 17 million and are expected to be carried out by third parties receiving financial support (see below).<sup>24</sup> This financial support will include a EUR 10 million financial contribution from the above indicative EFPIA contribution and the remainder from IMI2 JU funding. Therefore, at stage 1, applicant consortia should allocate half of the IMI2 JU contribution to the data harmonisation effort, to be primarily implemented as direct costs of providing financial support to third parties.

## Applicant consortium

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

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

As described above, the prime focus of the EHDN project is on implementation of established data standards to facilitate outcomes research in Europe. The ideal consortium therefore will contain a limited number of partners with proven expertise in the domain of real world data management and analysis, focusing on very specific goals. Data sources will not be part of the consortium, but will be financially supported as third parties, mainly due to their diversity and significant expected number. This model has been successfully used in e.g. EMIF-AD and in EPAD.

In their short proposal, the applicant consortium is expected to have a strategy on the translation of the relevant project outputs into regulatory, clinical and healthcare practice. A plan for interactions with regulatory agencies / health technology assessment bodies with relevant milestones should be included, and appropriate resources should be allocated to ensure this, e.g. qualification advice on the proposed methods for novel methodologies for drug development, qualification opinion. An outline plan for aspects related to sustainability, facilitating continuation beyond the duration of the action should also be proposed.

While the focus is on implementation, the EHDN project also wants to illustrate the value of the approach via a limited number of research ‘use cases’ that will demonstrate the societal value of the network. The applicant consortium is therefore also expected to have experience in the practical use of a federated network of data sets. The applicant consortium should also bring innovative approaches, for example in work package 3.

The applicant consortium should mobilise the following expertise:

- A limited number (ideally up to three) leading public partners in this domain:
  - They will serve as evangelists and key stakeholders. Ideally, these centres represent the various European regions. The ideal consortium will have a broad geographic representation throughout Europe. These centres will have practical expertise in working with real world data and the mentioned data standards e.g. OMOP CDM, ICHOM. As the EHDN project will also provide support for the OHDSI community in Europe, it is expected that the leading public partners will have active on-going or previous collaborations within this community. This will serve as an important additional “validation” of the approach of working with a network of harmonised data sets.
  - The centres are expected to contribute specific domain knowledge on applicable standards in medical coding and terminologies in the relevant disease areas. Decisions need to be made on how to implement the OMOP CDM in the identified disease areas and possible extensions to the applicable standards will need to be agreed upon.
  - An important element in the selection of relevant data sets is the data quality evaluation (considering the research question envisioned). Expertise in the deployment of data quality evaluation is necessary. Ideally, the EHDN project will develop a ‘data quality benchmark’ approach, allowing for a standardised and routine way of measuring data quality. We will leverage where possible, e.g. some work going on in the Institute for Innovation through Health Data (iHD)

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<sup>24</sup> Implemented through article 15.1 of the IMI2 model grant agreement. A small portion may also be awarded as prizes according to article 15.2 of the IMI2 model grant agreement. The open, transparent, objective process for awarding these prizes must be elaborated in the full proposal.

and other EU initiatives such as SPOR and IDMP<sup>25</sup>. As described above, EHDN will adhere to the FAIR principles.

- Having led similar initiatives on a local, regional or disease level across a significant set of data sources where a substantial harmonisation effort was required, is recommended.
- A limited number (ideally up to three) technical SMEs with the following capabilities:
  - Technical skills necessary to maintain and further develop the key infrastructural components, including the data catalogue solution, the central platform components and quality assessment solutions. Having developed or supported one or more of these applications in a public private partnership is required.
  - The technical knowledge to support extensions of the vocabulary mappings. Experience in different healthcare coding systems, master data management systems and/or terminology services is expected. This would include either existing commercial product offerings or services in this area by the respective SME or previous delivery of such solutions in other public private partnerships.
  - Technical capability to develop and improve interoperability solutions. EHDN may consider the development of 'inflow or outflows' from several common data formats instead of doing this for every data source independently. As an example, one could consider an outflow to i2b2 / TranSMART or to the backend of the hospitals data warehouse (e.g. i2b2) of institutions participating in the Champion Programme (follow-up from IMI-EHR4CR). Requests for interoperability with CDISC (SDTM, BRIDG) could also be expected. Experience in developing interoperability solutions and in one or more of the mentioned standards is required.

Please note that SMEs charged solely with the actual data harmonisation tasks are NOT expected to be part of the applicant consortium. Such activities are expected to be covered by the financial support to third parties described below.

- Given the challenges and potential risks with reuse of healthcare data, it is crucial to have deep experience in data governance aspects, as well as the privacy and ethical aspects of secondary data use. Legal expertise in data protection law is essential.
- The involvement of regulatory and HTA organisations is recommended:
  - Given the important regulatory and/or HTA context of the BD4BO projects, a strong link to EMA and/or an HTA body is a requirement. Ideally as part of the consortium, otherwise, these partners should be engaged in an advisory role. Experience from IMI projects like GetReal should be leveraged.
- At least one partner should be a pan-European patient advocacy group, in order to build trust and engage patients proactively in the definition of health outcomes driven use case selection. Participation of patient representatives would be very useful in e.g. WP 2 and 3.

It would be advantageous to include:

- Expertise in development of distributed statistical analysis or machine learning methods. A limitation of the current federated network is that a particular data analysis is performed at a single data set. A 'focused engagement' could be considered that explores the feasibility for executing data analysis methods across an entire set of data sources while preserving the applicable constraints of the federated network.
- Ability to render structured content harmonised to the applicable data standards from unstructured text (text mining).

### **Financial support to third parties<sup>26</sup> for the provision & harmonisation of data sets**

The EHDN project requires the recruitment, mapping and OMOP data model implementation of a EU-wide operational network of data sets. The providers of this data will mostly be third parties external to consortium

<sup>25</sup> See [http://www.ema.europa.eu/ema/index.jsp?curl=pages/regulation/general/general\\_content\\_000645.jsp](http://www.ema.europa.eu/ema/index.jsp?curl=pages/regulation/general/general_content_000645.jsp)

<sup>26</sup> In accordance with Annex K of the Horizon 2020 Work Programme and the article 15 of the IMI2 Model Grant Agreement.

that would be recruited during the project lifetime through open call(s) and would agree that their data is harmonised to the common data model. This will be normally done by qualified SME(s) hired by the same data-providers. Becoming a third party would allow the respective organisation to participate in the network of data sources and as such engage in different research initiatives but also requires the data source to:

- provide aggregate statistics on their data for inclusion in a data catalogue (e.g. number of patients per year of birth, gender distribution, distribution of person years covered, outcomes measured etc);
- agree to the publication of this metadata in a data set catalogue;
- have a documented governance process for engaging and / or reviewing research questions from participants in the consortium (including other data providers).

In order to cover the related costs for the above mentioned activities (i.e. hiring SMEs with the technical capability to implement the OMOP CDM), the EHDN consortium will provide financial support to the third parties of up to EUR 100 000 per third party<sup>27</sup>, selected under an open call launched by the selected consortium in the form of reimbursement of actual costs.

Therefore, in their full proposal, at stage 2, the consortium must clearly detail the objectives and the results to be obtained and include at least the following elements:

- a fixed and exhaustive list of the different types of activities for which a third party may receive financial support;
- the definition of the categories of legal entities which may receive financial support;
- the criteria for awarding financial support;
- the criteria for calculating the exact amount of the financial support;
- the maximum amount to be granted to each third party and the criteria for determining it.

## Suggested architecture of the full proposal

The applicants 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 members of the industry consortium.

In the spirit of the partnership, and to reflect how IMI 2 JU call topics are built on identified scientific priorities agreed together with EFPIA beneficiaries/large industrial beneficiaries, these beneficiaries intend to significantly contribute to the programme leadership and project and financial management.

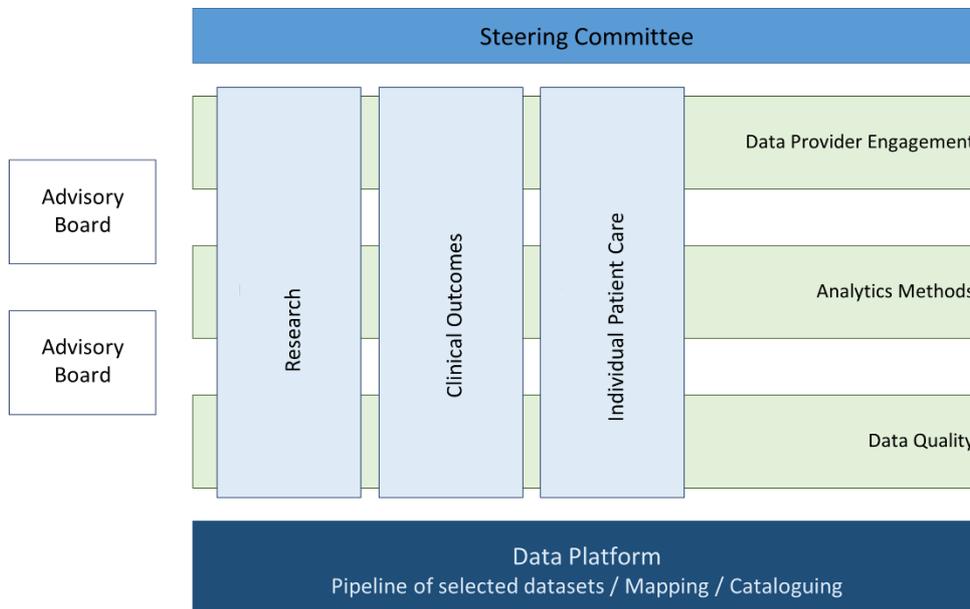
The final architecture of the full proposal will be defined by the participants in compliance with the IMI 2 JU rules and with a view to the achievement of the project objectives. The allocation of a leading role within the consortium will be discussed in the course of the drafting of the full proposal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

All beneficiaries are encouraged to discuss the project architecture and governance and the weighting of responsibilities and priorities therein. To ensure the project stays focused on the end users, the driving force of the project should come from the identified 'application domains'. These application domains (WP1 through 3) share a set of cross cutting concerns (e.g. data provider engagement, quality management, analysis methods) while the actual implementation of these concerns might be different. It is expected that the consortium will set up the necessary mechanisms to provide the coordination across these shared 'concerns'. A separate work

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<sup>27</sup> The costs of data harmonisation can vary greatly between different data sources. The harmonisation of existing, highly structured and integrated research databases may be relatively cheap, while harmonising unstructured or semi-structured data will be a resource-intensive effort. Therefore, the cost to perform such a conversion are estimated to vary between EUR 30 000 and EUR 100 000 per data source.

package will deal with the implementation of the technical platform and with the management of the ‘data harmonisation’ pipeline. Overall governance in the project will be done by a Steering Committee. Advisory boards could be anticipated for, e.g. data governance, analytics methods or data quality. The exact composition of the project will be subject of further discussion once the full consortium has been established.



The applicant consortium should submit a short proposal which includes their suggestions for creating a full proposal architecture.

### Work packages 1 to 3 – application domains

Each application domain focuses on a specific domain but shares common ‘process’ elements. These common elements include:

- Data provider engagement: Attracting relevant data sets through an open call for recipients of financial support based on needs of the other BD4BO projects and other criteria to be developed in the full proposal<sup>28</sup>. Contact and coordination with IMI-2 (BD4BO) and other projects to understand their data needs and /or to engage data sets in the respective BD4BO projects
- Data quality evaluation
- Requirements for the analytical methods: while it is not the objective of EHDN to perform the analysis (this should rather be performed in the BD4BO projects that are being supported) the EHDN will define the requirements that the analytical methods should adhere to and will provide input in how analytical methods can be shared / distributed across the network
- Identification and engagement with the relevant internal and external stakeholders (Regulators, HTA agencies, ...)

The specifics for WP1 to 3 are as follows:

#### Work package 1 – Application domain ‘research’.

Work package 1 focuses on setting up a network of organisations who, on the basis of a shared data model can execute research questions and facilitate research studies at an unprecedented scale, WP 1 will lead and shape that community, engage with the relevant data sources and the broader (global) community (the above mentioned OHDSI community). The analysis methods and the method to share or deploy them across the community is one of the key deliverables from this work package. A specific issue this WP will address deals

<sup>28</sup> In compliance with article 15.1 of the IMI2 Grant Agreement.

with the question of potential ‘information loss’ between source data and harmonised data. To develop reliable, acceptable ‘evidence’, it is necessary to show consistency from source data to harmonised data and to illustrate analytical rigour in the generation of evidence. This work package will seek input and definition from regulatory and HTA agencies as to what constitutes valid ‘real world evidence’ as it relates to applicable data input as well as the required analytical methods and tools which could be deployed against the common data model (pharmacovigilance, comparative effectiveness etc). Essentially this work package will develop the technological framework to enable connectivity with real world data from hospital and other sources, enabling health research (within e.g. IMI BD4BO), whilst working with key stakeholders, such as regulators to evaluate the methodological, analytical and data outputs for relevant quality requirements. While the main focus is on development of analytical methods, it may be efficient to work on a few ‘exemplar’ cases to develop and proof the method.

### **Work package 2 – Application domain ‘health care system efficiency – outcomes based models’**

The central theme to work package 2 will be the concrete implementation of transitioning to an outcomes driven healthcare system. This includes a specific collaboration with disease specific projects on applicable outcome measures, data source engagement to provide the appropriate outcome measures, translating the outcomes metrics to the common data model, defining quality criteria for applicable data sets and input from payers and providers on the barriers and tools required to implement outcomes based models. WP2 will also consider what other requirements might apply to outcomes based contracts and analytical tools which could facilitate benchmarking and contracting activities within health systems aimed at driving quality and efficiency. In summary, this work package will focus on how best to deliver real world data that is relevant to evaluating real world outcomes for therapeutic interventions, incorporating the required data connectivity, methodology, analytics and outputs that meet the needs of, and in conjunction with, healthcare payers.

### **Work package 3 – Application domain ‘individual patient care’**

WP3 is focused on the application of the federated data network to support patient level decision-making in clinical care. As such, it will integrate patient-generated data (e.g. clinical sensors, wearables, patient reported outcomes and others), as well as developing federated analytics to support clinical decision-making (e.g. , patient risk identification, patient disease prediction, advanced bioinformatic diagnostics, etc.) in designated use cases for evaluation. This work will necessitate further developing technical aspects (e.g. integration of digital health input, federated analytics, machine learning), as well as critical governance requirements with guidelines, policy and law. Given this is an area of fast and exciting technical developments, we are looking forward to public partners which have access to novel patient engagement technologies and/or novel ways of running (federated) analytics. As for work package 1, while most of the attention will be on the development of methods, it may be efficient to work on a few exemplar cases.

### **Work package 4 – Technical implementation**

This work package will focus on:

- set-up, maintenance and gradual improvements to the data catalogue;
- data harmonisation and standardisation of selected data sets;
- coordination of work with the use cases.

The EHDN will maximally leverage from ongoing or prior projects in this area such as EMIF, EPAD ([epad.org](http://epad.org)), EHR4CR. Part of the solution should be an integration of the full process, going from ‘finding relevant data sets’ to ‘reusing data sets’ under specific conditions. Important elements in the architecture are therefore also implementation of IT security, authentication and authorisation.

### **Work package 5 – Governance and adoption**

This work package will focus on:

- shaping of governance;
- ensuring optimal adoption among each of the stakeholders, given legal/data privacy context.

Clearly governance is a crucial element in safe reuse of patient level data. Where possible, we will leverage from other projects (IMI and other). The BD4BO coordinating project, DO->IT will be a prime source of input, but there are other projects from which solutions, tools and policy documents / approaches can be leveraged.

In the context of EMIF, an extensive document was developed describing the overall process of data cataloguing, data assessment (via predefined dashboards) and data reuse. This document (the EMIF code of practice, eCOP<sup>29</sup>) will be very helpful in establishing all required governance aspects for EHDN.

### Work package 6 – Overall project governance, project management, dissemination and sustainability

This work package will focus on:

- governance ensuring close alignment and collaboration across work packages;
- project Management Office;
- internal and external communication (dissemination to the greater research community);
- development of a sustainability model.

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## Glossary

|          |   |
|----------|---|
| BD4BO    | Big Data for Better Outcomes                                      |
| EHDN     | European Health Data Network                                      |
| EMA      | European Medicines Agency   |
| EFPIA    | European Federation of Pharmaceutical Industries and Associations |
| EU       | European Union  |
| FAIR     | Findable, Accessible, Interoperable and Reusable                  |
| HTA      | Health Technology Assessment                                      |
| ICHOM    | International Consortium for Health Outcomes Measurements         |
| iHD      | The Insitute for Innovation through Health Data                   |
| IT       | Information Technology  |
| OHDSI    | Observational Health Data Sciences and Informatics                |
| OMOP CDM | Observational Medical Outcomes Partnership Common Data Model      |

<sup>29</sup> [http://www.emif.eu/assets/e/m/emif\\_d10\\_4\\_first\\_draft\\_ethical\\_code\\_of\\_practice\\_exec\\_summary\\_website.pdf](http://www.emif.eu/assets/e/m/emif_d10_4_first_draft_ethical_code_of_practice_exec_summary_website.pdf)

|     |                                    |
|-----|------------------------------------|
| R&D | Research and Development           |
| RWD | Real world data                    |
| SME | Small and medium-sized enterprises |
| WP  | Work package                       |

## Topic 5 : Analysing the infectious disease burden and the use of vaccines to improve healthy years in aging populations

### Topic details

|                                 |                                       |
|---------------------------------|---------------------------------------|
| Topic code                      | IMI2-2017-12-05                       |
| Action type                     | Research and Innovation Actions (RIA) |
| Submission & evaluation process | 2 Stages                              |

### Specific challenges to be addressed

We observe that today the shape of the demographic pyramid in Europe evolves into a mushroom-like design [1] [2]. Multiple dynamic age-processes are tailoring this age-structure leading to the situation that the older population augments in size every year also because they live longer [3]. But older people are more vulnerable to infectious diseases because their immune system becomes weaker with age [4]. The consequences are that one may observe an increasing burden of infections in the elderly with a high transmission rate. They are often treated with antibiotics causing resistance. In addition, infectious diseases are often the trigger for an underlying manifestation of chronic disease conditions those elderly are suffering [5]. We therefore have to tackle two health problems with infectious diseases in the elderly: a volume problem and an inhomogeneous demand for health care. Older people need more costly treatment because of their increased frailty condition.

If those infections could be avoided, we should be able to delay, reduce, or avoid the exposure to institutionalised health care with lengthy and costly stays related to slow recovery. Avoiding infections, therefore, impacts the ambition of supporting healthy aging, a condition that helps optimise the opportunities of good health so that aged individuals maintain their activities of social life and enjoy an independent high quality of life [6]. A solution to avoid those infections is to develop a well-conceived vaccination programme for the elderly as we did for children years ago. If we apply the same strategy for the elderly we should help reduce the infection problem and its consequences of being exposed to anti-microbial resistance (AMR). But this whole situation has not been so well studied with enough detail in an integrated way. Rather bits and parts have been assessed but without having a clear overall picture on how this whole process of aging, infection exposure [7], immune response to vaccination [8], is developing and potentially evolving. Therefore, before getting to the programme of vaccinating the elderly, we need to study the infection problem in greater detail. We are therefore facing the following challenges in getting the full picture well presented:

1. getting access and demonstrating how to evaluate and report epidemiologic data for obtaining a clear picture on the infectious disease burden in the aged people (50 years +) (trend analysis, frequency, Quality of Life (QoL), and cost) split by specific age and gender groups, vaccine-preventable or upcoming vaccine preventable diseases, and exposure to the health care system (at home care, day care, medical care, institutional care (hospital, recovery));
2. better understanding the immune response in elderly (65 years +) by deciphering the changes taking place due to age and to other factors, the role of different facets of the immune responses, the role of new immune-modulation techniques, and to explore the potential for developing better vaccines for the elderly;
3. having disease and economic models available that predict how the current situation may further evolve without any specific intervention, and how we may project a change in disease frequency, cost and QoL of the elderly, if we implement an extended vaccination programme to reduce the burden of infections with the overall societal consequences;
4. being able to communicate an integrated view of the problem (epidemiology, cost, and QoL burden, vaccine and immunology working, economic consequences of implementing a vaccination programme among elderly) through training and education of health care professionals (HCP).

## Need and opportunity for public-private collaborative research

Public and private sectors are today involved at varying degrees in a variety of assessments on aging such as research on immune-senescence [4] [8] [9] [10], identifying external factors that could influence the process, epidemiology and the cost of vaccine preventable infectious diseases in elderly [7]. Industry has a long-lasting experience with approaches of vaccinating the elderly adults as demonstrated with the development of specific vaccines for that target group. For example, progress has been reported in the past few years by various industries in the development of vaccines for influenza, pneumococcal infections, and herpes zoster for elderly [11] [12] [13] [14]. However, success in these approaches is often based on empirical knowledge and observations rather than on understanding well the underlying mechanics of the vaccine working. On the other side, various public groups such as academic teams, governmental and public health bodies, small and medium-sized enterprises (SMEs) have an established track record of expertise and achievements in specific aspects of ageing (epidemiology, immunology, health economics, training). This suggests that a more integrated approach between public and private sectors may pave the way for a deeper understanding of the problem and a definition of novel solutions.

Only through joined efforts of public and private sponsors can a holistic approach be successful in adding value as compared with the many projects in the area of aging which mostly have focussed on a single aspect (most of the time on immune-senescence).

For example:

Vaccine industries and academic groups may currently perform their own epidemiologic studies with the collection of cost information and QoL data that are conducted independently from each other, using different types of analysis, QoL instruments, and reporting with different definitions because different age-groups have been selected or different time horizon perspectives have been considered. There is a need for more cooperation between the different groups, for sharing of information, pooled analyses of larger anonymised datasets, uniformed analysis and reporting. This should lead to more robust findings that will increase the credibility of the research.

Developing new programmes to study the immune response amongst aged persons is often a very costly undertaking, which makes it challenging for individual organisations or stakeholder sectors to conduct such studies. Collaboration between sectors will result in optimal use of financial resources and avoid duplication of efforts.

Vaccine industries and academic groups can develop their own disease and economic models to explore the cost-benefit of new interventions. While those models are today often developed in different environments with little incentive to share the full details of their construction, for third party evaluators they remain black boxes with a low possibility of achieving a high level of transparency. There is a need for working together on model development between industry and academia, and possibly governmental institutions, so that maximum transparency and agreement is reached on how the models are constructed, tested and validated. This should create a deeper trusted relationship, including with decision makers, about the model output and sensitivity analyses.

Once the problem is understood and once potential solutions are found, it will be key that the results become an integral part of communication and teaching programmes involving all stakeholders working with the elderly. Such communication and reporting about the project requires intense collaboration between public and private organisations, to develop joined messages for healthcare professionals and decision-makers.

## Scope

The scope of the project is to:

- obtain a clear picture on the infectious disease burden in an aging population (50 years +);
- quantify the problem such as number and type of hospitalisations and medical visits when the 50 years + group is exposed to the health care system;
- understand this evolution over the coming years;

- obtain a better insight in the immune response in the age-group of 65 years +;
- develop cost-benefit predictions based on an extended vaccination programme;
- better control the burden in that age-group through simulations with advanced disease models, and finally;
- develop strategies to educate all stakeholders working with the elderly.

The strength and attractiveness of the project is to achieve an integrated, multi-disciplinary approach of the problem making necessary links of collaboration between the different activities proposed in the different pillars presented hereunder.

Four pillars represent the objectives under the overall scope of the project. They are identified as burden of disease (pillar 1), immune response investigation (pillar 2), economic value (pillar 3), and communication (pillar 4). To reflect project priorities, pillar 1 and 2 would have main allocation of resources, but to reflect their significance, pillars 3 and 4 would still receive a significant allocation of the total indicative budget.

### **Pillar 1: Burden of infectious diseases in aging adults (50+)**

It is expected that the activities of this project will lead to the development of an appropriate protocol design for collecting epidemiologic and economic data about infectious diseases in an aged population (50 years +) across the health care systems in place. A starting point will be a pilot project in a specific region that has the facilities to develop and test in depth the designed approach for collecting and analysing the data. Based on that experience and depending on budget and time allocation, the programme could then progressively expand to different regions in Europe with the goal of obtaining a consolidated data-base system. It is not the ambition to be able to cover the whole of Europe within the budget and time frame but to demonstrate the applicability of the programme in different environments across Europe that best illustrate the heterogeneity of the problem from west to east and from north to south.

The protocol in the pilot region could begin with the collection and analysis of retrospective data, moving to a more advanced and well-established prospective epidemiologic study programme.

The primary objectives under this pillar are to:

1. obtain more accurate 'real world' knowledge on the epidemiology and the economics of infectious diseases in aging adults split into 2 categories: existing vaccine-preventable (VP) diseases and upcoming potential vaccine-preventable (PVP) diseases. VP includes vaccines against influenza, pneumococcal, zoster, pertussis, meningococcal, and rotavirus. PVP included vaccines against for example RSV, Clostridium difficile, staphylococcus, E. coli, enterococcus, urinary tract infections, and specific anti-microbial resistant germs;
2. be able to report precisely on specific mortality, morbidity, hospitalisation, medical visits, access to health care, cost and productivity loss, overall QoL, and specific QoL;
3. investigate and explore potential links to diseases/co-morbidities and risks in which infectious diseases could be the trigger for developing more complex disease conditions (cardio-vascular, respiratory, stroke, metabolic problems, etc.).
4. In addition, the project should explore the generation of a consolidated database on infectious disease burden in aging adults (epidemiology and cost) across Europe that can be consulted by decision makers when selecting new vaccines to be implemented.
5. The activities under this pillar might also support the development of an estimate of the increase of the infectious disease volume in the aged population and the level of heterogeneity of the problem (different demand of health support by age and gender), however this is not considered a primary objective of this action. Likewise, the activities under this pillar might be useful building blocks for creating a natural infectious disease pattern of the elderly, but this is not considered a primary objective of this action.

### **Pillar 2: Changes in immune response with age (65+ years compared to adults 18-50 years of age) and internal factors influencing the process**

The primary objectives under this pillar are to:

1. select novel approaches that enlarge our knowledge about what leads to the decline of immune response causing higher susceptibility to infectious diseases and poor vaccine response;

2. expand the field of investigating immune decline with age (termed immune-senescence) and identify the several compartments of the immune system that senesce with age;
3. develop and perform a prospectively designed clinical research study to assess the immune response of the elderly (65+ years) compared with adults (18-50 years) following vaccination. An appropriate informed consent would allow the collection of serum and whole blood to assess systems biology profiles and biomarker signatures. A frailty assessment at enrolment could be established. A state-of-the-art dissection of the immune response could be conducted focussed on immune compartments not well studied or not studied to date – for example, T-cell follicular help (T<sub>fh</sub>), individual cell profiling (e.g. RNA sequencing), mucosal markers and B-cell immune compartments. Particular attention should also be given to innate immunity in the peripheral blood and, whenever possible, at the site of priming of the immune system (e.g. skin, muscle, mucosal level). The role of dendritic cells, macrophages, NK cells is becoming more important in the events triggered by novel adjuvants, novel delivery systems, etc. Their role in the elderly is still poorly understood.
4. In addition, the project should also propose how the vaccination field of analysis could be expanded beyond influenza to create an optimal vaccination programme with durable protection for non-influenza vaccines in elderly, namely Tdap/Td, Herpes Zoster and Pneumococcal. This is particularly important for those vaccines for which the elderly are immunologically naïve and which should provide a strong priming, which is expected to be difficult to achieve in subjects with a paucity of naïve T and B cells. Therefore equal emphasis should be put in place on the assessment of immune-senescence in response to influenza and non-influenza vaccines.
5. The activities under this action might inform the following, however these points are not considered primary objectives of the action:
6. Application of the technique of machine learning to unravel the complex inter-relations between immunological biomarkers and vaccination in the elderly, to better understand complex patterns associated with aging and vaccination. New profiles of immune aging should direct areas of research for the application of immunomodulation and/or new vaccine technologies, able to overcome or mitigate immune devolution.
7. Hypothesis testing on extrinsic factors that could influence the immune response: nutrition, physical exercise, medical treatments, other technologies applied in medical care. It is well known that nutrition significantly influences immune responsiveness in the old subjects. Caloric restriction has a positive effect, while obesity has a negative effect on immune responses. In addition, some drugs have been recently unexpectedly shown to have either positive or negative effect on vaccination in old people. Prospective studies are needed to investigate the relationship and its strength.
8. The creation of the right vaccine development programme against certain infectious healthcare problems in elderly.
9. Application of new data analysis methods to derive immune profiles associated with aging.

### **Pillar 3: Vaccine impact assessment and economic value of vaccination in aging adults**

The primary objectives under this pillar are to:

1. be able to evaluate the effectiveness and impact of vaccination through modelling exercises with simulations and scenario-analysis (best, worst case) using well-developed epidemiologic and economic models including optimization and a vaccine portfolio management approach;
2. develop a natural disease model with data obtained from the epidemiologic studies that should also help in answering the questions: when do we need to vaccinate to obtain optimal results of prevention;
3. be able to elaborate on what could be the consequences expressed financially (private, public), in health gain (life years and quality life years), and in health care development (more beds, more home care, improvement in quality of care).

It is expected that the activities under this pillar will inform whether vaccination may help in reducing the anti-microbiological drug resistance over time.

The activities under this pillar might also support the development of an estimate of what the new threat of living longer under healthier conditions for our social security system with increased spending in pensions will be (do we need to work longer?), however this is not considered a primary objective of the action.

## Pillar 4: How to best communicate to stakeholders through education and training of HCPs

The objective under this pillar is to:

- build a framework of innovative educational and training initiatives on infectious diseases based on adequate prevention strategies including vaccination in aging adults for all HCPs.

## Expected key deliverables

The expected key deliverables of the project should be:

- a database on infectious disease burden in aging adults (repository of knowledge);
- standard methods and definitions on how to analyse and report the disease burden for that age-group;
- an estimation of the full burden of infectious diseases for VP and PVP. The burden should include frequencies, costs, Quality of Life (QoL), with trend results stratified by age-groups, risk level, relative importance of hospitalization/surgery, gender, social classes, access to medicine, underlying chronic diseases or sequelae;
- the identification and validation of intrinsic parameters impacting the decline of immune responsiveness with age characterised to advance the prevention of infectious disease in the elderly through vaccination;
- computational models to conduct simulations of immune function in elderly (with/without disease);
- the characterisation and validation of the role of external environmental factors (nutrition, physical exercise, pharmacological treatments, etc.) on the immune responsiveness in the elderly;
- models with scenario-testing that simulate the impact of different vaccination programmes based on their health benefit and economic consequences;
- a recommendation for optimal vaccination strategies of the older adults based on model simulations and the data collection;
- the development of a vaccine confidence roadmap targeting HCPs: understanding of the levers/barriers to vaccination and drafting of possible actions.

## Expected impact

The project will have an impact at many different levels:

- Societal gain for healthy aging: Based on the data-collection and model simulation, a recommendation will come out on how to create an optimal vaccination strategy for the older adults. If that strategy will be implemented, an evidence-based vaccination programme for the aging adult will enhance the health condition of the elderly, make important cost offsets in health care, result in benefits in leisure time of the target group and the care-givers, reduction in production loss of care-givers, and improve the quality of care. In addition, an enhanced overall knowledge of what matters among the elderly will be an important societal gain.
- Health science development: Agreed-upon standards of analysis and reporting in the field of epidemiology and economic evaluation in people over 50 years old will have a positive impact on the results of vaccination.
- Basic research in immunology and vaccinology: It is expected that the results of the project will significantly contribute to a deeper understanding of the immune-response in aging adults. This new knowledge would not be a stand-alone acquisition, but it would instead reside within the frame of a more comprehensive body of knowledge encompassing epidemiology, environmental factors, etc. The results should help to develop better vaccines or better vaccination-schedules/programmes for the target group.

- Economic analysis: The elderly are a challenging group to assess in health economic evaluations when it comes to measuring precisely health and health gain. In the elderly the cohort of evaluation is not fixed but reduces over time because of the deaths moving into the absorbing state. Many competing causes of death and interactions between various co-morbidities do not allow a readily available valuation of expected health benefits. This project should allow to more accurately estimate health gains achieved through new interventions like vaccination and cost calculations using more appropriate techniques of modelling.
- Communication strategies: Our society is evolving very rapidly in a modern area of communication that is well established in the young generation with the social media. Having a good communication strategy in place will enhance the promotion of prevention strategies such as new vaccination programmes to reduce the burden of infections in elderly.
- Through the participation of industrial partners, in particular small and medium-sized enterprises (SMEs), an additional impact in relation to strengthening the competitiveness and industrial leadership of Europe can be expected.
- Interaction with regulatory agencies. It is expected that some of the outcome of the project may be interesting for the regulatory bodies at international (e.g. EMA), national or regional level. For this reason, updates of the progress of the project will be provided regularly as appropriate.

## Potential synergies with existing consortia

The project is expected to directly contribute to the goals and activities of the European Innovation partnership on Active and on Healthy Ageing.

Applicant consortia will propose a strategy to emphasis/maximize potential synergies with other initiatives in the field of health interventions on aging adults such as epidemiology, economics, immunology, physiology, among other initiatives. For example, links to existing lists of initiatives within Horizon 2020, Millennium goals, Healthy Aging programmes via EuroHealthNet, should be explored, such as the H2020 I-MOVE+ project.

In addition, special consideration should be given to exploring synergies with existing IMI projects and utilising learnings generated there to build upon in this project. The following non-exhaustive list of IMI projects might be of relevance in this respect:

- projects under the **New Drugs for Bad Bugs (ND4BB)** programme, <http://www.imi.europa.eu/content/nd4bb> ;
- **RESCEU** (Respiratory syncytial virus consortium in Europe), [www.resc-eu.org](http://www.resc-eu.org);
- the **Better Data for Better Outcomes (BD4BO)** programme;
- **SPRINTT** (Sarcopenia and physical frailty in older people: multi-component treatment strategies), [www.mysprintt.eu](http://www.mysprintt.eu);
- other IMI projects dealing with vaccine data analysis, such as **ADVANCE (Accelerated development of vaccine benefit-risk collaboration in Europe)**, [www.advance-vaccines.eu](http://www.advance-vaccines.eu), and the project selected for funding under the topic **Joint influenza vaccine effectiveness** studies (IMI2 9<sup>th</sup> Call for proposals);
- any other project or initiative of relevance, in order to avoid duplication of efforts.

## Industry Consortium

The industry consortium is composed of the following EFPIA companies:

- GlaxoSmithKline (lead)
- Sanofi Pasteur
- MSD
- Janssen

- Pfizer
- Vaccines Europe/EFPIA

The EFPIA in-kind contribution will take the form of:

- personnel costs by providing expertise in health economics and outcomes, immunology, epidemiology, statistics, regulatory affairs, patients engagement, project leadership;
- conduct of a large prospective observational epidemiological study;
- giving access to a data-base that has already collected some critical information on the subject;
- disease and economic models already or being developed for elderly;
- roadmaps for good communication practices.

## Indicative duration of the action

The indicative duration of the action is 60 months.

### Future project expansion

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

A restricted Call may be launched as part of a future IMI2 JU Annual Work Plan to build upon the work carried out under this action under the different activities of the different pillars enhancing further development of the results to full deployment as necessary. Examples could be the full development of a database on infectious disease burden in aging adults, the assessment of volume increase of infectious disease over time, or creating a natural infectious disease model.

## Indicative budget

The indicative EFPIA in-kind contribution is EUR 5 500 000.

The financial contribution from IMI2 is a maximum of EUR 5 500 000.

## Applicant Consortium

The successful applicant consortium will be selected on the basis of the submitted short proposals and their experience in working in a multi-disciplinary environment including epidemiology, modelling, health economics, experience in conducting clinical studies, knowing well the other IMI projects.

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

The consortium should combine partners with established and well-recognized experience in the field of aging, encompassing aspects related to human vaccination, public health, human immunology, epidemiology, infectious diseases, physiology, medicine, nutrition, economics, advanced disease modelling, training and education capacities and experiences, etc.

The consortium should include partners with experience in assessing vaccination programmes and the decision-making processes leading to the implementation of new vaccination programmes, as well as regulatory experience.

The applicant consortium is expected to include the necessary project management skills suitable for the expected funded project.

It is expected that the applicant consortium will guarantee regular (at least annual) contacts with regulatory agencies (national and/or supranational) as appropriate to inform them on the progress of the project. This

could take place via regular teleconferences and/or face-to-face meetings as felt appropriate by the consortium and by the regulatory agency.

## 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 achieving the project objectives.

In the spirit of the partnership, and to reflect how IMI 2 JU call topics are built on identified scientific priorities agreed together with EFPIA beneficiaries/large industrial beneficiaries, these beneficiaries intend to significantly contribute to the programme leadership and project and financial management.

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

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

The architecture of the proposal is based on four major pillars. It is expected to support the development of a comprehensive programme about the relationship between vaccine and healthy aging. The architecture outlined below for the full proposal is a suggestion. Different innovative project designs are welcome, if properly justified, as long as the objectives of the project are fully supported.

It is expected that the objectives of the project can be achieved by the following five work packages.

### **Work Package 1 – To determine the burden of infectious diseases in aging adults (50+)**

The objectives of this work package will be as follows:

- Through retro- and prospective epidemiologic study design and review of existing databases, starting with a pilot project in a particular region in order to obtain a robust protocol of evaluation that can be expanded progressively over time;
- Acquiring a deeper knowledge on the epidemiology of infectious diseases split into 2 categories (existing vaccine-preventable (VP) diseases (e.g. influenza, pneumococcal, zoster, pertussis, meningococcal, rotavirus), upcoming potential vaccine-preventable (PVP) diseases (e.g. RSV, C diff, staphylococcus, E coli, enterococcus, urinary tract infections, specific anti-microbial resistance germs) in aging adults);
- Acquiring a deeper knowledge on the economics of the infectious diseases (cost of illness) split into the 2 categories (VP, PVP);
- Investigate potential links to diseases/co-morbidities and risks within that age group in which infectious diseases could be the trigger for developing more complex disease conditions (cardiovascular, respiratory, stroke, metabolic problems, etc.);
- The work package 1 should report about the volume increase of the infectious disease in the aged population because of the demographic age-change and about the level of heterogeneity in the target group related to possible immune response rates.

### **Work Package 2 – To better understand the immune response of aging adults (65+) and how it is modulated or affected by internal and external factors after vaccination**

The objectives of this work package will be as follows:

- Prospectively designed clinical research studies to assess the immune response of the elderly (65+ years) compared to adults (18-50 years) following vaccination. An appropriate informed consent

would allow the collection of serum and whole blood to assess systems biology profiles and biomarker signatures. Establishment of a frailty assessment related to the infection condition at enrolment.

- Learning about mechanisms leading to immune waning or reduced immune responsiveness at the level of both innate and adaptive (both T- and B-cell) immunity, and the ability to respond to vaccination with age.
- State-of-the-art dissection of immune responses at the site of the priming of the immune response (e.g. related to skin condition, muscle condition, mucosal conditions), role of B and T-cell immunity, immune modulators (PD-1) among others, in order to better understand why the immune-response reduces with age. This large field of exploration needs an urgent, well-focussed and designed research programme for obtaining reliable and workable results that can improve next generation of vaccines and vaccination-schedules and programmes for the elderly. The field is starting to know and observe important processes of immune-senescence occurring with age, but we need to focus on immune compartments pertinent to optimal vaccine elicited responses and other immune processes not yet adequately addressed such as T-cell follicular help (T<sub>fh</sub>), B-cell immunity, innate immunity (e.g. dendritic cells, macrophages, monocytes, NK cells, etc. in the blood and, whenever possible, at other priming and/or effector sites of the immune response), mucosal markers, antibody effector functions, immune profiling at the individual cell level (e.g. single cell RNA sequencing), among others.
- The waning of the immune responsiveness is not merely due to the 'physiological' decline by age, but also by extrinsic factor, which can accelerate or retard the decline. Understanding how these factors such as physical activity, nutrition, other medical treatments, existing comorbidities may affect the immune responsiveness in aging adults becomes important to better appreciate the heterogeneity of the phenomenon of immune-senescence.
- Application of new data analysis methods to derive immune profiles associated with aging. Machine learning should be applied to identify complex profiles of inter-related factors.

### **Work Package 3 – To assess with disease models the current management status of infectious diseases in older adults and to simulate the impact of (potentially) vaccine preventable infections**

The objectives of this work package will be as follows:

- The models should set new standards of analysing and reporting health economic results for such population (cost-effectiveness analysis, budget impact, optimisation modelling). It is expected to advance the impact options in a transparent way when analysing and reporting health economic results.
- Based on information collected in work package 1, developing advanced modelling programmes (agent-based modelling) simulating different conditions in which elderly people may normally operate (home care, day care, hospital care) to demonstrate the impact of vaccination according to various level of immune-senescence and to define best strategies to maximise the overall public health impact of vaccination for aging adults, taking into account potential enablers. The models developed through this programme, should be made available across all the participants of the project.

### **Work Package 4 – To develop a roadmap about training and education of HCPs**

The objectives of this work package will be as follows:

- Vaccination of adults and elderly subjects is not fully perceived as a major need with great value assessment for the target population and society, as compared with the vaccination of the paediatric age-group. Appropriate and innovative communication tools for all stakeholders (decision makers, prescribers, payers, target population) on the value of vaccines and on vaccination should represent a key need for achieving the scope of healthy aging.
- Building a framework of innovative educational and training initiatives on infectious diseases for all HCPs based on adequate prevention strategies including vaccination in aging adults.
- Developing a network of specialists/experts in the field across Europe to exchange experience and set-up new collaborative projects would be very helpful.
- Demonstrate how to secure training of the HCPs in charge of implementing adult vaccination: include systematic HCPs vaccination training both in curriculum and in Continuous Medical Education (CME)

(use of Massive Open Online Courses (MOOC) to be leveraged), taking into account that HCPs should include GPs, specialists, nurses and pharmacists

## Work Package 5 – Project coordination, management, and dissemination activities

The objectives of this work package will be as follows:

- Skilled project management support will be an essential part to ensure project success.
- Managing all aspects of project governance, management and coordination. Facilitation and streamlining of cooperation between the different partners of the project and between work packages.
- Carrying out all aspects of the dissemination of results, and communication strategy.
- Coordinating and communicating with other European initiatives and projects handling complementary activities.

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## Glossary

|       |   |
|-------|---|
| CME   | Continuous Medical Education                                      |
| EFPIA | European Federation of Pharmaceutical Industries and Associations |
| EMA   | European Medicines Agency   |
| HCP   | health care professionals   |

|      |                                    |
|------|------------------------------------|
| MOOC | Massive Open Online Courses        |
| PVP  | potential vaccine-preventable      |
| QoL  | Quality of life                    |
| SME  | Small and medium-sized enterprises |
| TfH  | T-cell follicular help             |
| VP   | vaccine-preventable                |
| WP   | Work package                       |

## Topic 6: Discovery and characterisation of blood-brain barrier targets and transport mechanisms for brain delivery of therapeutics to treat neurodegenerative & metabolic diseases

### Topic details

|                                 |                                       |
|---------------------------------|---------------------------------------|
| Topic code                      | IMI2-2017-12-06                       |
| Action type                     | Research and Innovation Actions (RIA) |
| Submission & evaluation process | 2 Stages                              |

### Specific challenges to be addressed

The **blood–brain barrier** (BBB) acts as a strict control point for what can enter the brain, and is created by drug efflux transporters (transport barrier) expressed on cerebrovascular endothelial cells and by tight junctions and adherens junctions between those endothelial cells (biophysical barrier) supported by basement membrane, astrocytic end-feet, pericytes, and neuronal innervation. The barrier functions of the BBB lie in the integrity and physiological regulation of the neurovascular unit (NVU). The BBB facilitates the passage of nutrients and metabolic necessities to the brain but restricts the entry of most blood-borne drugs and neurotoxic agents into the brain. The ability to cross the BBB must be considered for neurotherapeutics administered peripherally. In particular the BBB remains a major obstacle for biopharmaceuticals (e.g., antibodies, peptides) and restricts the choice to passive brain-permeable small molecules [1]. While there are examples of actively transported central nervous system (CNS) drugs (e.g. Lyrica®) the state of transporter substrate specificity understanding makes development of these largely dependent on luck rather than design. This also explains why no centrally acting biopharmaceuticals (e.g. antibodies, peptides, proteins, oligonucleotides) are currently on the market [2]. Transport receptors or carriers, mostly mediating receptor- or carrier-mediated transcytosis (such as transferrin (TfR) and insulin (InsR) receptors, Low density lipoprotein receptor-related protein 1 (LRP 1), Glucose transporter 1 (GLUT1), Amino Acid Transport Associated to Cluster of Differentiation 98 Heavy Chain (CD98hc)) triggered by antibodies or peptides, have been reported to ferry biopharmaceuticals across the BBB [3]. However, these systems have not totally proven their safety and efficacy yet and no development of transferrin receptor antibody-enabled biopharmaceutical has been reported to-date. Insulin receptor antibody has been recently employed to deliver iduronate-2-sulfatase to the brains of MPS-II (Type II mucopolysaccharidose or Hunter syndrome) patients in a phase II clinical trial (NCT02262338). It appears to be safe, tolerable and improve cognitive scores in the patients. In addition to Receptor Mediated Transcytosis (RMT) and Carrier Mediated Transcytosis (CMT) mechanisms, liposomes [4], nanoparticles, and more recently exosomes [5] have been explored to enhance brain delivery of therapeutics. These have targeted both passive and active uptake mechanisms and have shown mixed results to date. Studies have also explored approaches of employing viral vectors/particles/vesicles or protein fragments to deliver genes or biopharmaceuticals into the brain. Other approaches of drug delivery, such as intranasal delivery of therapeutics across the olfactory epithelia into the brain, still remain to be explored further. While all these results seem promising, a major challenge in this field is validation of the various transport mechanisms and drug delivery systems by independent researchers and further understanding challenges to advancing into clinical drug development by biotech/pharma.

A goal of the action to be generated by this topic is to work precompetitively to validate targets and transport mechanisms at the BBB and provide additional insight into any developmental challenges.

One of the central hurdles in driving structure-activity relationship (SAR) for brain uptake and in identifying new mechanisms of brain delivery is the lack of **blood-brain barrier models** truly predictive of *in vivo* exposures of biologics as well as lack of selective BBB targets for brain transport. Even if some reports in the literature present human inducible pluripotent stem cell (hiPSC)-derived BBB models [6], their robustness and predictability remain to be assessed, and no fully reconstituted human model convincingly mimicking the neurovascular unit has been successfully developed to-date [7]. To this end, 3D- or spheroid models and microfluidics could be ideally suited and a few interesting directions are starting to emerge in the literature [8]

even though some less reported models – at least in the context of BBB- such as hollow-fiber models could also be of use, provided that they bring value to the project.

A **compromised or altered permeability of BBB** has been reported in brain tumours and for several **neurological and metabolic diseases** [9]. Even though it is still a matter of debate, it seems increasingly evident that this BBB dysfunction might be at the very root and pathogenesis of some of these neurological diseases (such as multiple sclerosis and vascular dementia) [10]. And even though the pharmacological understanding of many of these diseases has identified attractive potential therapeutic targets, most of these are currently not believed to be developable due the hurdle of the BBB and the lack of predicted brain penetration based upon general understanding of BBB characteristics. Availability of *in vitro* and *in vivo* models of the BBB representative of those characteristics present in these diseases would allow much more aggressive testing of hypotheses around therapeutic delivery. This potentially may lead to greater investment in targeting these diseases due to the improved tools and mechanistic understanding to explore novel delivery strategies and to develop therapeutic agents. Both of these outcomes would improve the probability of developing successful therapeutic agents to treat these diseases. Moreover, it would provide a more expansive suite of experimental tools with which to further develop an understanding of the fundamental biology, which underpins the absorptive-/receptor-mediated processes across the BBB. **Thus, the physiology of the BBB and the transport mechanisms in health and diseases play a critical role in the development of brain delivery technologies for the treatment of neurodegenerative diseases.**

Human iPSC-derived cell models hold great promises for human ***in vitro* BBB and disease modelling** and could be used to understand the pathogenesis of neurodegenerative disorders, the roles of BBB in the pathogenic process, and to identify new potential improved screening tools for new drugs [11]. Thus iPSC cell-derived BBB models might represent a promising tool to link human neuropathology to BBB dysfunction and a screening tool for permeability, mechanistic and functional studies. However, there is no report on patient-derived human iPSC's BBB models or disease/genetic models generated by Clustered Regularly Interspaced Short Palindromic Repeats (CRISPR)-cas9 technology. In addition there is a general lack of a consensus on the clinical characteristics of such disease models and on what successful validation would be required.

Although results reported in the literature describing efforts to profile brain endothelium via microarray analysis, transcriptomics and proteomics approaches [12] are in principle useful, they do not necessarily resemble the disease situation. In this situation, the composition of the surface proteome of brain endothelial cells, the organization and interaction between cells and cell types and permeability in this barrier may be altered. This could strongly impair the efficacy of a brain delivery system if the employed **transport protein/receptor is down-regulated in disease**. As a consequence, the therapeutic efficacy of such a delivery system would be greatly reduced. The identification of transport mechanisms which remain stably expressed or, even better, upregulated in disease, would greatly improve the chances for a successful delivery of therapeutics for treatment of CNS diseases. There is also a lack of computational or *in silico* models for studying the pharmacokinetics (PK) of drugs and biopharmaceuticals as penetration of the BBB (levels and capacity of relevant receptors and carriers at the BBB for receptor/carrier-mediated transcytosis for drug delivery) and the distribution and clearance of drugs/biopharmaceuticals in different compartments of CNS under normal and disease conditions (such as interstitial fluid ISF, neurons, and cerebrospinal fluid (CSF)). *In vitro* and *in vivo* data from published sources or pharma industrial database may be collected to build such an *in silico* model. It is known that neurotropic viruses can selectively penetrate the BBB and CNS or infect nerve and neurons. However, the mechanisms of those viruses in penetrating BBB and CNS have not been fully characterised. Understanding the mechanisms of the viral mediated processes would generate useful knowledge to inform potential approaches for the development of brain selective delivery technologies.

Thus several challenges have yet to be addressed to better understand the role and alterations of the BBB and transport mechanisms in health and diseases. Relevant diseases are neurodegenerative diseases (e.g. Alzheimer and Parkinson's diseases, Amyotrophic Lateral Sclerosis (ALS)), vascular dementia, multiple sclerosis and metabolism-related central diseases (diabetes and obesity). It will be also important to understand the mechanisms of neurotropic virus-mediated BBB and CNS penetration, and to be able to apply this knowledge for the development of innovative drug delivery systems, especially for biopharmaceuticals, and the identification of novel drug targets.

## Need and opportunity for public-private collaborative research

In light of the above, the magnitude and complexity of the BBB in health and diseases is beyond the reach of a single company or institution, such that it can better be addressed by a major public-private-partnership

involving a variety of stakeholders and expertise. Shared understanding of measurable attributes of disease-specific BBB models combined with successful development of both the methodologies and technologies to identify validated predictive human models is necessary to enable significant advances in strategies to expand the brain-accessible repertoire and to encourage renewed investment to develop treatments for these disorders. Specific areas of immediate focus are identified in the Scope section. Because of the scale and scope of this endeavour, success will require the collaboration of a cross-functional/cross-institutional consortium of academic, SME/biotech and industrial scientists.

The engagement of leading pharmaceutical companies with detailed understanding of pre-clinical and clinical consequences of disease-modified BBB and with the chemical/analytical resources necessary to both validate and implement these models will enable the partnership to capitalise on the knowledge and innovation generated. The role of industry in this endeavour is crucial as they benefit from state-of-the-art equipment not always available to universities or academia (such as Next-generation sequencing (NGS) technologies or high throughput and robotized material for cell culture) and experienced people to run them, along with powerful and connected bioinformatics with a direct link into the clinic.

Biotech small and medium-sized enterprises (SMEs) would be very valuable in contributing with innovative technologies and tools and know-how in iPSC- or progenitor-derived cells and/or defined extracellular matrix hydrogels and/or human BBB models.

Academic groups will be necessary to provide strong know-how on BBB and disease models (neurodegenerative/metabolic) and to contribute on characterising the mechanisms of brain transport or virus-mediated transport. A few iPSC-based BBB models have been reported in recent years with good barrier properties and transport of various known brain-penetrating agents; however, their robustness and predictability needs to be put to the test [13] [14]. In addition, these models are based on 'healthy' iPSC clones and not based on iPSC cells from patients. The expertise of such academic partners in establishing iPSC-based endothelial cultures/models and in characterising brain transport mechanisms will be important for the successful conduction of the program. Even more so, the ideal situation would be to be able to develop a full BBB neurovascular unit with all cell types derived from patients and understand the mechanisms of brain transport under health and disease conditions. Successful collaboration and integration in a public private partnership of all these diverse stakeholders will be key for success in implementing the objectives of this topic.

## Scope

The **objectives** of the project to be delivered from this topic are:

- 1) establishment and characterisation of BBB models relevant for healthy and disease conditions for evaluation of disease-modifying agents (human *in vitro* cell based, in particular iPSC or progenitor-derived cells, and *in vivo*);
- 2) identification of translational readouts closer to the pathogenesis of neurodegeneration and mimicking altered BBB under disease conditions;
- 3) in-depth understanding of the biology of the BBB and characterisation of various transport mechanisms across the BBB (including virus-mediated BBB and CNS penetration);
- 4) discovery and development of innovative and efficacious brain delivery systems.

These objectives could be attained through the milestones shown hereunder. Each of them could represent an independent work package and will be described later in the topic text:

- 1) select specific genes and pathways expressed in endothelial cells of normal and/or diseased human brains or preclinical models;
- 2) validate *in vitro* and *in vivo* that these genes or pathways are responsible for normal/deficient/altered transport at the BBB and the impacts of disease development and progression on these genes or pathways;
- 3) this will enable the generation of improved BBB models for neurodegenerative/metabolic diseases predictive for the disease situation with optimized *in vitro-in vivo* correlation compared to established models; develop *in silico* models for predicting BBB penetration and PK of therapeutics in CNS;

- 4) identify and validate novel targets for brain delivery;
- 5) understand the mechanisms of neurotropic virus-mediated BBB and CNS penetration to inform innovative ways of brain-selective delivery.

The **diseases** in the scope of the topic are neurodegenerative diseases (in particular, Alzheimer and Parkinson's diseases), ALS, vascular dementia, multiple sclerosis, and metabolism-related central diseases (diabetes and obesity). **Metabolic disorders** such as type II diabetes (T2D) and **Alzheimer's Disease** (AD) were conceptually considered as two independent disorders. Recent evidence points to a link between impaired insulin signalling and dementia. This has even led researchers to propose the term "type III diabetes" for AD to capture the connection between these diseases. Impaired insulin signalling in the brain will cause neurodegenerative changes in cerebral glucose metabolism and can lead to mitochondrial dysfunction, excitotoxic damage to neurons, reactive oxygen species production, neuroinflammation etc., which can trigger apoptotic cell death and ultimately lead to dementia. This link is not only supported by impaired insulin signalling but also from other mechanistic pathways which are altered in obesity such as adipocyte secreted proteins, hormones as well as inflammatory cytokines which, when crossing the BBB, may be involved in the pathophysiological changes leading to dementia.

For example, a meta-analysis has shown that people with obesity (BMI >30 kg/m<sup>2</sup>) have an increased risk factor for AD, while there are several yet unclarified possible mechanisms for the obesity-AD connection ranging from changes in amyloid transport and clearance to alterations in lipid metabolism [15].

## Expected key deliverables

The overall aim of the proposed research topic is to further the understanding of the BBB in health and disease states towards the development of innovative brain delivery systems, especially for biopharmaceuticals (e.g., peptides, antibodies, etc.) and the identification of novel disease drug targets (Alzheimer's Disease, PD, etc.). The related key deliverables would be as follows:

- Identification and validation of specific genes and/or mechanisms which are altered in brain endothelial cells of the diseases of interest in this topic, namely neurodegeneration (AD/PD), vascular dementia, MS, ALS, central metabolic disorders, and which modify the BBB properties *in vitro* and *in vivo*.
- Generation, validation and characterisation of robust and predictive iPSC-derived BBB models: The developed models should be more reflective of the *in vivo* situation than existing models, in the healthy as well as in the disease state. The validation employing existing preclinical disease models should make them more predictable for the human clinical pathology. The use of defined media and hydrogel matrices will add to the robustness (reproducibility) and predictability of the BBB models.
- New, efficacious and safe mechanisms and technologies of brain delivery. Capitalising on the findings in particular from the IMI COMPACT consortium, namely several potential new targets for brain delivery identified through an -omics approach, could be a key asset in this endeavour [16], if this data becomes available at the time the consortium gets formed. The output of this topic should also result in an expanded and deepened understanding of the fundamental processes that underpin drug-trafficking across the BBB, which in turn can further support endeavours to elucidate novel and more efficacious brain delivery mechanisms.
- Characterised new genetic models for the diseases of interest in this topic which are better amenable to evaluate disease-modifying agents. Findings from the -omics studies on patient- or preclinical model-derived endothelial cells may give novel insights into disease pathways which may also lead to the development of new models that are more disease relevant.
- Characterised mechanisms of neurotropic virus-mediated BBB and CNS penetration for development of selective brain delivery systems.
- Established *in silico*/mathematical models in predicting BBB penetration of therapeutics (such as receptor- or carrier-mediated transcytosis for delivery across the BBB) and pharmacokinetics of biopharmaceuticals in different compartments of CNS.
- Identification of relevant translational readouts which are better amenable to elucidate the role of the BBB in the pathogenesis of neurodegeneration and could eventually lead to new targets for the treatment of the neurovascular causes of the diseases. The vascular hypotheses of some neurological diseases involve BBB dysfunction in their pathogenesis. However, to-date no compelling evidence allows to clearly assess whether these neurovascular dysfunctions are cause or consequence of the neurodegenerative

disease. Identification of specific readouts common to preclinical models and human pathologies would be a great advance for the field.

## Expected impact

The IMI2 action generated from this topic (“the project”) is expected to deliver new state of the art *in vivo* and *in vitro* validated models, validated new neurovascular targets to address the BBB and tools required to predict efficacy and safety of new therapeutic approaches.

The **potential impact of the deliverables** of the project to be created are several: The use of ‘healthy’ and patient-derived specimens, iPSC clones and other types of progenitors offers compelling approaches due to the direct connection to patients with the underlying disease.

The impacts of these new models could include: (1) yielding novel insights into currently identified BBB transport mechanisms for drugs, especially biopharmaceuticals, (2) allowing to use comparative assessment between ‘healthy’ and ‘diseased’ BBB, including *in silico* models, to prioritise some approaches for specific disease(s) because the transport mechanism is modified in the disease state, (3) leading to the identification and characterisation of novel transport mechanisms that are unaffected or upregulated in the disease or neurotropic virus-mediated, making them even more interesting, and (4) facilitating the discovery and characterisation of novel targets addressing the vascular aspect of neurological disorders like AD and thus open up novel routes for therapy.

These achievements will benefit the biomedical research community and will rapidly accelerate the pace of research in the development of new therapies and new delivery technologies for diseases for which there is a high unmet medical need, such as Alzheimer’s disease. As the project learnings might eventually enable brain access for large molecules, the project will facilitate academics/SMEs/pharma to open new ways for treatments and delivery systems, encouraging a renewed investment in developing drugs for neurodegenerative & metabolic disorders where the brain is the target. In particular biotech SMEs will be able to stress-test their technologies in a non-competitive open innovation environment which will help them to bridge the “valley of death” for turning these into products ready for market.

Thus, it can be anticipated that the results of the project will benefit patients and society through the accelerated discovery of new drugs targeting the brain and new delivery technologies, which will provide effective therapies for neuro-related diseases.

Altogether, the results generated from the implementation of this topic hold promise in many of the most important aspects of pharmaceutical R&D and therefore have a potential impact on the objectives of IMI2:

- improving the current drug research process by providing better translational tools and models to assess efficacy;
- improving the drug development process by providing biomarkers for diseases clearly linked to clinical relevance; better models (including *in silico* models) in predicting BBB permeability and PK of therapeutics in CNS;
- reducing the time to reach clinical proof of concept in the area of neurological and neurodegenerative diseases;
- increasing the success rate in clinical trials of highly challenging diseases such as those of the CNS;
- developing new delivery systems and/or therapies, based on characterisation and understanding of novel transport mechanisms and/or neurotropic virus-mediated transport, for diseases for which there is a high unmet need, such as Alzheimer’s disease and Parkinson’s disease;
- reducing the failure rate candidates in phase III clinical trials through new biomarkers for initial efficacy and safety checks.

## 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 capitalise on past achievements, available data and tools/models and lessons learnt where possible, thus avoiding unnecessary overlap and duplication of effort.

The project generated from this topic in particular should, among others, build strongly on reported achievements and knowledge from other relevant IMI projects such as COMPACT (<http://www.compact-research.org/> and <http://www.compact-research.org/publications/>).

As the current proposal focusses heavily on iPSC technology, it could have strong synergies with other iPSC-focused efforts like the IMI projects Stembancc (<http://www.stembancc.org/>) and EBiSC (<https://www.ebisc.org/>) which have established, characterised and banked Alzheimer's and Parkinson's disease patient-based iPSC clones. These clones could be a valuable tool for the identification of interesting clones for the establishment of BBB and/or disease models in this consortium and thus provide 'added value'.

The action generated from this topic should also consider relevant findings from the FP7 projects:

- **JUSTBRAIN** (<http://www.justbrain-fp7.eu/index.php?id=779>)
- **EURIPIDES** [http://cordis.europa.eu/project/rcn/88178\\_en](http://cordis.europa.eu/project/rcn/88178_en)
- **NEUROBID** (<http://www.neurobid.eu/>)

## Industry Consortium

The industry consortium is composed of the following EFPIA companies:

- Sanofi (Lead)
- Pfizer
- GSK
- Janssen
- Novartis
- NovoNordisk
- Fujifilm

The industrial consortium is expected to provide benchmarks biopharmaceuticals to validate the BBB models, access to iPSC's from patients, high capacities in transcriptomic and proteomic studies, disease models of neurodegeneration and knowledge on translational clinical design.

## Indicative duration of the action

The indicative duration of the action is 60 months.

## Indicative budget

The indicative EFPIA in-kind contribution is EUR 9 000 000.

Due to the global nature of the participating industry partners, it is anticipated that some elements of the contributions will be non-EU/H2020 Associated Countries in-kind contributions<sup>30</sup>.

The financial contribution from IMI2 is 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 (in which it would be of value to also include SMEs having relevant know-how and technologies) is expected to address all the objectives and make key contributions to the defined deliverables in synergy with

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<sup>30</sup> Note: This does not however constitute the justification referred to in Article 4(2) of the IMI 2 JU regulation.

the industry consortium which will join the selected applicant consortium in preparation of the full proposal for stage 2.

The applicant consortium should be able to demonstrate the full scope of expertise in order to address effectively and meet all goals outlined in this topic. This may require mobilising, as appropriate: expertise ranging from translational medicine, *in vivo* models of neurodegeneration, biomarker development to data and knowledge management, project management and professional communication expertise. In particular the following expertise and resources are highly relevant:

- Know-how on state-of-the-art BBB model (iPSC or progenitor-based would be high priority but any other cell model are acceptable), including 3D models, microfluidics or spheroids. Experience in this field would allow generation of innovative approaches to *in vitro* BBB modelling, from classical Transwell® models to more sophisticated, more *in vivo* like models.
- Expertise in mathematical/*in silico* modelling of BBB/blood-CSF-barrier and PK of therapeutics in CNS.
- Expertise and access in/to iPSC- or progenitors-derived endothelial cell models in mono- and co-cultures.
- Expertise in the biology of molecular transport systems of the BBB (endocytosis, receptor- or absorptive-mediated transcytosis, endosomal trafficking etc.), in discovery and characterisation of novel targets/mechanisms more specific for brain delivery, and in the design and development of delivery systems, such as antibodies, bispecific antibodies, liposomes/nanoparticles, aptamers, affimers, etc.
- Expertise and access to disease models in particular models of neurodegenerative diseases such as AD, PD, vascular dementia, MS, ALS, neuropathic/chronic pain, metabolic diseases of central mechanisms. In order to be able to assess the translatability of the developed *in vitro* models and to establish an *in vitro-in vivo* correlation, state-of-the-art disease models are needed.
- Expertise and know-how in the study of neurotropic viruses and their brain-penetrating mechanisms.

## Suggested architecture of the full proposal

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

The final architecture of the full proposal will be defined by the full proposal applicants 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 IMI 2 JU call topics are built on identified scientific priorities agreed together with EFPIA beneficiaries/large industrial beneficiaries, these beneficiaries intend to significantly contribute to the programme leadership and project and financial management.

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

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

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

It is suggested to organize the work-plan into six main themes (each corresponding to a specific work package, see chart at the end of the document):

### **Work package 1 – Selection of genes or pathways candidates associated with neurodegenerative diseases, expressed in brain endothelial cells and/or the neurovascular unit (NVU)**

Targets identified by different approaches like:

- genetic analyses of existing data (GWAS, other published databases);

- transcriptomic and proteomic profiling of patient primary brain endothelial cells, cells from the neurovascular unit or tissues;
- transcriptomic and proteomic profiling of preclinical disease models primary brain endothelial cells, cells from the neurovascular unit or tissues;
- glycomics of BBB cells and/or cerebral vasculature of diseased brains.

Deliverables: disease-associated or differentially expressed genes and/or pathways which play roles in the alteration of BBB integrity and transport mechanisms in endothelial cells/cells of the NVU of potential importance to brain delivery.

EFPIA contribution: patients primary cells, omics, genetic analyses, preclinical disease models.

Applicant consortium contribution: genetic analyses, omics.

### **Work package 2 – Phenotypic validation of the identified genes and/or pathways in brain endothelial cells/NVU:**

This could be achieved in four steps:

- generation of endothelial cells from iPSC or Progenitors;
- generation of iPSC cells from primary cells from patients;
- induce mutations of genes/pathways involving BBB permeability and transport by genome editing (such as CRISPR cas9 technology);
- produce evidence for phenotypic or transport differences in monocultures or 3D/co-cultures.

Many parameters could be analysed such as glucose and amyloid transport, immune cell migration, permeability to other specific proteins or toxics. The clones displaying phenotypic differences between healthy and disease situation might be prioritised for further work.

Deliverables: validated disease-specific or differentially expressed genes and/or pathways of potential relevance to brain transport.

EFPIA contribution: iPSC cells or progenitors, differentiation into endothelial cells and other cell types (astrocytes, pericytes, neurons...), monocultures, 3D/co-cultures, CRISPR.

Applicant consortium contribution: iPSC or progenitor cells, CRISPR, Benchmark tools and methods for transport analysis and other phenotypic investigations (IgG's, TfR Ab, InsR Ab ...).

### **Work package 3 – Develop best state-of-the-art (e.g. hiPSC- or progenitor-derived) BBB models (mono- or co-cultures, 3D, etc.) by differentiation into endothelial cells and barrier formation characterisation**

This could be done using mono- or co-cultures, 3D-setting, microfluidics or other settings by differentiation into brain endothelial cells and barrier formation characterisation. Full characterisation such as apical/basolateral receptor activity would be essential. The model would be considered as validated if it is able to predict *in vivo* exposures of biopharmaceuticals in the various disease or normal state. A last step would be the employment of validated models to further elucidate mechanistic studies pertaining to BBB absorption biology and transport mechanisms.

Mathematical/*in silico* modelling of receptor-/carrier-mediated transcytosis across the BBB (the capacity of each receptor in mediating transcytosis and brain delivery), and PK of biopharmaceuticals in the brain (particularly the PK and clearance of antibodies/proteins in ISF, neurons, and CSF) should be also a part of this characterisation, including disease conditions (such as the expression levels of relevant receptors, carriers and proteins).

Deliverables: characterise apical/basolateral receptor activity, validate model with a set of reference compounds with known *in vivo* BBB transport data, validate candidates *in vitro*; a more in-depth understanding of the fundamentals and principles of absorption-/receptor-mediated processes of transcytosis across brain capillary endothelial cells and validate candidates *in vitro*. At least one *in vitro* BBB-model and an *in silico* model reproducing/predicting disease features and BBB permeability *in vivo* are expected.

EFPIA contribution: BBB models, microfluidics, organ on a chip, spheroid technologies.

Applicant consortium contribution: benchmark tools for transport analysis (IgG's, TfR Ab, InsR Ab, small molecules with available *in vivo* neuro PK data); *in silico* modelling; complex 3D cell systems.

#### **Work package 4 – Characterisation of neurotropic virus-based BBB and brain penetration mechanisms**

A number of neurotropic viruses are capable of entering the CNS to infect neurons and/or glial cells, such as rabies virus, JC (John Cunningham) virus, West Nile virus, adeno-associated virus (AAV) variants. However, the mechanisms by which those viruses either penetrate the BBB or retrograde transport from peripheral nerve to CNS are not fully characterised. Understanding the mechanisms may help in the development of drug delivery technologies selective or specific to CNS.

Different approaches may be employed to characterise the mechanisms and/or to identify the targets/proteins/peptides for brain penetration:

- genetic and proteomics analyses of the viral genes, proteins and protein fragments for their interactions with human cells and proteins;
- cellular, molecular and biochemical characterisation of viral interactions with cellular proteins and/or receptors and virus-mediated penetration of BBB or peripheral nerve/neuronal cells;
- preparation and testing of viral particles (empty viral vesicles) for interactions and penetration across the BBB *in vitro* or *in vivo* animal models;
- viral proteins or protein fragments if identified for BBB penetration may be employed to functionalize liposomes and/or nanoparticles for crossing the BBB *in vitro* and/or *in vivo* animal models.

Deliverables: viral proteins and protein fragments and/or viral mechanisms and human proteins/receptors which play roles in virus-mediated BBB and CNS penetration.

EFPIA contribution: human cells, omics/genetic analyses.

Applicant consortium contribution: genetic analyses, omics, virology, *in vitro* and *in vivo* models.

#### **Work package 5 – Follow-up on identification and characterisation of new potential targets from WP1/WP2/WP4 for brain delivery.**

These targets could be investigated as new mechanisms of brain delivery. Building and providing tools and models for validation of the new mechanisms would be full part of this package (Ab's, ligands, cell lines). Testing tools against these novel targets *in vivo* will be an important aspect of the validation strategy as well. This could be done in disease models as well as in healthy wild-type model systems.

Deliverables: tools for validation and characterisation of the new mechanisms and targets (Ab's, ligands, cell lines). *In vivo* set ups for validation (including e.g. imaging). Validated new brain-delivery targets (by demonstration of increased *in vivo* brain exposure of Ab or ligand of the target). Validated new neurovascular target with potential for brain delivery in a neurodegenerative disease in disease models or validated such virus-based targets.

EFPIA contribution: preclinical disease models.

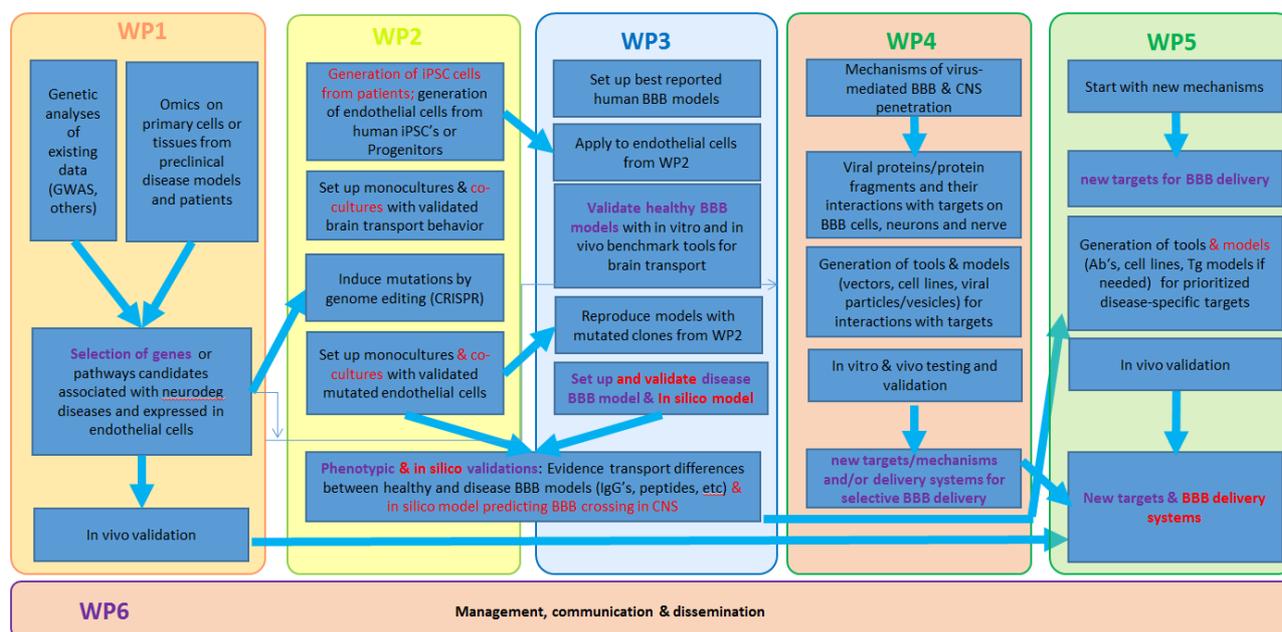
Applicant consortium contribution: tools for validation of the new mechanisms (Ab's, ligands, cell lines); *in vivo* PK; disease models.

The new targets identified in WP1 WP2 and WP4 should be fully characterised.

#### **Work package 6 – Management, communication & dissemination**

This work-package should be designed to be fit for purpose to govern and implement the project as a successful public-private partnership and cover all necessary activities for its governance, management, communication and dissemination. It should also include activities to ensure proper data and knowledge management of the results following the H2020 rules and guidelines.

## Flow Chart of Proposed Project



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## Glossary

|             |  |
|-------------|--|
| 3D          | Three dimensional                                    |
| AD          | Alzheimer's disease                                  |
| ALS         | Amyotrophic Lateral Sclerosis                        |
| BBB         | Blood brain barrier                                  |
| BMI         | Bone Mass index                                      |
| CMT         | carrier-mediated transcytosis                        |
| CRISPR/Cas9 | Plasmid Reagents for sgRNA Expression & Gene Editing |
| BhIPSC      | Human induced pluripotent stem cells                 |

|       |   |
|-------|---|
| EFPIA | European Federation of Pharmaceutical Industries and Associations |
| MS    | Multiple sclerosis  |
| NGS   | Next-generation sequencing  |
| RMT   | receptor-mediated transcytosis                                    |
| PD    | Parkinson's disease   |
| SAR   | Structure activity relationship                                   |
| SME   | Small and medium-sized enterprises                                |
| T2D   | Type II diabetes  |
| WP    | Work package  |

## Topic 7 : European Screening Centre: unique library for attractive biology (ESCulab)

### Topic details

|                                 |                                       |
|---------------------------------|---------------------------------------|
| Topic code                      | IMI2-2017-12-07                       |
| Action type                     | Research and Innovation Actions (RIA) |
| Submission & evaluation process | 2 Stages                              |

### Specific challenges to be addressed

The translation of novel biological concepts into drug discovery projects critically requires chemical matter that has the potential to become a valuable tool in the treatment of a disease [1]. The leveraging of basic biological research of SMEs, academia and their spin-offs into drug discovery and clinical applications still suffers from a scarcity of suitable chemical starting points that can be optimised into clinical candidate molecules allowing safe evaluation in patients. One of the key barriers is access to high-quality compound libraries and high throughput screening facilities.

Since January 2013, the European Lead Factory (ELF) project (<http://www.europeanleadfactory.eu>) [2] [3] a public-private consortium, has offered a unique high quality compound library and state-of-the-art industrial ultra-high throughput screening (uHTS) capabilities to targets submitted by the public (public targets). By having their targets screened on the compound library at this top tier screening facility, public target owners<sup>31</sup>, including biotechs/SMEs, obtain a qualified hit list (QHL) that can be used either as probe compounds to pre-clinically validate a disease hypothesis or as starting point for lead finding and optimisation. Participating pharmaceutical companies benefit from the mutual sharing of their respective libraries and early partnering opportunities with public target owners.

The ELF project is scheduled to finish at the end of 2017, but the necessity for public target owners to access high-quality compound libraries and high throughput screening facilities remains.

### Need and opportunity for public-private collaborative research

Universities, research organisations and SMEs have a diverse range of potential drug targets but cannot easily access suitable compound libraries and screening facilities. Pharmaceutical companies need access to high quality targets in order to bring innovative therapies to patients. Combining the large high-quality compound libraries held by the pharmaceutical industry with the innovative targets held by academic organisations in a public-private partnership offers an ideal platform to transform biological discoveries into medicines.

Confirmed HTS hits and leads are the chemical starting points for significant further investment to produce clinical candidates, and, eventually, new medicines. As such, a neutral, trusted honest broker is needed to facilitate sharing of confidential assay and compound data. In addition, all parties bringing targets [background] to the project (target owners) must be confident that they retain their rights to that background and are also able, where possible, to further exploit the resulting developments of their contribution.

Facilitating such a platform through a neutral, SME-led compound management and uHTS screening facility will allow all partners to participate in confidence that their targets will be screened in an independent way with maximal protection of their intellectual property. ESCulab will also provide the opportunity for academics /

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<sup>31</sup> The term 'public target owners' used throughout this text refers to academic groups, biotechs, SMEs, charity organizations and patient foundations.

SMEs to collaborate with EFPIA partners and see their projects moving ahead along the value chain, whereas the pharmaceutical companies have a chance to tap into innovative academic biology. ESCulab will also significantly lower the hurdles for charity organisations or patient foundations that want to initiate drug discovery in their specific field of interest.

## Scope

### 1. Screening library

The core of the ESCulab library will ideally consist of 350 000 compounds from the pharmaceutical companies, and 200 000 compounds provided by the short proposal applicant consortium. Additional compounds may be added if further pharmaceutical companies join. The 200 000 compounds contributed by the applicant consortium must be novel, drug-like, not commercially available, and show a high fraction of sp<sup>3</sup> hybridised carbon atoms (sp<sup>3</sup> count > 0.48, MW ~430, clogP ~2.3) without structural overlap with four reference libraries: The Maybridge Screening Collection, Molecular Libraries and Small Molecule Repository (MLSMR), ChEMBL and eMolecules [4] [5] [6].

### 2. Compound logistics and uHTS screening facilities

Appropriate industry-like infrastructure, including laboratory automation / robotics to support both compound logistics and HTS will be provided, as well as: firewalled IT solutions to support the compound management of the compound library; HTS data management from quality control to chemo-informatic analysis of HTS results; the evaluation and confirmation of hits through medicinal chemistry follow-up activities.

### 3. Assay development

In order to access a broad range of innovative biology, ESCulab will support the conversion of public target assays into an automation-friendly format, both in target-focused and phenotypic approaches.

### 4. Screening

ESCulab is expected to run 50 public programmes. The project is also expected to develop a strategy to enable the screening of externally-funded screens on top of the IMI-funded activities. Each industry partner will schedule 20 programmes or 10 programmes, the IMI2 Associated Partner 5 programmes (135 screens in total, including phenotypic screens). The inclusion of phenotypic screening will allow the development of cellular models of increasingly more translational value using, for instance, patient derived material or human induced pluripotent stem (iPS) cell-derived phenotypes.

### 5. Hit Confirmation

The outcome of the screening campaign should be a qualified hit list (QHLs) with max. 50 compounds.

### 6. Long-term sustainability

In addition to the IMI2 JU-funded screens, ESCulab should offer screening on targets proposed by charity organisations, patient foundations and other organisations against external funding. Thus, it should establish itself as the centre for translating basic biology into chemical matter. Mechanisms and terms and conditions to secure maintenance and continued access to the compound library after termination of ESCulab will be negotiated with the partners providing compounds.

## Expected key deliverables

### 1. Screening Centre

The screening centre will host the compound library and manage the logistic processes around the library to support compound logistic processes for up to 37 HTS projects per year. The screening centre will also support assay development and perform HTS campaigns & follow-up tests for academic groups, biotechs, SMEs, charity organisations and patient foundations.

### 2. Hit Confirmation

Responsible for providing a list of confirmed hits constituting the QHL which affords medicinal chemistry expertise.

### 3. Sustainability plan

A business model based on fee-for-service and milestone-based income to ensure self-sustainability at the end of the ESCulab period; the funding of screens by charity organisations or patient foundations already during the ESCulab term serves to explore the business model.

Establishing the maintenance of the compound library beyond the lifetime of the ESCulab project.

## Expected impact

The project is intended to lower the hurdles for academic groups and SMEs to translate early innovative biology into chemical series that have the potential to be optimised into drug candidates. The delivery of up to 50 public and 135 EFPIA/IMI2 AP QHLs should create value from the libraries and cut timelines to arrive at clinical proof of concept in diseases with unmet medical need, such as cancer, immunological, respiratory, neurological and neurodegenerative diseases<sup>32</sup>, anti-infectives, and neglected (tropical) diseases.

By including phenotypic screening that mimics cellular events relevant in disease, hit series that show clear structure-activity relationships might trigger target deconvolution activities that ultimately might lead to the discovery of novel pathways / drug targets.

Including SMEs in the applicant consortium should contribute to strengthening the competitiveness and industrial leadership of Europe.

To ensure the maximum impact of the project and stimulate the significant future investment needed to develop the project results into new medicines, it is necessary for the target owners to secure ownership of the results of their screens. Therefore, in the short proposal, the applicants must briefly demonstrate that they can provide target owners with this security by, for example, developing a strategy for the transfer of ownership upon generation of the screening results to the target owners. This strategy should be further determined between the parties at the full proposal stage and the terms be agreed between the beneficiaries as part of the consortium agreement.

At the end of the IMI funding term, there must be a self-sustainable, well recognised screening centre with access to a high-quality library which adopts a business model relying on externally funded screens.

ESCulab should be the operational partner of choice for scientists to bring modulation of their targets with small molecules from theory into practice.

## Potential synergies with existing consortia

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

Applicants should consider any relevant projects from IMI, FP7, H2020, as well as other relevant European research infrastructures such as **EU-OPENSREEN** ([www.eu-openscreen.eu](http://www.eu-openscreen.eu)) and other initiatives outside the EU. With respect to IMI projects:

- **European Lead Factory** ([www.europeanleadfactory.eu/](http://www.europeanleadfactory.eu/))
- The ESCulab consortium should liaise with the ELF so that the libraries and target programmes not fully exploited within ELF could be carried through to ESCulab. Also, they should explore whether the ELF database could be used as a resource to support ESCulab hit selection activities.

Projects potentially allowing access to novel screening assays

- **BTCure** ([www.btcure.eu/](http://www.btcure.eu/)), **UltraDD** ([www.ultra-dd.org/](http://www.ultra-dd.org/)), Autism Spectrum Disease (IMI2 Call 10) for potential targets;
- **ND4BB (New Drugs for Bad Bugs)**, ([www.nd4bb.eu/](http://www.nd4bb.eu/)) to discover and develop new, effective antibacterial strategies for the treatment of infections caused by antibiotic-resistant pathogens;
- **NEWMEDS** ([www.newmeds-europe.com/](http://www.newmeds-europe.com/)) to identify biomarkers to allow more targeted treatments for schizophrenia and depression;

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<sup>32</sup> Council Regulation (EU) No 557/2014, art. 2 (ii) and (iii). <http://eur-lex.europa.eu/legal-content/EN/TXT/?uri=CELEX%3A32014R0557>

- **EUROPAIN** ([www.imieuropain.org/](http://www.imieuropain.org/)), to better understand chronic pain mechanisms to aid the development of novel analgesics;
- **IMIDIA** ([www.imidia.org/](http://www.imidia.org/)) to generate novel tools and fundamental knowledge on  $\beta$ -cell organisation to accelerate the path to improved diabetes management;
- **PREDECT** ([www.predect.eu/](http://www.predect.eu/)) to develop new models for novel treatment for cancers of the breast, prostate, and lung;
- **PHAGO** ([www.phago.eu/](http://www.phago.eu/)) to discover novel drug targets along TREM2/CD33 pathway in Alzheimer's disease.

## Industry consortium

The industry consortium is composed of the following EFPIA companies

- Bayer (lead)
- AstraZeneca
- Grünenthal
- Janssen
- Merck
- Sanofi
- Servier
- UCB

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

- Malaria Medicine Ventures

The companies in the industry consortium will bring at least 350 000 screening compounds at the beginning of the project and run 130 screens in their own facilities. The IMI2 JU associated partner will run 5 screens at the ESCulab facility.

After the establishment of an agreement on appropriate access rights terms, and until the submitted compounds have been consumed, EFPIA companies will allow their compound set to be offered to charity organisations and patient foundations for externally funded screening, on terms and conditions to be decided.

## Indicative duration of the action

The indicative duration of the action is 60 months.

## Indicative budget

The indicative in-kind contribution is EUR 18 250 000. This contribution comprises an indicative EFPIA in-kind contribution of EUR 17 500 000 and an indicative IMI2 Associated Partners in-kind contribution of EUR 750 000.

The financial contribution from IMI2 JU is a maximum of EUR 18 250 000.

## Applicant consortium

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

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

- Strong European-wide network for public target recruitment with outreach to ongoing and future IMI projects and other European and national initiatives.
- Professional, industry-like management of compound logistics process centred around a single entity for the collection, storage, distribution and management of the ESCulab compound library.
- The consortium must include a specialised party ('honest data broker') who can manage and broker (blinded and un-blinded) confidential information on compounds and screening results data according to the honest data broker concept, i.e. one single, centralised unit with dedicated staff bound by confidentiality and non-use obligations.
- Strong experience in assay development, miniaturisation, validation for HTS both employing platform techniques and introducing novel experimental approaches. Capabilities to develop HTS/HCS ready target-focused and phenotypic cellular assays.
- Extensive experience in the execution of HTS to industry standards, providing solutions also for complex experimental protocols, e.g. with multiple liquid handling and signal detection steps, kinetic readouts, etc. Necessary expertise in molecular and cellular pharmacology and medicinal chemistry to drive a rigorous hit characterisation process.
- Industrial-like experience and proven track record for successful hit confirmation including expertise in medicinal chemistry and pharmacology.
- Extensive experience in applying IT solutions to the management of compound collections, HTS data management from quality control to chemo-informatic analysis of HTS results.
- Project management capabilities supporting overall governance and steering and experience developing business plans to ensure the long-term sustainability of the project.

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

- A library of approximately 200 000 screening compounds. Applicants should demonstrate that their compounds are suitable for HTS, i.e. novel, drug-like, not commercially available, with high  $sp^3$  count ( $sp^3$  count > 0.48, MW ~430, clogP ~2.3), clearly differentiated from vendor libraries.
- A centralised facility for carrying out the HTS screening operations on the targets originating from public target owners. Preferably, the HTS screening operations are performed in a country with a research exemption limiting IP complexity.
- Software to support the blinding and un-blinding of information
- A firewalled IT infrastructure to handle data related to the compound library.

In their short proposal, applicants should provide an initial plan for the sustainability of the platform beyond the IMI2 JU funding term. This outline plan should also benchmark the proposed ESCulab project against existing screening infrastructures.

## Suggested architecture of the full proposal

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

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

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

efficient negotiation of project content and required agreements. All beneficiaries are encouraged to discuss the project architecture and governance and the weighting of responsibilities and priorities therein.

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

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

### **Industry contribution**

All EFPIA participants contribute screening compounds as indicated above and will run screens of the compound library in the course of the ESCulab project. Assay development and screening efforts are EFPIA participants' in-kind contributions. With these in-kind contributions, EFPIA participants enhance the database for developing public QHLs and increase the value of hits from the public compound collection. For the sustainability of the platform beyond the ESCulab lifetime, the EFPIA partners will negotiate terms to maintain the compound library after the project ends.

### **Work package 1 – Programme recruitment**

With a strong emphasis on innovative biology, recruitment of targets and biology amenable to phenotypic screens need to be gathered across Europe intensively with the entrance barriers considerably lowered for ESCulab.

Over a 4 year period of target sourcing, the goal should be to recruit more than 100 proposals.

Programmes from other IMI projects will be proactively sought and will include:

- proposals that still require assay development activities;
- phenotypic, target-agnostic programmes;
- targets from foundations and charities worldwide to reserve screening slots in exchange for a monetary contribution.

Targets can be screened several times, but qualified hits will be removed from the compound library.

### **Expected applicant consortium contribution:**

Professional target / programme recruitment acquiring 100+ public proposals from academics / SMEs over four years for selection. Therefore, a strong European-wide network for public target recruitment with focused outreach to ongoing and future IMI projects is essential.

### **Work package 2 – Review and selection**

The review and selection of target proposals offers an opportunity to connect target owners to pharma partners early on. Therefore, the review body must be staffed with external experts and EFPIA delegates. Targets proposed by charities and foundations who fund the screen are exempt from the review process.

### **Work package 3 – Compound logistics**

Hosting the physical compound collection, plating and distributing screening decks and samples for retests is the remit of this work package. Costs incurred should be in alignment with benchmarking references.

Once fully operational, the centre will need to accommodate resources sufficient to support compound logistic processes for up to 37 HTS projects per year (10 from public projects, 27 from EFPIA projects) providing plated copies of the compound library for public and pharma screening programmes.

- The pharma companies will receive a copy of the library and perform the screening at their disposal in a blinded fashion.

### **Expected applicant consortium contribution:**

- Professional, industry-like management of the compound logistics process centred around a single entity for the collection, storage, distribution and management of the ESCulab compound library.

#### **Work package 4 – Assay development**

Allowing for target proposals which are not yet assay-ready and phenotypic programmes requires an effort in assay development and screening. The adaption of academic test systems to suitable HTS formats needs professional expertise and needs to be properly staffed. For pharma screens the assay development will be done at the pharma partners' facilities, as follows:

- Development and/or adaptation of target or pathway-specific bioassays for HTS;
- Development and/or adaptation of phenotypic assays.

#### **Expected applicant consortium contribution:**

A proven track-record in assay development. A track-record in automated image capturing and multi-parametric automated image analysis will be crucial to master phenotypic assay development. The applicant consortium is expected to progress the 5 projects of the associated EFPIA partner from assay development through QHL.

#### **Work package 5a – Target-based ultra high throughput screening**

##### **Industry contribution:**

EFPIA screens will be run at pharma screening sites or their selected subcontractors.

##### **Expected applicant consortium contribution:**

Industry-like uHTS infrastructure and expertise (e.g. proven experience in 1536 MTP format HTS)

#### **Work package 5b – Target-agnostic cellular screening**

##### **Industry contribution:**

EFPIA phenotypic screens will be run at pharma screening sites or their selected subcontractors.

##### **Expected applicant consortium contribution:**

Industry-like equipment and know-how (endpoints, counter-screens) to run phenotypic assays in a high throughput format (1536 MTP format, at least 384 low volume MTP format).

#### **Work package 6 – Hit characterisation and confirmation**

- Re-synthesis of hits and confirmation of activities to assemble a qualified hit list (QHL).
- Support the assembly of a programme dossier for an option notice for public target owners.

##### **Expected applicant consortium contribution:**

Industrial-like experience and proven track record for successful hit confirmation including respective expertise in medicinal chemistry and pharmacology.

#### **Work package 7 – Information technology**

The honest data broker will be the data repository to handle IP sensitive information in a secure manner, and an annotated data source for hit-to-lead activities and library analyses.

#### **Work package 8 – Project management**

Overarching project management independent from the day to day consortium activities should steer the administrative aspects referring e.g. to budget and legal aspects including continuous legal support.

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## Glossary

|       |   |
|-------|---|
| EFPIA | European Federation of Pharmaceutical Industries and Associations |
| ELF   | European Lead Factory   |
| HCS   | High Content Screening  |
| HDB   | Honest Data Broker  |
| HTS   | High Throughput Screening   |
| IP    | Intellectual Property   |
| iPSC  | induced Pluripotent Stem Cell                                     |
| MLSMR | Molecular Libraries and Small Molecule Repository                 |
| PK    | Pharmacokinetics  |
| QHL   | Qualified Hit List  |
| SMEs  | Small and Medium-sized Enterprises                                |
| 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](https://ec.europa.eu/research/participants/portal/doc/call/h2020/common/1595113-h2020-rules-participation_oj_en.pdf)), the Commission Delegated Regulation with regard to IMI2 JU (<http://eur-lex.europa.eu/legal-content/EN/TXT/PDF/?uri=CELEX:32014R0622&from=EN>) and the relevant general conditions of the IMI2 JU AWP2017.

Applicants intending to submit a Short proposal in response to the this first 2017 Call should read this topics text, the [IMI2 JU Manual for submission, evaluation and grant award](#) and other relevant documents (e.g. [IMI2 JU model Grant Agreement](#)).

|  |   |
|--|---|
| <b>Call Identifier</b>                               | <b>H2020-JTI-IMI2-2017-12-two-stage</b>         |
| <b>Type of actions</b>                               | <b>Research and Innovation Actions (RIA)</b>    |
| <b>Publication Date</b>                              | <b>19 July 2017</b>                             |
| <b>Stage 1 Submission start date</b>                 | <b>19 July 2017</b>                             |
| <b>Stage 1 Submission deadline</b>                   | <b>24 October 2017 (17:00:00 Brussels time)</b> |
| <b>Stage 2 Submission deadline</b>                   | <b>16 May 2018 (17:00:00 Brussels time)</b>     |
| <b>Indicative Budget</b>                             |   |
| From EFPIA companies and IMI2 JU Associated Partners | EUR 62 362 000                                  |
| From the IMI2 JU                                     | EUR 64 077 000                                  |

## Call Topics

|                        |   |   |
|------------------------|---|---|
| <b>IMI2-2017-12-01</b> | The indicative contribution from EFPIA companies will be EUR 2 830 000<br>The indicative IMI2 JU Associated Partners contribution will be 725 000<br>The financial contribution from IMI2 JU will be a maximum of EUR 5 000 000 | Research and Innovation Actions (RIA)<br>Two-stage submission and evaluation process.<br>Only the applicant consortium whose proposal is ranked first at the first stage is invited for the second stage. |
| <b>IMI2-2017-12-02</b> | The indicative contribution from EFPIA companies will be EUR 3 730 000<br>The financial contribution from IMI2 JU will be a maximum of EUR 4 000 000  | Research and Innovation Actions (RIA)<br>Two-stage submission and evaluation process.<br>Only the applicant consortium whose proposal is ranked first at the first stage is invited for the second stage. |
| <b>IMI2-2017-12-03</b> | The indicative EFPIA in-kind contribution will be EUR 8 200 000<br>The financial contribution from IMI2 JU will be a maximum of EUR 8 200 000   | Research and Innovation Actions (RIA)<br>Two-stage submission and evaluation process.<br>Only the applicant consortium whose proposal is ranked first at the first stage is invited for the second stage. |

|                        |  |   |
|------------------------|--|---|
| <b>IMI2-2017-12-04</b> | The indicative EFPIA in-kind contribution will be EUR 14 127 000<br>The financial contribution from IMI2 JU will be a maximum of EUR 14 127 000  | Research and Innovation Actions (RIA)<br>Two-stage submission and evaluation process.<br>Only the applicant consortium whose proposal is ranked first at the first stage is invited for the second stage. |
| <b>IMI2-2017-12-05</b> | The indicative EFPIA in-kind contribution will be EUR 5 500 000<br>The financial contribution from IMI2 JU will be a maximum of EUR 5 500 000  | Research and Innovation Actions (RIA)<br>Two-stage submission and evaluation process.<br>Only the applicant consortium whose proposal is ranked first at the first stage is invited for the second stage. |
| <b>IMI2-2017-12-06</b> | The indicative EFPIA in-kind contribution will be EUR 9 000 000<br>The financial contribution from IMI2 JU will be a maximum of EUR 9 000 000  | Research and Innovation Actions (RIA)<br>Two-stage submission and evaluation process.<br>Only the applicant consortium whose proposal is ranked first at the first stage is invited for the second stage. |
| <b>IMI2-2017-12-07</b> | The indicative EFPIA in-kind contribution will be EUR 17 500 000<br>The indicative IMI2 JU Associated Partners contribution will be 750 000<br>The financial contribution from IMI2 JU will be a maximum of EUR 18 250 000 | Research and Innovation Actions (RIA)<br>Two-stage submission and evaluation process.<br>Only the applicant consortium whose proposal is ranked first at the first stage is invited for the second stage. |

The following general conditions shall apply to the IMI2 JU Calls for Proposals:

## List of countries and applicable rules for funding

By way of derogation<sup>33</sup> 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;

<sup>33</sup> 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

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

(c) the Joint Research Centre;

(d) international European interest organisations.

Participating legal entities listed in (b) above established in a third country may receive funding from the IMI 2 JU provided their participation is deemed essential for carrying out the action by the IMI 2 JU or when such funding is provided for under a bilateral scientific and technological agreement or any other arrangement between the Union and the country in which the legal entity is established<sup>34</sup>.

## Standard admissibility conditions and related requirements

Part B of the General Annexes<sup>35</sup> to the Horizon 2020 – Work Programme 2016 – 2017 shall apply *mutatis mutandis* for the actions covered by this Call for proposals.

In addition, page limits will apply to proposals as follows:

At stage 1 of a two-stage call, the limit for short proposals is 30 pages.

For stage 2 of a two-stage call, the limit for full proposals is 70 pages.

## Eligibility conditions

Part C of the General Annexes to the Horizon 2020 – Work Programme 2016 – 2017 shall apply *mutatis mutandis* for the actions covered by this Call for proposals.

In addition, under all two-stage submission procedures the following additional condition applies:

The participants from EFPIA constituent entities and affiliated entities and other Associated Partners which are pre-defined in the topics – under the section ‘Industry consortium’ – of a call for proposals do not apply at the stage 1 of the call. The applicant consortium selected from the stage 1 of the Call for Proposals is merged at the stage 2 with the EFPIA constituent entities or their affiliated entities and other Associated Partners.<sup>36</sup>

## Types of action : specific provisions and funding rates

Part D of the General Annexes to the Horizon 2020 – Work Programme 2016 – 2017 shall apply *mutatis mutandis* for the actions covered by this Call for proposals.

## Technology readiness levels (TRL)

Part G of the General Annexes to Horizon 2020 – Work Programme 2016 – 2017 shall apply *mutatis mutandis* for the actions covered by this Call for proposals.

## Evaluation rules

Part H of the General Annexes to the Horizon 2020 – Work Programme 2016 – 2017 shall apply *mutatis mutandis* for the actions covered by this Call for proposals:

### Award criteria and scores:

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<sup>34</sup> In accordance with Article 10(2) of the Regulation (EU) No 1290/2013 and Article 1 of Commission Delegated Regulation (EU) No 622/2014

<sup>35</sup> [http://ec.europa.eu/research/participants/data/ref/h2020/other/wp/2016-2017/annexes/h2020-wp1617-annex-ga\\_en.pdf](http://ec.europa.eu/research/participants/data/ref/h2020/other/wp/2016-2017/annexes/h2020-wp1617-annex-ga_en.pdf)

<sup>36</sup> Article 9(5) of the Regulation (EU) No 1290/2013 of the European Parliament and of the Council of 11 December 2013 laying down the rules for participation and dissemination in “Horizon 2020”

Experts will evaluate the proposals on the basis of criteria of “Excellence”, “Impact” and “Quality and efficiency of the implementation” according to the submission stage and type of action, as follows:

| Type of action   | Excellence  | Impact   | Quality and efficiency of the implementation <sup>37</sup>   |
|--|---|--|--|
| <b>RIA and IA<br/>1st stage<br/>evaluation</b>                           | <p>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:</p> <p>Clarity and pertinence of the proposal to meet all key objectives of the topic;</p> <p>Credibility of the proposed approach;</p> <p>Soundness of the concept, including trans-disciplinary considerations, where relevant;</p> <p>Extent that proposed work is ambitious, has innovation potential, and is beyond the state of the art;</p> <p>Mobilisation of the necessary expertise to achieve the objectives of the topic, ensure engagement of all relevant key stakeholders</p> | <p>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:</p> <p>The expected impacts of the proposed approach as mentioned in the call for proposals</p> <p>Added value from the public private partnership approach on R&amp;D, regulatory, clinical and healthcare practice as relevant;</p> <p>Strengthening the competitiveness and industrial leadership and/or addressing specific societal challenges;</p> <p>Improving European citizens' health and wellbeing and contribute to the IMI2 objectives<sup>38</sup>.</p> | <p>The following aspects will be taken into account:</p> <p>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;</p> <p>Complementarity of the participants within the consortium (where relevant) and strategy to create a successful partnership with the industry consortium as mentioned in the topic description in the Call for proposal;</p> <p>Appropriateness of the proposed management structures and procedures, including manageability of the consortium.</p> |
| <b>RIA and IA<br/>Single<br/>stage, and<br/>2nd stage<br/>evaluation</b> | <p>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:</p> <p>Clarity and pertinence of the proposal to meet all</p>  | <p>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:</p> <p>The expected impacts of the proposed approach as mentioned in the call for proposals;</p> <p>Added value from the public</p>   | <p>The following aspects will be taken into account:</p> <p>Coherence and effectiveness of the project work plan, including appropriateness of the roles and allocation of tasks, resources, timelines and budget;</p> <p>Complementarity of the</p>   |

<sup>37</sup> In a single-stage, or in the second-stage of a two-stage evaluation procedure, experts will also be asked to assess the operational capacity of applicants to carry out the proposed work

<sup>38</sup> Article 2 of the Council Regulation (EU) No 557/2014 of 6 May 2014 establishing the Innovative Medicines Initiative 2 Joint Undertaking (O.J. L169 of 7.6.2014)

| Type of action | Excellence  | Impact   | Quality and efficiency of the implementation <sup>37</sup>   |
|----------------|---|--|--|
|                | key objectives of the topic;<br><br>Credibility of the proposed approach;<br><br>Soundness of the concept, including trans-disciplinary considerations, where relevant;<br><br>Extent that proposed work is ambitious, has innovation potential, and is beyond the state of the art;<br><br>Mobilisation of the necessary expertise to achieve the objectives of the topic, ensure engagement of all relevant key stakeholders. | private partnership approach on R&D, regulatory, clinical and healthcare practice as relevant;<br><br>Enhancing innovation capacity and integration of new knowledge;<br><br>Strengthening the competitiveness and industrial leadership and/or addressing specific societal challenges; Improving European citizens' health and wellbeing and contribute to the IMI2 objectives; <sup>39</sup><br><br>Any other environmental and socially important impacts;<br><br>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. | participants within the consortium (where relevant);<br><br>Clearly defined contribution to the project plan of the industrial partners (where relevant);<br><br>Appropriateness of the management structures and procedures, including manageability of the consortium, risk and innovation management and sustainability plan. |

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

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

For the evaluation of first-stage proposals under a two-stage submission procedure, the threshold for each one of the two first criteria ('excellence' and 'impact') will be 3. There is no overall threshold. For the evaluation of second-stage proposals under a two-stage submission procedure the threshold for individual criteria will be 3. The overall threshold, applying to the sum of the three individual scores, will be 10.

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

The full evaluation procedure is described in the IMI2 JU Manual for submission, evaluation and grant award in line with the H2020 Rules for Participation.<sup>40</sup>

Under the two-stage evaluation procedure, and on the basis of the outcome of the first stage evaluation, the applicant consortium of the highest ranked short proposal<sup>41</sup> (first stage) for each topic<sup>42</sup> will be invited to discuss with the relevant industry consortium the feasibility of jointly developing a full proposal (second stage).

<sup>39</sup> 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)

<sup>40</sup> [http://www.imi.europa.eu/sites/default/files/uploads/documents/IMI2\\_CallDocs/IMI2\\_ManualForSubmission\\_v1.5\\_July2017.pdf](http://www.imi.europa.eu/sites/default/files/uploads/documents/IMI2_CallDocs/IMI2_ManualForSubmission_v1.5_July2017.pdf)

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

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

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

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

## Indicative timetable for evaluation and grand agreement

|            | Information on the outcome of the evaluation (single stage, or first stage of a two-stages) | Information on the outcome of the evaluation (second stage of a two stages) | Indicative date for the signing of grant agreement                 |
|------------|---|---|--|
| Two-stages | Maximum 5 months from the submission deadline at the first stage.                           | Maximum 5 months from the submission deadline at the second stage.          | Maximum 8 months from the submission deadline at the second stage. |

## Budget flexibility

Part I of the General Annexes to the Horizon 2020 – Work Programme 2016 – 2017 shall apply *mutatis mutandis* for the actions covered by this Call for proposals.

## Actions involving financial support to third parties

Part K of the General Annexes to the Horizon 2020 – Work Programme 2016 – 2017 shall apply *mutatis mutandis* for the actions selected under topics covered by this Call for proposals.

## Conditions related to open access to research data

Part L of the General Annexes to the Horizon 2020 – Work Programme 2016 – 2017 shall apply *mutatis mutandis* for the actions covered by this Call for proposals.

<sup>41</sup> Under exceptional circumstances, and subject to objective criteria based on grounds which could not be reasonably expected to be known by the evaluation panel, the IMI2 JU Governing Board may decide by motivated decision to invite the next-ranked applicant consortium in priority order.

<sup>42</sup> In cases clearly identified in the relevant call for proposals where a given topic is composed of two or more sub-topics, one short proposal per sub-topic will be invited.

However, should a project “opt-out” of these provisions, a Data Management Plan must still be prepared. A template for the Data Management Plan is available on the [IMI website](#).

## Submission tool

Proposals in response to the IMI2 Call 12 must be submitted on-line, before the call deadline, by the coordinator via the Electronic Submission Service of the Participant Portal:

<http://ec.europa.eu/research/participants/portal/desktop/en/home.html>

No other means of submission will be accepted.

## Others

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

[http://ec.europa.eu/research/participants/data/ref/h2020/other/legal/templ/h2020\\_tmpl-clinical-studies\\_en.pdf](http://ec.europa.eu/research/participants/data/ref/h2020/other/legal/templ/h2020_tmpl-clinical-studies_en.pdf)

In the first stage of a two-stage evaluation procedure, this template should not be submitted. However, applicants may integrate relevant aspects of this information in their short proposal (within the page limit). In the second stage of 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 Annual Work Plan shall not be selected.<sup>43</sup>

In order to ensure excellence in data and knowledge management consortia will be requested to Disseminate scientific publications on the basis of open access<sup>44</sup> (see “Guidelines on Open Access to Scientific Publications and Research Data in Horizon 2020”).

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

Applicants intending to submit a proposal in response to the IMI2 JU Calls should also read the topic text, the IMI2 JU Manual for submission, evaluation and grant award, and other relevant documents<sup>45</sup> (e.g. IMI2 JU model Grant Agreement).

## Consortium agreements

In line with the Rules for Participation and Dissemination applicable to IMI2 actions<sup>46</sup> and the IMI2 model grant agreement, participants in IMI2 actions are required to conclude a consortium agreement prior to grant agreement.

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<sup>43</sup> Article 19 of Horizon 2020 Framework Programme, and Articles 13 and 14 of the Horizon 2020 Rules for Participation.

<sup>44</sup> 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

<sup>45</sup> [http://www.imi.europa.eu/content/documents#calls\\_for\\_proposals\\_-\\_imi\\_2\\_programme](http://www.imi.europa.eu/content/documents#calls_for_proposals_-_imi_2_programme)

<sup>46</sup> Regulation (EU) No 1290/2013 of 11 December 2013 and Commission Delegated Regulation (EU) No 622/2014 of 14 February 2014.