IMI2
5th Call for proposals

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Contents

Introduction

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

- Research related to the future of medicine should be undertaken in areas where societal, public health and biomedical industry competitiveness goals are aligned and require the pooling of resources and greater collaboration between the public and private sectors, with the involvement of small and medium-sized enterprises (SMEs).
- The scope of the initiative should be expanded to all areas of life science research and innovation.
- The areas should be of public health interest, as identified by the World Health Organisation (WHO) report on priority medicines for Europe and the World (2013 update: http://www.who.int/medicines/areas/priority_medicines/en/).

The initiative should therefore seek to involve a broader range of partners, including mid-sized companies[2], from different sectors e.g. biomedical imaging, medical information technology, diagnostic and/or animal health industries (while ensuring gender dimensions are considered). Involving the wider community in this way should help to advance the development of new approaches and technologies for the prevention, diagnosis and treatment of diseases with high impact on public health.

The IMI2 Strategic Research Agenda (SRA) is the main reference for the implementation of research priorities for IMI2 (http://www.imi.europa.eu/sites/default/files/uploads/documents/IMI2_SRA_March2014.pdf). The scientific priorities for 2015 for IMI2 have been prepared based on the SRA, and include health priorities on neurodegenerative diseases, diabetes and metabolic disorders, and medicines adaptive pathways to patients (MAPPs), which are addressed in this call.

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

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

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

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

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

Topic 1: Patient perspective elicitation on benefits and risks of medicinal products, from development through the entire life cycle, to inform the decision-making process by regulators and Health Technology Assessment bodies

Topic details

Topic code	IMI2-2015-05-01
Action type	Research and Innovation Action (RIA)
Submission & evaluation process	2 stages

Background and problem statement

There is an emerging consensus among stakeholders that patients' values and perspectives should inform the decisions taken during the development of medicines as well as during the approval and post-approval phases. Stakeholders recognise that the robustness and transparency of pharmaceutical development, regulatory approval deliberations and health technology assessments (HTA) have been improved by information on patients' values. Such input is not necessarily restricted to preference elicitation on identified benefits and risks but could also include patient input across the entire drug development lifecycle. Specifically, patient perspectives could be very useful to gather insights into the patient experience, such as the major symptoms of the illness, so that the medicines are developed with patient-centric attributes. This information on patients' values and perspectives would aid in the design and execution of drug development, improving the clinical trial experience for patients and ultimately facilitating higher quality decision making by regulators and HTA bodies.

Patient engagement is of increasing importance, with patients desiring to see even greater input into regulatory and reimbursement decision-making. Patients have expressed interest in seeing the decision-making processes of the European Medicines Agency (EMA)/Committee for Medicinal Products for Human Use (CHMP) take patient considerations even more into account, for example, the appropriate design of pre- and post-approval studies and risk management plans. For benefit-risk assessment in particular decisions should take into consideration not only patient reported outcomes but also outcomes that patients regard as relevant, preferred treatment options, impact of the disease and willingness to accept trade-offs between favourable and unfavourable effects.

While stakeholders are in agreement regarding the high value of patient input, it is acknowledged that an appropriate structured approach, including a set of systematic methodologies, is needed for inclusion and engagement of patient perspectives during the development phases as well as during the approval and post-approval phases. This approach should accommodate the requirements of both regulators and HTA bodies. Such patient perspectives could theoretically be provided by individual patients, patient association representatives or by a wider group of patients. It could also come from healthy individuals if preventive therapies are concerned, or from caregivers if care is a critical aspect of the illness or if patients cannot speak on behalf of themselves, for example children or cognitively impaired subjects.

Methodologies for patient value elicitation are available and have been used frequently in market research, in health economics and outcomes research to substantiate real-life evidence and more recently in patient readability (user) testing. However there is no systematic use of these methodologies in the regulatory licensing and HTA processes. Additionally, it is unknown which of the existing methods are optimal to satisfy the needs of multiple stakeholders in diverse situations.

What is missing to date is:

- An understanding of when and under what circumstances patient perspective elicitation on benefits and risks of medicinal products is most valuable, in particular:
    - A process analysis to identify which stages of the drug development life cycle are most suitable for patient involvement and of highest value to the different stakeholders, including patients, industry, regulators and HTA bodies before/during/after the phase III programme. Also missing to date is an outline of the circumstances which are most suitable for patient input, as it may not be very productive to involve patients in likely uncontroversial regulatory decisions or in cases where for example, a sophisticated clinical pharmacology issue is the main obstacle to a positive decision.
    - Recommendations on how and under what terms the results of patient preference studies could be incorporated in marketing authorisation applications, for evaluation by regulators, HTA bodies and payers.
- An understanding of how patient perspective elicitation on benefits and risks can best be performed to inform decision-making processes, in particular:
    - The appraisal of methodologies feasible for use by relevant stakeholders (that are easy to understand and respond to by the patient) and allow gathering and documenting perspectives of a wide patient or subject group. These methods should be characterised based on reliability, required interfaces, and analytical methods to evaluate the data as well as appropriate documentation of the results. The focus should be to identify methods specifically to elicit patient preferences for different benefit and risk outcomes in the treatment of specific diseases or disease areas, capturing weights to quantify the relative attractiveness of those outcomes, patients' willingness to accept uncertainties and adverse effects and identification of factors that influence patient preferences.
    - The evaluation of methodologies providing preferences that are representative of a wider group of patients. Benefit-risk considerations are often different for an individual patient as compared to the larger patient population. The individual patient may have different circumstances to take into consideration including co-morbidities and particular genetic/gender/age profiles. Specific groups affected by the disease may require particular attention based on their mobility or other restrictions. Ultimately, a trade-off must be made between benefits and risks at the individual patient level. It is acknowledged however that regulatory agency decisions will be made at the population level, therefore patient preference input in these decisions has to be representative of a wider group of patients. Systematic research evaluating existing methodologies is needed to ensure that the variability between individual patient perspectives can be captured and that sensitivity analyses are possible to understand the impact of the preferences of various subgroups of patients on the decision. An improved understanding of the variability between individual patient perspectives will facilitate the informed decision-making as to how best to integrate patient preferences into benefit-risk assessments.
- Experience with applying methodology to collect patient preferences:
    - Further establishment of the applicability of methodologies in case studies. Providing a structured approach on when to collect what information in the drug development life-cycle and specifically address the required type of patient input at each stage of the drug development life-cycle.
    - The identification of scientific, regulatory and legal limitations and biases and opportunities of such methodologies. These may well depend on the sponsors conducting such research, i.e., industry, academia, HTA bodies, payers or regulators. Clear rules of engagement are needed. Also, clear rules for the validation of patient preferences across different populations (region, culture, language) are needed.
- Consensus on these issues between patients, physicians, regulators, HTA bodies, academia and industry stakeholders:
    - Despite the strong consensus among stakeholders that patients' values should inform the determination of benefit-risk throughout the lifecycle, there are widely divergent views between stakeholders on how this should be done. Establishing recommendations for guidance designed specifically for the use of preference assessment methods with patients and in the context of

development and regulatory needs will help identify the issues upon which this divergence is based and find common ground for potential implementation in health-care practice.

Need and opportunity for public-private collaborative research

The magnitude and complexity of the issue is such that it can only be addressed by a major public-private-partnership involving a variety of stakeholders. This is a program that cannot be accomplished by an individual research group or company and will require a strong collaborative effort to be successful.

Need

Decisions by regulators, HTA bodies and other decision makers regarding medical treatments are made after the careful evaluation of population-based clinical evidence. To date, there is no similar collection of population-based perspectives or views from patients. It is indisputable that if patients' values are to inform the regulatory decision-making process of regulators and HTA bodies, data regarding patient preferences must also be robust and representative of the patient population. Knowledge of patient values and preferences can also inform the regulator and HTA body decisions in the relevant sub-populations.

To move from the era of individual patient testimony, we must develop the science of patient input. This change in science practice and processes requires a significant evolution within pharmaceutical, regulatory, and HTA bodies and patient communities. A non-competitive public-private partnership is necessary to develop and advance the science, since it is too large an endeavour for any one organisation to effectively address alone. A collaborative approach also contributes to and helps to maintain a commitment to scientific excellence, with the joint research leveraging unique, broad and complementary sets of expertise in resource-efficient ways. Such a partnership will help establish a consensus among stakeholders, who currently have widely divergent views on how patients' views inform the determination of benefit-risk throughout the lifecycle. By identifying the issues upon which this divergence is based, the partnership can find common ground for potential implementation in healthcare practice.

Opportunity

Several regulatory, industry and initiatives have laid the foundations for ways to elicit patient perspectives and preferences and the role of these preferences in regulatory review. The action generated from this topic will build upon these initial efforts, starting with a detailed review, a discussion with their leaders, and an assessment of the most critical next steps. This will provide an understanding of the existing infrastructure for using patient preference studies to inform regulatory decisions. A brief list of these efforts and the web references include:

- Food and Drugs Administration (FDA) Centre for Drug evaluation and Research (CDER)'s Patient-Focused Drug Development: http://www.fda.gov/ForIndustry/UserFees/PrescriptionDrugUserFee/ucm326192.htm
- FDA Centre for Devices and Radiological Health (CDRH) Patient Preference Initiative: http://www.fda.gov/medicaldevices/newsevents/workshopsconferences/ucm361864.htm
- Medical Device Innovation Consortium (MDIC) Patient-centred Benefit-risk project: http://mdic.org/pcbr/
- Health Canada: http://news.gc.ca/web/article-en.do?nid=873619 EMA's pilot project on patient input for drug review: http://www.ema.europa.eu/docs/en_GB/document_library/Other/2014/09/WC500173509.pdf
- Pharmaceutical Research and Manufacturers of America (PhRMA), the Biotechnology Industry Organization (BIO) and other pharmaceutical and patient group organisations detailed commentary to the FDA's request for public comment on strategies to obtain the views of patients during the medical product development process and ways to consider patients' perspectives during regulatory discussions: http://www.regulations.gov/#!docketBrowser;dct=PS;rpp=100;so=DESC;sb=docId;po=0;D=FDA-2014-N-1698

- European Medicines Agency (EMA) initiative for engagement with patients and consumers including the Human Scientific Committees' Working Party with Patients' and Consumers' Organisations (more commonly known as the Patients' and Consumers' Working Party or PCWP)

There are also historical examples where patient groups/associations have provided perspectives to decision making, e.g. European regulators have received input on HIV, Duchenne's Disease and Multiple Sclerosis. Melanoma Patient Network Europe and Myeloma Patients Europe are conducting pilot studies on eliciting patient preferences, under the EMA framework for patient interaction to increase patient involvement in the benefit risk assessment. Recent effort by the patient advocacy group Parent Project Muscular Dystrophy resulted in the group conducting an FDA-attended patient-focused drug development meeting, a patient preference study and being invited by the FDA to draft a guidance document for medical treatment development in Duchene Muscular Dystrophy.

The EFPIA (European Federation of Pharmaceutical Industries Association) Patient Task Force provides a resource of expertise for advice on patient perspectives that should be considered.

Overall objectives

The overall objective of the action is to establish recommendations with the view of supporting the development of guidance for industry, regulators and HTA bodies on how and when in the product life-cycle to consider patient perspectives on benefits and risks of medicinal products to inform the decision-making process by regulators and HTA bodies. This objective would be achieved through a review of existing methodology and selection of methodology to take forward for testing via case studies. Recommendations would be developed based on the experience gained through the case studies.

Applicants are expected to address all the above objectives in the Short Proposal (within the available duration and maximum IMI2 contribution) and demonstrate a relevant strategy for achieving them, through partnership with the industry consortium.

This will have to be fully developed with the industry consortium in the Full Proposal.

Potential synergies with existing consortia

Applicants should take into consideration, while preparing their Short Proposal, relevant national, European, and non-European initiatives. Synergies and complementarities should be considered, building from achievements, and incorporating when possible, data and lessons learnt while avoiding unnecessary overlapping and doubling of efforts. Collaboration by design should be a cornerstone of the proposed strategy.

The proposal should build on achievements and knowledge from relevant IMI projects. In particular the activities of this action would strongly build on the project started by IMI PROTECT WP5 (Benefit-risk integration and representation)/ WP6 (Replication studies) that finished in Q1 2015. http://www.imi-protect.eu/index.shtml).

The following IMI and FP7/H2020 related projects, ongoing funded projects might also be considered:

- IMI project EUPATI: European Patients Academy on Therapeutic Innovation http://www.patientsacademy.eu/index.php/en/.
- IMI project ADVANCE: Accelerated development of vaccine benefit-risk collaboration in Europe http://www.advance-vaccines.eu/?page=home.
- The Advance HTA project (www.advance-hta.eu), which aims in particular at improving the robustness of the evidence on the elicitation of preferences by deriving these in more realistic settings, by drawing on the wider EU citizenship and from within the patient community.
- IMI Coordination and support action (CSA): enabling platform on Medicines Adaptive Pathways to Patients. Planned initiation of this CSA in July 2015.

http://www.imi.europa.eu/sites/default/files/uploads/documents/IMI2 Call4/IMI2 Call4_TopicTextWebFINAL.pdf

A strategy for interacting with the upcoming action that will result from the topic 'Knowledge repository to enable patient focused medicine development' of IMI2 Call 3 should also be considered to evaluate synergies and avoid duplication of efforts http://www.imi.europa.eu/sites/default/files/uploads/documents/IMI2 Call3/IMI2 Call3_TopicTextWebFINAL.pdf.

Synergies with academic institutions such as the Patient-Centered Outcomes Research Institute (PCORI) involved in preference research should be encouraged to leverage existing experience, for example with regard to exploring the possibilities offered in clinical trials for collecting patient feedback and preferences.

Expected key deliverables

Deliverable 1:

- selection of methods of patient perspective elicitation on benefits and risks of medicinal products for further evaluation in case studies;
- recommendations as to how, and at which stage(s) of drug development, such methods could be best applied;
- aligned with the above outputs identification of case studies to evaluate the selected methods of patient perspective elicitation at the recommended stage(s) of drug development;
- define criteria that will be used to assess the case studies.

It is expected that this deliverable is achieved with the first year of the action to allow time for the subsequent deliverables.

Deliverable 2:

- an assessment of the selected methodologies via case studies against the criteria agreed in deliverable 1;
- an assessment of the type of patient input at each stage of the drug development life cycle;

It is expected that this deliverable is achieved within the first four years of the action to allow time for the last deliverable.

Deliverable 3:

Based on experience gained from case studies:

- recommendations to support the development of guidance for industry describing:
    - when and how to include patient preferences to inform benefit-risk decision-making throughout the product life-cycle;
    - a set of methodologies suitable for patient involvement, acceptable to regulators and HTA bodies.
- recommendations to support the development of guidance by regulators and HTA bodies on use of patient preferences to support assessment and licensing decision making, and help regulators to provide useful information to inform doctor-patient decision-making.

Industry Consortium

AbbVie, Actelion, Amgen, Astellas, Astra Zeneca, Bayer, CSL Behring GmbH, Eli Lilly, J&J, MSD, Merck Serono, Novartis, Pfizer, Roche, Sanofi, Takeda

Industry will provide expertise in regulatory, HTA/pricing and reimbursement, R&D, clinical development, clinical trials, benefit-risk assessment, medical and health affairs and communication. The industry consortium will contribute to all deliverables including case studies. The case studies could include (but are not limited to) patient preference elicitation on benefits and risks of medicinal products in development and authorised medicinal products.

Indicative duration of the action

The indicative duration of the action is 60 months.

Indicative budget

The indicative EFPIA in kind contribution will be EUR 6 000 000. Due to the global nature of the participating industry partners and in order to leverage optimal expertise it is anticipated that considerable elements of the EFPIA contribution will be provided from non-EU/H2020 associated countries.

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

Applicant consortium

The applicant consortium will be selected on the basis of the submitted Short Proposal.

Applicants are expected to address all the above objectives in the Short Proposal (within the available duration and maximum IMI2 contribution) and demonstrate a relevant strategy for achieving them, through partnership with the industry consortium.

This may mean a requirement to mobilise, as appropriate, expertise in the area of Patient Preference Research and could come from various backgrounds – health technology outcome research, pharmaceutical and device development, biostatistics, epidemiology, behavioural research, experts in scientific communication to lay audiences, experts in benefit-risk decision making.

Patient expertise is key in this action.

The Applicant consortium is expected to enable effective collaboration with key stakeholders i.e. health-care professionals, regulators, and HTA bodies as a prerequisite for the success of this action, for example to discuss what use can be made of the data gathered by the identified methodologies in the decision-making process.

Therefore the successful consortium will either include representatives of these key stakeholders and/or have the ability to bring in the necessary stakeholders.

Suggested architecture of the full proposal

In their Short Proposal the applicant should have previously provided their suggestion for the project architecture, taking into consideration the industry contributions and expertise.

The final architecture of the Full Proposal will be defined together with the industry consortium and should enable activities aiming at achieving all objectives and deliverables as indicated in the previous relevant sections and in collaboration with the EFPIA partners.

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

The consortium is expected to have a strategy on the translation of the relevant project outputs into regulatory, clinical and healthcare practice. A plan for interactions with regulators and HTA bodies with relevant milestones and resources allocated should be proposed to ensure this.

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

Work Package 1: Project management and communication

- establish a governance structure;
- establish a communication structure and implement on project basis;
- organise project-wide meetings;
- work with Work Package leaders to create a detailed project plan for each Work Package;
- establish accurate and auditable financial systems;
- communicate with the project team as well as outside the project to ensure alignment with all stakeholders, collaboration with other relevant projects and initiatives and to ensure external awareness.

Work Package 2: Patient preference elicitation approaches

Building on the knowledge available in this area:

- identify which stages of benefit-risk evaluation are most suitable for patient involvement and of highest value to the different stakeholders, including patients, industry, regulators and HTA bodies;
- review and critically appraise available patient preference research methodologies (including methodologies for ranking of patients' preferences, and trade-offs between benefits and risks) in terms of strengths, weaknesses and lessons learned;
- identify a set of candidate methodologies to go forward for testing (identifying and implementing any required adaptations), and make recommendation as to how and at which stage(s) these could best be applied;
- identify case studies to evaluate the selected methods of patient perspective elicitation at the recommended stage(s) of drug development. The aim is to cover a good choice of therapeutic areas of relevance for patient preferences, and to take into account the heterogeneous nature of the patient population;
- define criteria that will be used to assess the case studies.

Work Package 3: Case studies

- test and compare the candidate approaches to eliciting patient preferences for benefit-risk from Work Package 2 via case studies;
- assess the case studies versus the criteria agreed in Work Package 2;
- use the case studies to assess the recommended type of patient input at each stage of the drug development life-cycle.

Work Package 4: Recommendations

Using the experience gained from Work Packages 2 and 3:

- establish recommendations to support the development of guidance for industry describing:
  - when and how to include patient preferences to inform benefit-risk decision-making throughout the product life-cycle;
  - a set of methodologies suitable for patient involvement, acceptable to regulators and HTA bodies;
- establish recommendations to support the development of guidance by regulators and HTA bodies on use of patient preferences to support assessment and licensing decision making and help regulators to provide useful information to inform doctor-patient decision-making.

Topic 2: Diabetic Kidney Disease Biomarkers (DKD-BM)

Topic details

Topic code	IMI2-2015-05-02
Action type	Research and Innovation Action (RIA)
Submission & evaluation process	2 stages

Background and problem statement

Worldwide, diabetic kidney disease (DKD) is the leading cause of end stage renal disease (ESRD), and its global incidence and prevalence are both increasing. For over 10 years, Renin-Angiotensin-Aldosterone System [RAAS] blockade has constituted the backbone of standard of care therapy in this disease. Yet, patients continue to experience progression to ESRD and die. The 5-year survival of a dialysis patient with DKD is less than 25 percent—worse than most cancers—and new treatments are desperately needed to slow and/or reverse disease in this high-risk patient population. Several large recent studies have failed to demonstrate efficacy and/or safety, including for example the BEACON, ALTITUDE and SUN trials, and there has been increasing recognition that this is due, at least in part, to a failure to identify the appropriate patient segment to test a particular novel therapy in development. In order for DKD trials to be more successful in the future, the research community will need to advance a concerted effort to identify personalised biomarkers to identify patients at high risk of progression, and patient subpopulations that are likely to respond to candidate therapeutics and to provide early indications of potential safety issues linked to candidate therapeutic agents.

- generating candidate biomarkers from existing clinical longitudinal databases, including the possibility that the studies generating these databases might be expanded by these efforts;
- using these clinical biomarkers to assess preclinical model systems, and select the most appropriate for future translational investigations;
- back-translating clinical database findings to develop improved *in vitro* and *in vivo* models of DKD;
- incorporating these novel biomarkers into clinical trials in order to enhance the precision of application and chances of success of future novel therapeutics aimed at slowing and/or reversing this disease.

The development and application of these novel biomarkers to DKD clinical development will require full engagement with global regulators. Finally, the proposal should include plans for how findings will be communicated to critical DKD stakeholders, including patients, clinicians, and payers, including how they bear on HTAs.

The potential impact gained from the identification and use of new DKD prognostic, predictive and safety biomarkers as well as from improvement preclinical model selection for testing new therapeutics under development is substantial. The overall Project is expected to yield the following main benefits:

- significantly advance the understanding of the pathophysiology, heterogeneity and natural history of DKD in patients;
- improve the knowledge on translatable preclinical models for DKD;
- facilitate the development of standardized biomarker panels with both prognostic and predictive capacity to serve as entry criteria for future clinical trial protocols evaluating novel therapies for DKD.

These benefits and identification of predictive progression biomarkers would allow a stratification of patients regarding their responsiveness and benefit to novel target approaches. Furthermore, the clinical development process for new therapeutics would become more efficient and faster due to a possible reduction in the size of future confirmatory pivotal trials needed for regulatory approval. Finally, new therapeutics which are approved

using these new biomarkers are more likely to garner favourable Health Technology Assessments (HTAs) by global payers, due to the evidence of a likely enhanced efficacy signal seen in biomarker-selected patients.

Need and opportunity for public-private collaborative research

The global standard of care for patients with DKD has remained unchanged for over a decade, and essentially includes RAAS blockade using either an angiotensin converting enzyme (ACE) inhibitor and/or an angiotensin receptor blocker (ARB), along with general therapeutic measures to control the underlying diabetes and blood pressure. Although RAAS blockade has slowed somewhat the progression of DKD, the current progression rate to end-stage renal disease (ESRD), and the cardiovascular (CV) and overall mortality rates, remain unacceptably high.

Highly predictive dynamic biomarkers of efficacy and safety are lacking. With regard to efficacy, proteinuria (specifically albuminuria) is typically used in phase II clinical trials as an early marker, potentially indicative of hard outcomes such as doubling of serum creatinine, ESRD or both. Albuminuria does have some prognostic significance in assessing risk for ESRD but has significant liabilities, including substantial intra-patient variability, its non-linearity in predicting risk, and the fact that substantial cohorts of patients exist who have advanced DKD but are normo-albuminuric[3] Like albuminuria, other potential candidate biomarkers predictive of decline include Chronic Kidney Disease (CKD) progression markers identified recently in the IMI SUMMIT project[4]. There is also a need to validate highly predictive safety biomarkers such as those identified through consortia such as the Predictive Safety Testing Consortium (PSTC)[5] to provide early clues to the salutary or harmful effects of novel therapeutic agents. The nephrology research community needs to continue developing the evidence to identify precise safety and efficacy biomarkers that are acceptable to the regulatory agency, patients, nephrologists, and ultimately payers.

Hence, a collaborative research program based on a network of academic medical institutions, basic and clinical research experts in the fields of biomarkers, bioinformatics, preclinical DKD models – both *in vitro* and *in vivo*, biomedical approaches including renal imaging, along with the clinical development expertise of the pharmaceutical industry is necessary. This is seen as the first prerequisite for a successful advancement of both prognostic and predictive biomarkers to enable greater efficiency and success.

Overall objectives

Future successful development of therapeutics for DKD will depend in large part on the proper selection of appropriate patients for evaluation. These patients will be identified through the application of highly accurate biomarkers, to identify fast-progressing DKD patients in whom the novel agent is likely to be efficacious. Equally the inclusion of biomarkers predictive of adverse events will permit those subjects to be excluded from the trial and decrease risks of safety signals.

Candidate biomarkers and/or biomarker panels can potentially be identified from existing longitudinal databases containing historical, clinical chemistry, imaging, biopsy and other data collected over several years in DKD patients, and correlating progression with hypothesised biomarkers. Positively identified biomarkers can then be validated in other longitudinal databases which are tracking similar patients over time. Identification of these biomarkers will enable enhanced understanding of key driver pathways that accelerate progression of DKD, as well as pathways that enable and drive the pathogenesis of DKD in the overall context of diabetes itself. Differences between DKD associated with Type 1 DM and Type 2 DM will be assessed. In parallel with this early work in biomarker identification and profiling of people with DKD, preclinical efforts will leverage longitudinal clinical database findings to identify better *in vitro* and *in vivo* models of DKD, identify

[3] Jha JC et al. New Insights into the Use of Biomarkers of Diabetic Nephropathy. *Advances in Chronic Kidney Disease*, Vol 21, No 3 (May), 2014: pp 318-326
[4] Biomarkers of Rapid Chronic Kidney Disease Progression in Type 2 Diabetes. *Kidney International* 2015. In Press.
[5] http://c-path.org/programs/pstc/regulatory-successes

predictive biomarkers for both efficacy and safety, and identify new druggable target pathways for future drug development.

It is also the intention to engage with one or more imaging partners to identify key imaging features of kidney disease which can be quantitated as a novel prognostic and/or predictive biomarker. One of the overall goals of these efforts will be to provide therapeutic developers with new tools that are acceptable to global regulators to enable and facilitate drug development, for example companion diagnostics.

Applicants are expected to address all the above objectives in the Short Proposal (within the available duration and maximum IMI2 contribution) and demonstrate a relevant strategy for achieving them, through partnership with the industry consortium.

This will have to be fully developed with the industry consortium and or associated partners in the Full Proposal.

Early, close, and continued interactions with regulators within this consortium are highly desired.

Potential synergies with existing consortia

It is expected that this action will find synergies and build on the accessible resources, data and results from the IMI project SUMMIT. This project has generated a candidate panel for the identification of patients showing a rapid progression of chronic kidney disease typically defined by an annual loss of 5 ml/min/1.73m² of glomerular filtration rate as the principal measure of kidney function, or greater. The predictive performance of this panel in populations and ethnicities beyond those tested in SUMMIT needs to be determined. Biomarkers, which inform on subjects likely to respond to a particular therapy, and/or give earlier information on improved renal function, still need to be defined.

In addition synergies should be sought with other previous and ongoing projects in Europe and the US, from the IMI initiative, FP7 programme and US-based activities such as:

- the IMI Diabetes platform consortia IMIDIA (Improving ß-cell function and identification of diagnostic biomarkers for treatment monitoring of diabetes http://www.imidia.org/) and DIRECT (Diabetes research on patient stratification http://www.direct-diabetes.org/);
- FP7-funded projects like KIDNEYCONNECT (http://www.kidneyconnect.eu/), and DN CURE;
- US-Consortia like the Kidney Health Initiative https://www.asn-online.org/khi/ and the Predictive Safety Testing Consortium (PSTC) http://c-path.org/programs/pstc/ at the Critical Path Institute.

Expected key deliverables

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

DKD Biomarker Identification, Validation & Use Within Therapeutics Development

- identify/validate new biomarkers from, and applicable to, broad populations in order to differentiate Fast from Slow Progressors of DKD;
- identify clinical predictor biomarkers of efficacy response, compatible with regulatory decision making process;

- qualify clinical biomarkers that can be used within (A) Confirmatory Studies and (B) Development of Companion Diagnostics;
- development of imaging technology and biomarkers validated by renal biopsy features and biopsy biomarkers. Correlate prognostic and predictive imaging surrogate measures with DKD kidney biopsy findings, renal function, and serum/plasma and urinary biomarkers in DKD patients;
- identify 'dynamic biomarkers' that are informative in monitoring efficacy over time with experimental therapeutic and/or standard of care treatment;
- identify predictor biomarkers of hard safety outcomes (e.g. cardiovascular events) in diabetic kidney disease patients. This will occur only as a secondary opportunistic effort from other work packages in this call topic;
- develop or extend an existing prospective cohort (N>500) of DKD patients to follow & collect periodic longitudinal data over several years, focusing on CKD stages 2-4;
- pave the way for implementing specific *personalised* diagnostics in DKD by communicating value proposition to target audiences (i.e. Global Regulators, Patients, Practitioners, and Payers).

DKD Target Pathway Identification

- identify causal mechanisms and pathways for developing *de novo* DKD;
- identify mechanisms and pathways that can be targeted to improve/stop deterioration of renal/glomerular function;
- identify differences in pathway drivers for DKD between T1D and T2D patients.

Industry Consortium & Associated Partner

The EFPIA participants are: AbbVie (coordinator), Eli Lilly, Novo Nordisk, Bayer, Sanofi, and Merck Sharp & Dohme (MSD). The Associated Partner is the Juvenile Diabetes Research Foundation (JDRF). The JDRF (http://jdrf.org/) is a not for profit patient organization focusing on patient advocacy as well as funding of research in the field of T1DM and its complications.

Indicative duration of the action

The indicative duration of the action is 60 months.

This duration allows in-depth systematic molecular analysis and immune and metabolic phenotyping of retrospective and prospective collected clinical and biological samples from DKD patient cohorts. Further, the obtained insights will be integrated into novel to-be-established and existing models.

Future action expansion

Potential applicants must be aware that IMI2 may publish another Call for proposals restricted to those projects already selected under this Call at a later stage, in order to enhance their results and achievements by extending their duration and funding, if this is foreseen in the applicable annual work plan. Consortia will be entitled to open to other beneficiaries as they see fit.

In the context of this topic, the EFPIA companies envision the possibility in the future to expand Work Package 1 to support the construction and maintenance of a longstanding clinical data repository to serve as a future source of biomarker identification and/or validation. Such further work would be the natural progression of the project leveraging any success achieved. Building on these prior successes and positive results would maximise the long term impact of the larger project, and engender continued future successes

in making the clinical development of new therapeutic and their application in the clinic both more fruitful and more efficient. This proposed project extension would also take advantage of already established collaborations and networks forged in the overall project, thereby maximising efficiency on time and resources. A restricted Call may allow achieving this in the most efficient way. The detailed scope of the Call will be described in the relevant annual work plan.

Indicative budget

The indicative contribution from the EFPIA companies is estimated at a total of EUR 13 235 000 and from the IMI2 Associated Partner at EUR 1 851 000. 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.

AbbVie, MSD, and Eli-Lilly are expected to contribute significant non-EU in kind contributions to this project. The full time employee equivalents committed to this initiative are based in the U.S. These scientists are experts in the development and implementation of a broad range of biochemical/biomarker assays and approaches to develop existing and novel DKD biomarkers including statistical and computational approaches. Additionally, they will support efforts involving PK/PD, and safety, and analyses. Also note that JDRF will provide some non-EU contribution.

The indicative IMI2 contribution will be up to EUR 15 086 000.

Applicant consortium

The applicant consortium will be selected on the basis of the submitted Short Proposal.

The applicant consortium is expected to address all the research objectives and make key contributions to the deliverables in synergy with the industry consortium and complementing the contributions of the participating EFPIA partners.

It is envisioned that a multidisciplinary network will be established in response to this topic and it will include: research physicians (nephrologists, endocrinologists and clinical pharmacologists), basic researchers in the field of *in vitro* and *in vivo* modelling of DKD, biomarker/diagnostics specialists (who could be SMEs), investigators with access to bio-specimens from longitudinal cohorts, bio-informaticians and big data analysts, regulatory health authorities, imaging specialists, translational medicine experts. Cross-fertilisation and demonstrated ability to collaborate well with each other and the pharmaceutical companies also showcased in prior working groups/consortia will be critically important for all participants. Subject to a successful stage one evaluation outcome, the selected applicant consortium will join the industry consortium to build a seamless, collaborative and fully-integrated final full consortium and make key contributions on the defined deliverables in full synergy with the industry consortium.

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

- clinical cohorts (N>500, with a minimum of 4 years of follow-up) and with fully accessible and adequately stored serum/plasma and urine samples associated with longitudinal clinical phenotypes including measures of serum creatinine and/or Cystatin C, proteinuria, and ESRD, obtained at regular intervals following baseline measures is required;
- DKD renal biopsy samples associated with longitudinal phenotypes that are adequately stored/preserved to enable RNA, protein, and epigenetic analyses;
- institutional/Individual expertise with respect to animal and/or *in vitro* models relevant to DKD;
- institutional/Individual expertise with respect to serum/plasma, urine and/or imaging biomarker development. Included in this is large scale data management and computational expertise.

Cross-fertilisation in this team of experts is the key for the success of the initiative.

Suggested architecture of the action

The final architecture of the Full Proposal will be defined together with the industry consortium and should enable activities aiming at achieving all objectives and deliverables as indicated in the previous relevant sections and in collaboration with the EFPIA partners.

The above descriptions of cross-functional and cross-sector team members are advised to work together in dedicated Work Packages addressing the different aspects of the overall Call. Each Work Package team should consist of academic and industrial/biotech members, manifesting as examples of inherently public-private collaborations, with regular interactions to ensure knowledge exchange between the different expertise. Inter-Work Package knowledge transfer should be ensured at all times via regular management board meetings.

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

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

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

It is suggested that this project is organised into six major work packages:

Work Package 1:

- validate (and possibly identify) new serum/plasma and urinary biomarkers from, and applicable to, broad populations in order to differentiate fast from slow progressors of DKD in both T1D and T2D;
- develop or extend an existing prospective cohort (N>500) of Type-2 Diabetes Mellitus (DM) - DKD patients to follow & collect periodic longitudinal data over several years, focusing on CKD stages 2-4.

Work Package 2:

- identify clinical predictor serum/plasma and urinary biomarkers of efficacy response including ‘dynamic biomarkers’ that change with experimental therapeutic and/or SOC treatment;
- back-translate clinical findings to identify predictor biomarkers of efficacy response (Preclinical and Clinical);
- identify Mechanisms and Pathways that can be targeted to reduce the slope of estimated glomerular filtration year (eGFR/yr). loss curves and back-translate clinical findings to select/improve Preclinical (*in vitro /in vivo* models) that correlate with Human DKD;
- opportunistically identify predictor biomarkers of safety (e.g. cardiovascular) outcomes in Type-2 DM - DKD patients.

Work Package 3:

- validate clinical serum/plasma and urinary biomarkers that can be used within;

- registration trials;
- development of companion diagnostics.

- implement specific *personalised* diagnostics in DKD by communicating value proposition to target audiences (i.e. regulators, patients, practitioners, and payers).

Work Package 4:

- development of imaging technology and related biomarkers (BM);
- identify imaging BMs, including prognostic and predictive imaging BMs;
- develop imaging biomarker approaches that are validated by associated DKD kidney biopsy findings (fibrosis, inflammation, etc.) obtained at approximately the same time as imaging measures.

Work Package 5:

- identify causal mechanisms and pathways for developing *de novo* DKD. Correlations should be made with biomarkers identified from biopsy samples;
- identify differences in pathway drivers for DKD between T1D and T2D patients.

Work Package 6:

Consortium management and administration

Topic 3: Inflammation and AD: modulating microglia function – focussing on TREM2 and CD33

Topic details

Topic code	IMI2-2015-05-03
Action type	Research and Innovation Action (RIA)
Submission & evaluation process	2 stages

Background and problem statement

The overall goal is to identify druggable points of interaction in the TREM2 and CD33-signalling pathways to modulate microglial or macrophage function for the treatment of Alzheimer's disease (AD).

Neurodegenerative diseases such as AD have devastating effects on the nervous system that lead to progressive cognitive, behavioural, motor dysfunction and general functional decline. With improvement in overall medical care, the importance of these age-related diseases to society is rising. In the U.S. and Europe, it is estimated that the cost of dementia care alone is already greater than that of cardiovascular disease and cancer. The number of affected individuals and the cost of caring for them are expected to triple in the next 50 years in the absence of effective disease-modifying treatments. While there are several treatments that are useful for the treatment of Parkinson's Disease (PD) and multiple sclerosis, there are no treatments known to delay the onset, or impact disease progression of AD.

Thus, developing a better disease understanding in conjunction with identification of relevant drug targets for efficacious treatment for these disorders is paramount.

AD is characterised by the accumulation of amyloid beta- and tau-aggregates in the brain, processes which ultimately lead to neuronal cell death and a 'neuroinflammatory response' i.e. reactive astrocytosis and activated microglia. The microglial system is considered to constitute the immune system of the Central Nervous System (CNS). It is involved in responding to injury or disease through actively monitoring the brain parenchyma thereby ensuring tissue homeostasis e.g. by scavenging cell debris and protein aggregates by phagocytosis and shaping inflammatory responses. Proinflammatory processes mediated by microglial cells are responding and adapting continuously to changes caused by ageing and onset and progression of AD.

While inflammation is considered as a pathological hallmark of AD and characterised by increased number of 'morphologically activated' microglia and reactive astrocytes, the exact state of functional activation of these cells is still unknown. In addition, the ultimate causative link between inflammation or microglia activity and AD is still an under-explored area of research. For example we need to understand the inflammatory process mediated by microglial cells and activated macrophages better. Highly inflammatory microglial cells can induce other cells from the immune system to switch into the inflammatory mode. As a consequence macrophages may invade the AD brain and further stimulate inflammatory damage.

These inflammatory processes might be a response to AD-related changes in the brain in order to counteract progression. However, prolonged inflammation or an inappropriate trigger of microglia-mediated molecular pathways by e.g. the increasing amyloid beta-plaque load or accompanying co-morbidities in the course of the disease as well as the dysfunction of key players in microglial activity might trigger or accelerate AD.

Multiple Genome-wide Association Studies' (GWAS) and integrated systems biology approaches have identified and linked genes involved in modulating and executing microglia mediated inflammation to AD.

Amongst those are genes expressed predominantly by microglia and macrophages, including TREM2[1,2], CD33[3,4,5], ABCA7[6], CR1[7]. TREM2 variant R47H is the second strongest genetic risk factor for late onset AD (LOAD) after ApoE4[1]. A recent integrated system approach study further confirmed the linkage to LOAD of CD33 and TREM2 suggesting a key role for microglia activity in the development of LOAD[8].

TREM2 signaling is thought to promote phagocytosis of proteinaceous and neuronal debris, while keeping microglia from adopting a cytotoxic activation state. Rare mutations in TREM2 increase the risk for several neurodegenerative disorders in addition to AD, such as PD, Amyotrophic lateral sclerosis (ALS) and fronto-temporal dementia (FTD) and cause the early-onset neurodegenerative disorder Nasu-Hakola when both alleles are affected. Kleinberger *et al*.[9] showed that mutations associated with neurodegenerative diseases interfere with TREM2 function by preventing its maturation, transport to the cell surface, and shedding. The Q33X variant provides further evidence for TREM2's involvement in neurodegeneration because heterozygotes have increased risk in AD and homozygotes develop Nasu-Hakola disease. In addition rare loss-of-function mutations in TyroBP/Dap12 (one of the signaling partners of TREM2), has also been identified in Nasu-Hakola, further highlighting the relevance of TREM2 signaling to neurodegenerative diseases[10]. Expression of mutant TREM2 led to reduced phagocytic activity, suggesting that removal of amyloid deposits and cellular debris by microglia in the brain might be affected in patients with TREM2 mutations leading to increased plaque-deposition and AD progression. A further attractive feature of TREM2 is that signaling generally has an anti-inflammatory effect hence, impairment in expression or maturation has been hypothesized to lead to microglia-mediated increased inflammation and cytotoxicity[11]. A preclinical study has suggested that TREM2 knock-out leads to reduced plaque burden in the hippocampus of APP/PS1 mice[12] whereas another study shows that TREM2 deficiency augments amyloid beta accumulation[13]. Thus there is uncertainty in the field regarding the benefit, or otherwise, of engaging the TREM2 pathway in AD and it would be of high value to understand these apparently contradictory results.

CD33, a member of the sialic acid-binding Ig-superfamily of lectins (SIGLECs), is expressed on monocytes and brain microglia and is another modulator of the brain innate immunity. The binding of sialic acid activates CD33, leading to monocyte/microglial inhibition through the ITIM domains[14]. The minor allele of the CD33, SNP rs3865444, which confers protection against AD, is associated with reductions in both CD33 expression and insoluble amyloid beta 42 (Ab42) levels in AD brain[15]. This allele is also associated with an increase in the proportion of CD33 lacking exon 2 (D2-CD33)[16] which is required for sialic acid binding and, thus CD33 activation. Furthermore, CD33 expression reduces amyloid beta phagocytosis, and monocytes from individuals carrying the risk alleles also show reduced amyloid beta phagocytic activity[17].

Thus, a working hypothesis may be that these genes confer increased risk of AD by reducing the phagocytic activity of microglia leading to reduced clearance of Amyloid beta aggregates and cell debris, as indicated by Malik *et al*. [16].

This hypothesis is further supported by recent preclinical studies that demonstrated that indeed microglia in proximity to amyloid plaques while appearing 'morphologically activated' and producing cytokines, display strong deficit in phagocytic and motility activity suggesting a 'non-functional' altered state of microglial activation[18, 19]

However, this goes against a widely-held view that microglial activation is a contributor to the neurodegenerative process in AD. Thus, it is imperative to resolve the role that these risk genes play in microglial function in brain but also peripheral tissues and in the modulation of their activity in LOAD in order that they, or associated pathways, may be targeted appropriately as potential treatments.

Need and opportunity for public-private collaborative research

The magnitude and complexity of the issue is such that it can only be addressed by a major public-private-partnership involving a variety of stakeholders. This is a program that cannot be accomplished by an individual research group or company and will require a strong collaborative effort to be successful.

A consortium of academic laboratories and small and medium size enterprises (SMEs), with access to necessary innovative tools like animal models, gene expression tools and tool compounds, the understanding of molecular mechanisms of disease and translational expertise and industry partners which endorse the

approach and have a complementary experience and expertise, is well-positioned to make a significant progress into the understanding of these fundamental processes. The engagement of leading pharma partners will enable the partnership to capitalise on the knowledge and innovation to identify druggable[6] points of interaction to regulate the microglial system in order to find novel approaches to treat AD.

Overall objectives

The overall objectives of the action generated from this topic are the following:

- explore whether a decrease or an increase of brain microglia phagocytic activity and/or cytokine release is causative for or protective to neurodegenerative/ageing phenotypes, and if so;
    - at what stage in the progression of AD-related phenotypes;
    - and if modulation of microglia is able to delay progression of AD-phenotypes;
    - and what are the effects of activated microglial cells (e.g. Iba-1 positive) on T cells and B cells;
- discern whether receptor-mediated microglial phagocytosis of debris can be dissociated from a more generic inflammatory response in the brain, providing insights on whether such a dissociation can be exploited therapeutically;
- to explore the roles of CD33 and TREM2 in microglia activity with the goal of identifying druggable points of interactions/pathways modulating the receptors and microglial function/brain inflammation and in particular:
    - determine what differentiates a tissue protective or even restorative microglial cell from a tissue destructive one;
    - determine how this phenotype can be influenced;
    - determine the relative roles of microglial-bound TREM2 and CD33 receptors versus their shed counterparts and in which cell populations the receptors are expressed;
    - since shedding of TREM2 is both constitutive and induced by inflammation study how these processes can be influenced and how/if it is possible to modulate the relative amounts of cell-bound and shed receptors.
- to achieve these goals tools not readily available, like e.g. improved antibodies directed against TREM2, will be identified or developed;
- conduct limited drug screening to provide tool compounds to contribute to the above objectives;
- explore if there are important differences between mice and human immune system, and particularly between mice microglia and their human counterparts. Human systems should be integrated to maximise the relevance of the studies.

Applicants are expected to address all the above objectives in the Short Proposal (within the available duration and maximum IMI2 contribution) and demonstrate a relevant strategy for achieving them, through partnership with the industry consortium.

This will have to be fully developed with the industry consortium and or associated partners in the Full Proposal.

[6] Druggable/Druggability is a term used in drug discovery to describe a biological target (such as a protein) that is known to or is predicted to bind with high affinity to a drug. Furthermore by definition, the binding of the drug to a druggable target must alter the function of the target with a therapeutic benefit to the patient. The concept of druggability is most often restricted to small molecules (low molecular weight organic substances)[1] but also has been extended to include biologic medical products such as therapeutic monoclonal antibodies.

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, building from achievements, and incorporating when possible, data and lessons learnt while avoiding unnecessary overlapping and doubling of efforts. For example related consortia are active in the EU Joint Programming Initiative – Neurodegenerative Disease Research (JPND http://www.neurodegenerationresearch.eu/about/) and within ERA-Net NEURON (http://www.neuron-eranet.eu/). Synergies could be considered also with the InMind project (www.uni-muenster.de/InMind/) and consideration paid to build on knowledge acquired from the ADAMS project (http://cordis.europa.eu/project/rcn/93053_en.html).

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

In addition applicants should be aware of other relevant ongoing public-private partnerships either in IMI (e.g. AETIONOMY (http://www.aetionomy.eu/index.php?id=5263) and ULTRA-DD: http://www.nature.com/naturejobs/science/jobs/502223-postdoctoral-research-scientist-in-statistical-functional-genomics-within-ultra-dd)), elsewhere in Europe (e.g. the Welcome Trust inflammation AD and Psychiatry consortium (http://www.wellcome.ac.uk/News/Media-office/Press-releases/2014/WTP058231.htm) and the Structural Genomic Consortium(http://www.thesgc.org/)) and outside Europe (e.g. the Alzheimer's pillar of the Accelerating Medicines Partnership: http://www.nih.gov/science/amp/alzheimers.htm).

Expected key deliverables

Key deliverables are:

Knowledge:

Applicants should explore whether the activity of the microglial system is causative or a response to the progression of AD-related phenotypes. For this purpose various types of cell, animal, and preclinical models should be employed where the microglial system can be manipulated and analysed in the context of AD-related phenotypes and their relevance to human biology. Expected outcomes should include:

- confirmation if an early (related to AD-phenotypes *in vivo* , e.g. plaque load or tau pathology) increased or decreased activation of microglia impacts on neuronal function;
- analysis if a late (related to AD-phenotypes *in vivo* , e.g. plaque load or tau pathology) increased or decreased activation of microglia worsens AD-related phenotypes;
- identification of CD33 and TREM2 pathways offering druggable intervention to modulate microglia phagocytic/motility function.

Tools:

Once suitable entry points into the regulation of disease relevant microglial pathways have been identified the proposal should aim:

- to validate tools to knock-down and over-express targeted genes and identify suitable reagents to quantify knock down or overexpression, to confirm findings by gene knock-down or over-expression studies in disease relevant preclinical models;
- to identify small or large direct molecule modulators of CD33 or TREM2 or pathways regulating both genes microglial function by:
  - provision of robust assays for constitutive and inflammatory shedding of TREM2;

- provision of standard cell lines (preferably human) expressing TREM2 +/- CD33 +/- DAP12;
- provision of a robust TREM2 -and CD33-dependent phagocytosis assay in cell culture;
- provision of a robust TREM2- and CD33-signalling reporter line in cell culture.

- to identify and characterise endogenous ligands of CD33 and TREM2.

Industry Consortium

Janssen, Abbvie, Eli Lilly, Sanofi, Lundbeck, Roche, Orion, Astra Zeneca/MedImmune.

Indicative duration of the action

The indicative duration of the action is 60 months.

Indicative budget

The indicative EFPIA in kind contribution will be EUR 8 838 000. Due to the global nature of the participating industry partners it is anticipated that part of the EFPIA contribution will be provided from non-EU/H2020 associated countries.

The indicative IMI2 contribution will be a maximum of EUR 8 838 000.

Applicant Consortium

The applicant consortium will be selected on the basis of the submitted Short Proposal.

Applicants are expected to address all the above objectives in the Short Proposal (within the available duration and maximum IMI2 contribution) and demonstrate a relevant strategy for achieving them, through partnership with the industry consortium.

This may require mobilising as appropriate, expertise in AD and in neuro-inflammation linked to AD (including in particular expertise on neuro-inflammation studies using *in vivo* preclinical models of AD or *in vivo* models where key components of microglia are genetically modified with emphasis on TREM2 and CD33, analysis of brain innate immunity cells), small animal imaging, *in vivo* and *ex vivo* pharmacology, translational medicine to bridge findings and results of neuro-inflammatory processes/pathways from preclinical species to humans, IT (in particular data communication and data basing) and project management.

It may also require mobilising as appropriate, the following resources: access to relevant preclinical models (e.g. transgenic AD, TREM2, CD33 models, TREM2 and CD33 cellular models), translational tools, access to state of the art *in vivo* facility and small animal imaging, biomarkers, bioinformatics tools, biobanks and bio-samples (e.g. AD brain tissue, samples for GWAS TREM2/CD33), engagement of SMEs able to contribute relevant technologies.

The applicant consortium partners that will provide data and samples from existing clinical studies and repositories need to demonstrate in their application that those envisaged resources can be shared among all the partners. Thus the applicants have to document in their short proposal that applicable legal, ethical and data privacy laws allow sharing such data and samples within the consortium and with timelines compatible with the needs of the action.

Suggested architecture of the Full Proposal

The applicant should include their suggestions for creating the Full Proposal architecture in their Short Proposal taking in consideration the industry contributions and expertise below:

The indication addressed by this topic is AD and the focus is the role of neuro-inflammation mediated by microglia. As described above the topic will be addressing several areas from basic research (e.g. understanding the pathways and mechanisms that regulate microglial activity and, as specific examples, TREM2 and CD33 function) to validation and drug development-processes typical for the pharma industry. Basic research will be focusing on *in vitro* and *in vivo* methodologies (molecular biology, *in vivo* experiments e.g. small animal imaging) accompanied by comprehensive analysis tools covering deep sequencing, pathway/systems biology approaches to understand the role of key regulators of microglia function preferably in an AD-background.

In summary the Work Plan should enable activities aiming at:

- identification of druggable entry points for regulation of microglial activation:
  - 'Omics' approaches to understand regulatory pathways;
  - In vitro/*in vivo* validation of identified targets regulating microglia.
- setting up and analysing translational models by:
  - Imaging
  - Biomarkers
- small-scale screening and identification of tools useful for *in vivo* validation;
- characterization of tool compounds (e.g. pharmacokinetics (PK), absorption, distribution, metabolism and excretion (ADME).

EFPIA's contribution will be to provide joint scientific leadership, coordination and project management expertise to optimise the consortium's efforts and a sound track record and experience in AD preclinical and clinical research. Industry contributions will be supporting these efforts by contributing to all Work Packages, but in particular the industry consortium will bring in expertise in later-stage activities like small molecule identification and qualification.

Contributions will be on:

- assay development
- *in vivo* pharmacology
- drug screening
- glycochemistry
- medicinal chemistry
- *in vitro* pharmacology
- ADME-T / PK
- imaging
- IT (deep sequencing, systems biology/bioinformatics)

In addition the following tools and support will be made available to consortium partners:

- transgenic mice:

- TREM2 Knock in (Ki) and TREM2 overexpressing mice ; behavioural and structural characterization (MRI/fMRI);
- TREM2 ki and TREM2 overexpressing mice, crossed with tg AD mice (with Ab/tau-related pathology); behavioural and structural characterization (MRI/fMRI);
- TREM2 ko mice;
- animal models of tauopathy (injection model with 'true' neuronal loss);
- samples from different amyloid (e.g. J20) and tau (e.g. tg4510) mice for studies to look at progression of microglial pathology;
- genetically-modified mouse: generation and characterization of humanized and Knock out (ko) CD33 mice.

- bioinformatics support to analyse microglia proteome and expression profiles e.g. RNAseq (isolated from transgenic AD mouse models, TREM2 ko/ki mice, or potentially from human iPSCs-derived microglia);
- assays: phagocytosis assay using human AD tissue brain slices or macrophage/microglia-like cell lines;
- development of methods to knockdown CD33 *in vitro* and *in vivo* using antisense oligonucleotides;
- high-content imaging devices and technology for quantitative assessment of inflammation status as well as AD pathology in the brains of animal models;
- state of the art compound collections, medicinal chemistry expertise, ADME-T, and screening facilities. In particular tool compounds that inhibit/modulate microglial activity (i.e. small molecules and large molecules) for *in vitro* and *in vivo* target validation;
- small animal proton emission tomography (PET) imaging, including test tool compounds *in vivo* for microglial activity detection via translocator proteine ligands (TSPO)-PET;
- measurements of TREM2 in cerebrospinal Fluid (CSF) as a potential pharmaco-dynamic marker;
- development of antibodies against TREM2;
- establishment of human iPSCs harbouring the GWAS gene variants (or knock out) plus protocols to differentiate iPSCs into microglia.

The final architecture of the Full Proposal will be defined together with the industry consortium and should enable activities aiming at achieving all objectives and deliverables as indicated in the previous relevant sections and in collaboration with the EFPIA partners.

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

Work Package 1: Project management Project management

Project management:

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

Work Package 2: Microglia–status of activation during progression of AD

Microglia–status of activation during progression of AD and elucidating the role of disease linked mutations on CD33 and TREM2 regulation of microglial activity:

- identify and evaluate pathways determining AD risk;
- 'Omics' analyses;
- identification of druggable points of intervention (focus TREM2 and CD33).

Work Package 3: *In vitro* and *in vivo* models of AD-related neuro-inflammation

In vitro and *in vivo* models of AD-related neuro-inflammation:

- role of TREM2 and CD33 in development of AD-related phenotypes in model systems;
- get insight into differences in immune response on AD pathology between human and rodents;
- evaluate systemic effects of CD33/TREM2 modulation / potential side effects;
- biomarkers;
- neuroimaging.

Work Package 4: Identification of small and / or large molecule modulators of microglia effects

Identification of small and / or large molecule modulators of microglia effects on progression of AD-related pathology mediated CD33 and TREM2-signaling / pathways.

Work Package 5: Data and knowledge management

Data and knowledge management including:

- establishment of data format and content standards for data collection and data management in order to ensure interoperability to quality standards and optimal use of IMI resources (e.g. technical solutions for data storage, management, analysis or visualisation should always re-use existing solutions where possible in preference to the development of new resources);
- development and delivery of the data and knowledge management plan, illustrating clearly how the guidelines above are being adhered to (see details of expectations in the general conditions of the Call).

Glossary:

Ab42	Amyloid beta 42
AD	Alzheimer Disease
ADME-T	Absorption, Distribution, Metabolism, Elimination –Toxicity
APP	Amyloid Precusor Protein
ALS	Amyotrophic lateral sclerosis
CD33	Cluster of differentiation 33
CSF	Cerebro spinal fluid

DAP12	DNAX-activating protein of 12kDEFPIA European Federation of Pharmaceutical Industries and Associations
fMRI	functional Magnetic Resonance Imaging
FTD	Frontotemporal dementia
GWAS	Genome-wide Association Studies
IT	Information Technology
ki	knock-in
ko	knock out
LOAD	Late Onset Alzheimer's Disease
MRI	Magnetic Resonance Imaging
PD	Parkinson's Disease
PET	Positron Emission Tomography
PK	Pharmacokinetics
PS1	Presenilin-1
SIGLECs	Sialic Acid-binding Ig-Superfamily of Lectins
SMEs	Small and Medium Size Enterprises
tg	Transgenic
TREM2	Triggering Receptor Expressed on Myeloid cells 2
TSPO	Translocator Protein

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Topic 4: Understanding the role of amyloid imaging biomarkers in the current and future diagnosis and management of patients across the spectrum of cognitive impairment (from pre-dementia to dementia)

Topic details

Topic code	IMI2-2015-05-04
Action type	Research and Innovation Action (RIA)
Submission & evaluation process	2 stages

Background and problem statement

Alzheimer's Disease (AD) has an ever increasing impact on patients and healthcare systems as the number of people afflicted worldwide with dementia is currently estimated to be over 40 million and is projected to be over 75 million in 2030 (Alzheimer's Disease International). The need to manage this disease through effective intervention is becoming ever more essential as populations age, especially in lower and middle income countries where the fastest growth in the aging populations are observed.

The diagnosis of AD depends mainly on the identification of clinical symptoms in patients with cognitive impairment and on the clinical exclusion of other dementia subtypes. However, diagnosis is complicated by the similar clinical presentations of different dementia subtypes, overlapping proteinopathies, and the fact that today a definitive diagnosis of AD is only possible post-mortem. Delayed diagnosis may lead to poor management, reduced treatment effectiveness and subsequent worsening of patient outcomes while inaccurate diagnosis of dementia subtypes may lead to ineffective management, including inappropriate treatments that may worsen patients' symptoms, cause severe adverse events (AEs), or both. A meta-analysis of patients from US based AD centres aligned to the National Institute of Aging indicated that clinical diagnosis had varying levels of sensitivity (70.9 to 87.3%) and specificity (44.3 to 70.8%) compared to neuropathological analysis as the gold standard[1].

The shortfalls of clinical diagnosis have also hampered the development of new treatments for AD. The reliance on clinical diagnosis for identifying clinical trial subjects has resulted in the inclusion of patients who do not meet the clinical-pathological criteria of AD. Most recently[2] it has been reported that over 40% of patients being included in critical phase III anti-amyloid therapy studies had quantitative levels of amyloid pathology in the brain that would be considered to be normal indicating that clinical diagnosis alone is not sufficient as an inclusion criterion for these studies. Hence, by demonstrating the presence of cortical β-amyloid in-life and enabling the accurate identification and stratification of patients in clinical trials it is possible to improve the likelihood of detecting therapeutic efficacy through novel trial design, while ultimately improving outcomes for patients and healthcare systems. Additionally it would be possible to develop a deeper understanding on how amyloid quantification and localization can impact disease modelling especially in the preclinical stage of the disease.

In-vivo imaging of β-amyloid deposition in the brain provides information on the distribution and severity of one of the two key histopathological hallmarks of AD. Clinical studies of Positron Emission Tomography (PET) amyloid imaging agents (eg [^{18}F]flutemetamol and [^{18}F]florbetaben) now approved in both Europe and the US for routine clinical use have demonstrated high sensitivity and specificity, using histopathology as the standard of truth.[3,4] However while some studies have shown an impact of β-amyloid imaging on diagnostic confidence and management, some healthcare systems are reluctant to reimburse for the use of β-amyloid imaging in their populations due to uncertainty in its value in contributing to treatment decisions. Therefore, there is a

need to understand the role and value of β-amyloid imaging in current care pathways as well as its use in patient enrichment in therapeutic clinical trials.

Despite the magnitude of efforts both current and future in the field of AD targeted therapeutics, it cannot be predicted when disease-modifying drugs with an acceptable risk/benefit profile will be available for routine clinical use. Therefore, establishing the clinical utility of amyloid imaging in not only the presence but also the absence of such drugs is warranted. Even if such drugs were to be approved tomorrow, many patients who currently have AD would likely be at too advanced a stage to benefit from it, and it would take many years for the preventive benefits of such a drug to eradicate AD or at least substantially reduce its prevalence. This time lag would result in a care gap, i.e. large numbers of 'orphaned' patients whose main therapeutic options are the drugs available today. The role of amyloid imaging in this population is poorly understood but nevertheless may provide some benefits to improve their management and ultimately their quality of life.

Need and opportunity for public-private collaborative research

The magnitude and complexity of the issue is such that it can only be addressed by a major public-private-partnership involving a variety of stakeholders. This is a program that cannot be accomplished by an individual research group or company and will require a strong collaborative effort to be successful.

Collecting data and come to some relevant conclusions on how β-amyloid imaging can aid diagnosis, management and clinical trial success requires the concerted action of several stakeholders. In terms of value in current clinical practice, it is proposed a tight collaboration with academic researchers and clinicians who are managing and treating cognitively impaired patients, reimbursement/health technology assessment authorities in EU member countries, and patient/disease associations.

None of these groups could conduct this piece of research on their own. Furthermore, the enrichment of clinical trials based on amyloid pathology has obvious importance to therapeutic manufacturers and regulatory authorities in addition to the stakeholders mentioned previously and their involvement and input in the partnership is critical for the success of this initiative.

Overall objectives

In recognition of the two major unmet scientific and clinical needs outlined above, the purpose of this action is to utilise existing Europe-wide clinical and imaging networks to effectively and accurately assess amyloid status as assessed by PET imaging (eg by either [^{18}F]flutemetamol or [^{18}F]florbetaben imaging) in a large number of subjects with a view to:

- establishing the value of the knowledge of amyloid status in current diagnosis and patient management decision trees;
- understanding the use of amyloid imaging to ultimately improve clinical outcomes in novel therapy trials as a result of studying more homogenous, enriched populations.

Both of these aims will lead to enhanced treatment and care pathways and bring significant value to future clinical research in the dementia field.

It is anticipated that the amyloid enrichment study would be the larger component of the action and the diagnosis and patient management element would be a smaller component.

For the purposes of this topic document the aims outlined above will be assigned the following titles:

- Amyloid diagnostic and patient management study;
- Amyloid enrichment study.

Building on currently available AD and dementia platforms a sufficiently large number of subjects should be characterised by amyloid imaging, such that the following objectives can be met:

- Amyloid diagnostic and patient management study

  The understanding of the utility of β-amyloid imaging in the context of other biomarkers and diagnostic tests in current clinical practise, where knowledge of patient pathological status would help in current and future decision making and refinement of both diagnosis and patient management. Not only understanding the diagnostic value of a positive scan but also that of having an amyloid negative scan needs to be assessed.

- Amyloid enrichment study

  The understanding on how the use of AD-related biomarkers and specifically amyloid PET, can be used to enrich clinical trial populations to accelerate development of therapeutics effective in the preclinical/pre-dementia stage of the disease and be incorporated in disease modelling and in adaptive clinical trials.

- Combined objective

  The integration of population enrichment strategies and improved knowledge of diagnostic pathways in the AD space, to enhance current and future research in the management of AD and dementia. One example of a synergy in this space could be an increased understanding of how quantitative and region-specific image analysis techniques could be used in the future to understand pre and post therapy amyloid levels which in turn may guide the best time-window for intervention, and to better understand the mechanism of action of therapeutics and how these measures influence treatment regimes.

- Acquiring and analysing CSF samples to determine amyloid status is not an objective of this proposed action but comparison of available CSF amyloid data with imaging status will be of value.

It is expected that applicants address all the above objectives in the Short Proposal (within the available duration and maximum IMI2 contribution) and demonstrate a relevant strategy for achieving them through partnership with the industry consortium.

This will have to be fully developed with the industry consortium in the Full Proposal.

Potential synergies with existing Consortia

Considering the envisioned timelines and budget of this action, the planned work will build and leverage as much as possible on available assets and resources to successfully achieve its objectives. Synergies and complementarities should be considered, building from achievements, and incorporating when possible data and lessons learnt, while avoiding unnecessary overlapping and doubling of efforts. Collaboration by design should be a cornerstone of the proposed strategy.

In particular it is expected that this action will collaborate - including data leveraging and sharing - with the projects under the umbrella of the IMI Alzheimer's Research Platform (http://horizon2020projects.com/sc-health/imi-alzheimers-projects-launch-joint-platform/) and in particular with:

- EPAD http://synapse-pi.com/epad/index.html : the European Prevention of Alzheimer's Dementia (EPAD) project aims to develop an infrastructure that efficiently enables the undertaking of adaptive, multi-arm Proof of Concept studies for early and accurate decisions on the ongoing development of drug candidates or drug combinations. This includes evaluating patients' reactions to a drug early in a clinical trial and modifying the trial according to these reactions. The EPAD project will initially run for five years. EPAD clinical phenotyping and genotyping information will have to be tied to the amyloid PET results obtained in the action generated by this topic to guide the disease modelling and adaptive clinical trial.
- EMIF (http://www.emif.eu/): The European Medical Information Framework is an IMI project integrating existing in-depth AD databases with large scale electronic health records. One of IMI-EMIF's goals is to establish and qualify early biomarkers of AD that might be beneficial in early intervention trials.

Furthermore synergies should be considered at the European level with relevant EU Joint Programming Initiative – Neurodegenerative Disease Research (JPND) actions

(http://www.neurodegenerationresearch.eu/initiatives/), other European research projects (e.g. PREDICTAD: http://www.predictad.eu/, the LUPAS project http://www.lupas-amyloid.eu) and research infrastructure initiatives, as well as at national level with relevant actions.

To optimise impact of this action, collaboration and synergies with other relevant non-European initiatives should also be considered (see for example the Alzheimer's pillar of the Accelerating Medicines Platform (AMP-AD: http://www.nih.gov/science/amp/alzheimers.htm); the Alzheimer's Disease Neuroimaging Initiative (ADNI: http://www.adni-info.org/); the Australian Imaging, Biomarker & Lifestyle Flagship Study of Ageing (AIBL: http://www.aibl.csiro.au/).

Expected key deliverables

Deliverable 1 Amyloid Diagnostic and Patient Management Study

Diagnosis of Alzheimer's disease based on clinical grounds alone has shown to be difficult and hampered by a significant error rate[2]. In addition, there is a known delay in providing an accurate diagnosis, with an average time from symptom onset to final diagnosis being around two years.

As a result key deliverables from this study should include:

- demonstration with appropriately powered statistical significance of the utility of β-amyloid imaging in a clinically relevant population, such as subjective memory complainers (SMC) and individuals with mild cognitive impairment (MCI) due to suspected AD, through execution of a prospective cohort study. Endpoints could include changes in diagnostic confidence, changes in diagnosis, and changes in planned and actual patient management plans, and additional data that could be used to assess cost effectiveness. The study should be designed to demonstrate clinical utility by way of having a diagnosis with high clinical certainty, understanding the contribution of different imaging biomarkers used in terms of diagnostic accuracy and certainty and time to diagnosis;
- understanding and demonstration of clinically relevant outcomes including optimisation of patient management as determined by their PET β-amyloid scan (in the context of other available clinical information);
- demonstration of the clinical utility of an accurate diagnosis in a clinically uncertain patient, including change in patient management (pharmacological and non-pharmacological intervention) and patient reported outcomes;
- increased understanding of the natural history of β-amyloid negative cognitive impairment by possible follow up of amyloid PET scanning in all relevant subjects.

Deliverable 2 Amyloid Enrichment Study

- a Europe-wide investigator network, with all the necessary training and instrumentation to conduct a multi-site clinical study in the field of AD and the opportunity to generate unique longitudinal data;
- a cohort of at risk preclinical subjects (evidence of amyloid pathology but no clinical symptoms) and early clinical subjects (subjects with MCI due to AD or prodromal subjects – and not mild dementia patients), n = ± 6000, suitably characterised through amyloid imaging, enabling patients with an AD biosignature to be available for therapeutic intervention by inclusion in therapeutic clinical trials;
- a multimodal biomarker approach enabling a deeper understanding of biomarker changes early in the clinical course of the disease;
- provision of information on the accumulation, and location of β-amyloid in subjects undergoing amyloid PET imaging will provide information on the accumulation, and location of pathology facilitating a greater understanding of the changes taking place as disease progresses or as a result of therapeutic intervention;

- the definition of the optimal predementia/preclinical population as a function of the combination of amyloid and other imaging modalities;
- the basis to ensure the optimal design of secondary prevention trials and the optimal window of opportunity for intervention. In the framework of this topic, secondary prevention is defined as a delay in the onset of clinical symptoms among people with preclinical evidence for Alzheimer Disease pathology (i.e. Preclinical Alzheimer Disease as per NIA-AA and similar definitions) and a delay in the onset of clinical dementia among people with such evidence who also already show some clinical symptoms (i.e. MCI due to Alzheimer Disease or prodromal Alzheimer Disease and similar definitions);
- contribution to the creation of novel clinical trial approaches for the future prevention of AD which involve sharing and rotating control/placebo groups in order to ensure maximal exposure to participants to receive therapeutic interventions.

Combined Deliverables

- preliminary Scientific Advice (SA) from key regulatory bodies on appropriate design of clinical studies integrated into existing frameworks in line with the expectations of the European Medicines Agency;
- improved knowledge of how biomarkers can be integrated into clinical practice and guide optimal patient population for new treatments;
- correlation of clinical phenotype (semiology and severity) with β-Amyloid density (SUVR) and location throughout the disease continuum from pre-dementia to dementia;
- generation of meaningful clinical and health economic endpoints (after feedback from Health Technology Assessments (HTAs)) assessing cost effectiveness, change in patient management, clinical outcome improvement and/or utilisation of healthcare resources that is suitable for future reimbursement purposes;
- a strategy to obtain Scientific Advice from key regulatory bodies and interaction with HTA programs will be required to optimise opportunity to change healthcare practices on completion of the programme.

Industry Consortium

GE Healthcare Life Sciences, Janssen, Piramal Imaging

The industrial participants includes medical devices (for example image analysis software and associated expertise) and imaging tracer expertise (including the ability to set up required manufacturing centres to appropriate GMP standards, site set up including image acquisition, image reader training and provision of central support for more advanced image analysis techniques).

Indicative duration of the action

The indicative duration of the action is 60 months.

Indicative budget

The indicative in kind contribution of EFPIA and EFPIA IMI2 Partners in Research will be EUR 12 000 000. Due to the global nature of the participating industry partners it is anticipated that part of these contribution will be provided from non EU/H2020 Associated Countries.

The indicative IMI2 contribution will be a maximum of EUR 12 000 000. Sufficient budget will have to be reserved for Scientific Advice at the European Medicine Agency (EMA) to support relevant activities (see WP 1,2,3).

Applicant Consortium

The Applicant consortium will be selected on the basis of the submitted Short Proposal.

Applicants are expected to address all the above objectives in the Short Proposal (within the available duration and maximum IMI2 contribution) and demonstrate a relevant strategy for achieving them, through partnership with the industry consortium.

The applicant consortium is expected to make key contributions to all the defined deliverables in synergy with the industry consortium and complementing their contributions and expertise. It is expected to be multidisciplinary and to enable effective collaboration between key stakeholders (e.g. academia, hospitals, SMEs, patients and patient organisations, public health organisations, regulatory agencies, health technology bodies).

This may require mobilisation as appropriate of expertise in: dementia current diagnostic algorithms and patient management; design and execution of multi-site clinical trials in accordance to GCP and real world clinical research capabilities; subject recruitment and diagnostic work-up consistent with protocol requirements; willingness to follow up patients longitudinally; site and subject monitoring capabilities; PET scanning, image acquisition image read training and analysis (with image transfer to central analysis if required); experience in amyloid imaging specifically; biostatistics and data management; understanding of Regulatory and HTA requirements in EU; large program oversight, governance and project management; CRO capabilities/management; site set up including camera set up; scientific and media communications expertise, ethical expertise and outreach to patients and other key stakeholders.

It may also require mobilising as appropriate, the following resources: a distribution network for short-lived radioisotopes to be shipped to clinical centres, Imaging software and hardware, access to relevant clinical cohorts and patient groups in the routine clinical setting, Involvement of patient organisations.

Due to the complexities of running a large multi-centre clinical trial designed to support regulatory submissions, it is common practice of both industry funded and H2020 projects to engage a Contract Research Organisation (CRO) (ideally as a partner) to implement and monitor the clinical sites to ensure compliance, thus it is expected that the applicant consortium will provide this capability.

Suggested architecture of the full proposal

In their short proposal the applicant should come with their suggestion for such architecture taking in consideration the below industry contributions and expertise.

The final architecture of the Full Proposal will be defined together with the industry consortium and should enable activities aiming at achieving all objectives and deliverables as indicated in the previous relevant sections and in collaboration with the EFPIA partners.

The below suggested architecture is just an example and different designs are welcome, if properly justified.

The proposal should provide the first five year grant period research plan. It is expected that the majority of subjects will be identified from within existing registries and longitudinal cohorts, though additional subjects may be required to fulfil the needs of the Amyloid Diagnostic and Patient Management Study.

Four main work packages are suggested: For each Work Package key tasks required are outlined as well as the key contributions provided by the industry partners.

Work Package 1: Overall Project Governance, Strategic Oversight and Programme Management

(includes both amyloid diagnostic and patient management study and amyloid enrichment study)

A governance structure is required to provide scientific oversight and guidance to the overall project. It will also be required to ensure appropriate integration of the action generated by this topic in the IMI Alzheimer's Research Platform and connectivity between the two elements of the topic as well as managing synergies with any on-going research programs or existing consortia that this project may be accessing.

It is expected that members from both private and public partners will serve on the steering and management boards and together they will develop alignment on the governance structure (overall and at Work Package level). This will support the necessary level of project management for effective planning, design, operationalisation and delivery of the two studies and all their objectives within a harmonised framework and the analysis of their data in a timely and effective manner to an agreed communication and publication plan. It should also provide a forum to resolve any key issues or risks that develop during the lifetime of the studies.

The work will also consist of the exact definition of the patient population and protocols to be included in the two studies, the following through with EMA and HTAs of the critical/strategic parts whilst other research objectives continued to be in order for the action to fulfil within timelines and budget the objectives and achieve the key deliverables as in section 6 part C.

This Work Package should also operationalise how multiple PET amyloid tracers could be used in both studies such that all data generated are valid with respect to determining scientific and clinical objectives, how a continuous and efficient supply of amyloid PET tracers is available on a both routine and countrywide basis to meet the goals of the two studies, and deliver a qualified Clinical Imaging Network able to achieve the objectives of the program in an efficient manner.

EFPIA Contribution:

- clinical, imaging and regulatory expertise in amyloid imaging clinical studies;
- in house data and know-how on imaging amyloid in various populations;
- statistical expertise in imaging clinical studies;
- expertise in large program oversight, governance and management;
- imaging clinical trial protocol development;
- strategic expertise in set up, maintenance, production and delivery logistics of amyloid PET manufacturing facilities.

Work Package 2: Delivery of Amyloid Diagnostic and Patient Management Study

The aim of this Work Package is to ensure the effective functioning of the action in order to achieve the objectives on time and within budget and achieve the key aims of Deliverable 1. Specific tasks groups will be required to take on these responsibilities between EFPIA and the other partners, such groups could include project management, clinical operations, regulatory interactions, manufacturing logistics, data management. Critical to this Work Package will be the identification of imaging sites to be included in the clinical utility study and the setup of these sites to participate and the execution of the study including all aspects of the clinical trial, recruitment, scanning, data management, statistics, how best to deploy quantification software and optimal management of clinical doses from available manufacture batches of amyloid imaging agent. In particular it is expected the applicant consortium works with the EFPIA consortium to identify the most cost effective use of amyloid PET tracer availability by working with manufacturing imaging sites to schedule subjects suitably. (It is expected that up to 1000 doses will be required to deliver this objective depending on the final clinical trial design).

The Work Package should insure clinical trial project management covering all aspects such as clinical operations, data management, imaging operations etc. It is expected that opportunities for synergies across clinical project management across all aspects of this project and associated programs will be demonstrated. The work will include Data analysis, reporting and publication as appropriate, production of documentation (e.g. protocol synopsis, full protocol, case report forms, statistical analysis planning, background packages)

for EMA and HTA interactions and interaction with operational delivery teams to ensure accurate translation of strategic initiatives into operational setup, execution and delivery.

EFPIA Contribution

- operational expertise to ensure cross site consistency of general site set up and patient recruitment methods;
- 1200 batches of PET amyloid PET radiopharmaceutical equally distributed between [^{18}F]flutemetamol and [^{18}F]florbetaben (enabling up to 3-6000 clinical doses if managed effectively) (to be split between work packages 2 and 3);
- image Reading Expertise available to all sites performing amyloid imaging;
- cloud based β-Amyloid Imaging Software development, site training and Software license availability for the quantitation and analysis of β-Amyloid;
- manufacturing (GMP) site set up and maintenance. Manufacturing planning and logistics in place to ensure timely and consistent delivery of tracer;
- internal project management, clinical, regulatory, imaging and software resource as required;
- clinical study synopsis and protocol/case report form development expertise;
- trial analysis expertise.

Work Package 3: Delivery of Amyloid Enrichment Study

The aim of this Work Package is to ensure the effective functioning of the action in order to achieve the objectives on time and within budget and achieve the key aims of Deliverable 2. Delivery of the Amyloid Enrichment Study will require expertise from both the industry partners and the applicant consortium in order to deliver routine access to amyloid scans for the purpose of characterisation of the majority of the modelling cohort and the achievement of the key deliverables. Importantly this will include the optimal management of clinical doses from available manufacture batches of amyloid imaging agent. It is expected the applicant consortium works with the EFPIA consortium to identify the most cost effective use of amyloid PET tracer availability by working with manufacturing imaging sites to schedule subjects suitably.

EFPIA Contribution

- clinical medical, statistical expertise in clinical trial design and regulatory agency interactions;
- internal project management, clinical, regulatory, imaging and software resource as required;
- manufacturing (GMP) site set up and maintenance;
- 1200 batches of PET amyloid PET radiopharmaceutical, equally distributed between [^{18}F]flutemetamol and [^{18}F]florbetaben (enabling up to approximate 3-6000 clinical doses if managed effectively) (to be split between work packages 2 and 3;
- manufacturing planning and logistics in place to ensure timely and consistent delivery of tracer;
- site set up including camera set up, image acquisition and image read training if required;
- cloud based β-Amyloid imaging software development, site training and Software license availability for the Quantitation and Analysis of β-Amyloid;
- image analysis expertise for amyloid PET imaging.

Work Package 4: Communication and Dissemination.

Set up an effective communication infrastructure and tools, and foster the integrative process both within the consortium (between work packages, team members, EFPIA stakeholders and other participants) as well as

outside the project to ensure alignment with all stakeholders and collaboration with other relevant projects and initiatives. This should include platform(s) for information sharing (e.g. sharepoint or similar for file-sharing, version control) as well as communication tools (e.g. templates, branding, teleconference, video conference, live filesharing etc). It will include development of plans for final reporting, conference presentation and dissemination of data by other means (media, internet, books etc.) and feedback of final report to Regulatory Agencies and HTAs.

EFPIA Contribution

- interaction with physicians and other industrial collaborators to ensure other ad-hoc analyses are incorporated into work streams if required;
- legal and IP expertise, regulatory expertise;
- publication planning and medical writing expertise.

Glossary

AE	Adverse Events
AD	Alzheimer's Disease
CRO	Contract Research Organisation
EFPIA	European Federation of Pharmaceutical Companies and Associations
EMA	European Medicines Agency
GCP	Good Clinical Practice
GMP	Good Manufacturing Practice
HTA	Health Technology Assessment
IP	Intellectual Property
MCI	Mild Cognitive Impairment
PET	Positron Emission Tomography
SMC	Subjective memory complainers
SUVR	Standard Uptake Value Ratio
US	United States

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Topic 5: Evolving models of patient engagement and access for earlier identification of Alzheimer's disease: Phased expansion study

Topic details

Topic code	IMI2-2015-05-05
Action type	Research and Innovation Action (RIA)
Submission & evaluation process	2 stages

Background and problem statement

The clinical paradigm for Alzheimer's disease (AD) largely engages patients in the later clinical stages of disease, with the majority of patients and caregivers not seeking and/or receiving care until moderate or severe dementia has ensued. The current clinical paradigm does not support or emphasise the need for early detection, diagnosis or action when symptoms of AD first begin. To compound the issue, many physicians are reluctant to provide a diagnosis, because they perceive AD as an incurable disease without adequate treatment and supports. This lack of urgency not only currently compromises the quality of patient care, but also robs patients of access to available support resources and services. This lack of system preparedness for early action will also dramatically impact patient care once disease modifying agents are available.

The scientific community, many regulatory agencies, and advocacy groups are now aligned on the understanding that AD is a pathophysiologic neurodegenerative brain disorder that begins one or two decades prior to symptomatic presentation. Initial efforts in AD treatment development and clinical diagnostic paradigms focused on the most clinically evident stage of AD, dementia. The dementia stage is now clearly identified as a late stage in the pathological progression of the disease. Despite a shift in the scientific paradigm to address the disease in its earlier pathological stages such as mild dementia, prodromal AD and even at the time of preclinical pathology, the front line of clinical management continues to focus on the later stages of the disease, with most diagnoses occurring at the moderate and severe stages of dementia. Yet, at the same time, treatment development has clearly begun a shift to an earlier paradigm, seeking volunteers at earlier stages of disease (prodromal, mild, and in some geographies, preclinical). This dissociation between when patients are identified by their healthcare providers as having AD and the patient populations needed to develop disease modifying therapies at earlier stages of disease is a significant impediment to successfully accomplishing clinical research with a goal of discovering impactful treatments.

However, clinical trial participation is not the only benefit to a timely diagnosis. Many advocacy groups and AD specialists are now demonstrating that, aside from the clinically available therapies which provide modest benefit, non-pharmaceutical interventions are also available and beneficial for the caregiver and patient. For example, for the patient, increased socialisation, exercise, art programs, nutritional education, cognitive therapy, and clinical trial participation can prove valuable. For the caregiver, appropriate counselling on a variety of topics (such as driving safety/cessation, finances, life planning, non-pharmacological management of behavioural symptoms) can provide substantial improvement in quality of life for both the patient and caregivers. To have the greatest impact, these interventions are best employed in the earliest clinical stages of disease to maximize the benefit throughout all stages of disease. With over 34 million AD patients worldwide, the current clinical paradigm of diagnosing AD in later clinical stages does a disservice. By this time, patients have often declined to the point they lack the insight and judgment to play a participative role in their care, and certainly have declined too far to have participation in clinical trials be an option that they and their loved ones can consider. The field must shift to greater public awareness of the importance of an early diagnosis and improved medical efficiency in identifying AD as soon as clinical symptoms emerge.

Not only could these efforts improve clinical access to treatment and support resources and patient engagement earlier in the stages of disease, they will also help widen the funnel for clinical trial recruitment and earlier treatment development.

There is a need to proactively assess the obstacles to patient presentation and diagnosis. There is a need to determine optimal patient engagement practices in the AD healthcare and clinical trial environments to evolve the field toward improved early patient identification and clinical research involvement. In order to achieve these goals, several broad steps are required:

- to collect data on a new early paradigm for diagnostic and therapeutic advancements to help local decision makers;
- to broaden the understanding of the experience of AD beyond the last few years of its course;
- to increase the connectivity between AD thought leaders and AD clinicians;
- to create a sense of urgency for the societal and economic impact of AD, especially among policymakers and governments.

Need and opportunity for public-private collaborative research

The magnitude and complexity of the issue is such that it can only be addressed by a major public-private-partnership involving a variety of stakeholders. This is a program that cannot be accomplished by an individual research group or company and will require a strong collaborative effort to be successful.

Potential framework for patient access work stream:

In order to evolve to a paradigm of earlier disease identification and patient engagement, there must be a shift from the current clinical paradigm and identify new solutions. Achieving this goal cannot be accomplished by any individual effort or single solution. It can only be achieved through a consortium of industry, academia, practitioners, advocacy groups, and other committed stakeholders who are willing to test new solutions. These solutions may be assessed across multiple countries and clinical care communities for their ability to address the needs of patients and caregivers.

The evolution of the current AD environment can be achieved in a variety of ways that will require customization for different types of clinics, trial centres, localities and regulatory environments. By setting up models of patient engagement and access throughout Europe, using a variety of methods and metrics of success, we can develop options for efficient resource utilization that can be implemented broadly to provide larger numbers of AD patients with appropriate care resources, and establish an enhanced portal for bringing volunteers into clinical trials to speed research & development.

Overall objectives

Overall Hypothesis

We hypothesize that conducting multi-site comparable experiments of patient access and engagement models in a variety of communities that are successful in the identification and diagnosis of early stages of symptomatic AD will facilitate development of enhanced resource access models for care, assist integration with educational/awareness programs, thereby driving enrolment into clinical trials.

It is of critical importance that multiple models are experimented, tested and shared, as no one model is likely to work across all healthcare systems in the EFPIA geographies.

For purposes of this proposal, 'community' is broadly defined as a self-organized, tightly-linked, geographic collection of resources and stakeholders collaboratively working to improve services and support to engage, diagnose, and treat people with AD, with the aim of accomplishing some or all of the steps outlined above.

The overall objectives of the action generated from this topic are the following:

Objectives (restricted scope is expected for Phase 1)

- to establish multiple key regional project sites (demonstration sites) across Europe to identify and test models of efficient earlier identification of mild AD dementia and prodromal AD patients, and awareness of AD risk;
- to assess key tools, mechanisms and processes for community engagement and patient identification and resource utilization in various communities;
- to compare and contrast various patient access models and how they contribute to improved detection, diagnosis, and clinical research in these communities;
- based on findings, to establish archetypes of patient access models for implementation in similar communities, in synergy and collaboration with existing country specific government and non-government stakeholders;
- to advocate and distribute access models for broader application and for replication.

Applicants are expected to address all the above objectives in the Short Proposal (within the available duration and maximum IMI2 contribution) and demonstrate a relevant strategy for achieving them, through partnership with the industry consortium.

This will have to be fully developed with the industry consortium and or associated partners in the Full Proposal.

Potential synergies with existing Consortia

Applicants have to take in consideration for the development of their short proposal that there are already several initiatives on-going in the field, both in Europe and globally. Non-government advocacy organisations can and should be considered as potential collaborators *in applicant proposals*.

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

This action is intended to provide the opportunity within IMI2 to leverage substantial AD-related patient engagement efforts with existing efforts, including efforts to bring national advocacy agendas to the local level.

- JPNP – Joint Programme – Neurodegenerative Disease research: as a global research initiative, this program is aligning research across Europe with collaborative projects that will provide insight and value for this IMI2 proposal: http://www.neurodegenerationresearch.eu/;
- ADI – Alzheimer's Disease International (http://www.alz.co.uk/) has accepted the task of developing an AD clinical trial consumer campaign in conjunction with the Organisation for Economic Co-operation and Development (OECD), Global CEO Initiative (in Alzheimer's) (CEOi) and World Dementia Council. Such material could be leveraged/tested in these demonstration communities;
- ALCOVE (http://www.alcove-project.eu/)– as a joint action funded by the European Commission to produce recommendations for policymakers in dementia, this program promotes a timely diagnosis of AD and will provide synergy and collaborative opportunities with the current proposal;
- IMI-EPAD (http://www.synapse-managers.com/epad/index.html) – the IMI European Prevention of AD program will provide additional opportunities to develop patient access models in early AD populations as part of its efforts in prevention trial design;

- Alzheimer's Europe – The annual Value of Knowing Survey (http://www.alzheimer-europe.org/Research/Value-of-Knowing) , conducted by Alzheimer's Europe and the Harvard School of Public Health measures the public perceptions and awareness of AD and the AD diagnosis rates in several major European countries and may be able to be used as baseline data and/or a common survey tool;
- OECD – During the course of 2015 the Organisation for Economic Co-operation and Development is developing AD metrics that can be used by its 34 member countries. The successes and challenges of the measurements in the Demonstration sites may be able to help inform that initiative;
- In-MINDD - an FP7 funded initiative (http://www.inmindd.eu/) that seeks to promote long term brain health and prevent or at least delay the onset of dementia by combining social innovation, multifactorial modelling and clinical expertise. Collaborations and synergies may exist for proposed tactics.

Expected key deliverables

This action will promote establishment of model demonstration sites implementing successful approaches for engaging patients and providing access to support resources and services. Tactics in various regional, demographic, regulatory, payer, and care-model micro-environments should be measured by a few key universal metrics across project sites and programs and specific local metrics as recommended by the investigators. In addition to testing of established tactics and metrics, opportunity will be available for development of novel and assessment metrics. Ideally some tactics would need to be implemented at multiple regional sites for comparison across regions.

Examples of potential key methods (this should not be considered an exhaustive list*):*

- resource availability: diagnostic expertise, specialized biomarker programs, genetics, counselling, support/education services, social services, caregiver services/support, financial programs, treatment charity programs, networking of local resources, day programs and respite services;
- screening tools: development or validation of efficient screening tools for clinics and health fairs to facilitate universal acceptance of early identification program;
- educational Programs: community outreach, public forums, etc. Education to impact belief and behaviours related to the benefit of early diagnosis and understanding of what is available to help families and patients manage care and plan for the future. Understanding of Alzheimer's pathology as a process that begins decades before clinical symptoms. Difference between normal aging and AD. Education and awareness programs on AD risk factors such as type 2 diabetes, other cardiac and vascular risk factors, genetics, family history, diet, exercise and cognitive engagement;
- patient recruitment tools: community lectures, local engagements, referrer education and engagement, health fares, memory screening events, advertising of expertise, local media (TV, radio, web, print). Specialized Website, timely electronic magazines;
- public awareness: Leverage public awareness campaigns about benefits of earlier diagnosis with the appropriate community partners. Broad awareness programs on risk factors for AD;
- patient flow: Establishment of systematic patient flow and communication between community physicians and AD specialists, researchers and/or memory clinics;
- economic impact: evaluation and education regarding economic impact on early diagnosis and the value of knowing ones diagnosis;
- advanced diagnostic tools: Educate on benefits of advanced diagnostic biomarkers to assess value for patient awareness and brining patients in to the clinic;
- technology: Utilization of new technologies for patient data collection, utilization, monitoring, distributions of information, training, recruitment and education;
- alternative care: exercise programs, dietary programs, art/music/dance engagement, community event programs, support groups, caregiver counselling groups, brain/cognitive health programs, cognitive

stimulation therapy, and other person-centred care models (establishing a local care community). How do these programs impact bringing earlier patients in to the clinic and clinical trials?;

- collaborative partnerships: among community stakeholders to facilitate earlier diagnosis and access to treatment and support for people with AD and their families;
- social Media: Facebook, Twitter, blog sites, YouTube channel;
- healthcare data and digital access: The use of patient databases to provide insights into the natural and treatment history of AD;
- registry development: Creation of local and broader community registries of people interested in AD information and research. Educating and providing links to existing registries and resources.

POTENTIAL UNIVERSAL METRICS – requires a known local baseline

- change in enrolment in clinical trials;
- change in patient visits/referrals from baseline;
- change in accuracy of diagnosis (e.g. biomarker based, or compared to pre-referral diagnosis);
- change in percentage of earlier stage diagnoses;
- change in time from symptom presentation and initial assessment to diagnosis.

OTHER POTENTIAL LOCAL METRIC CATEGORIES

- change in demographics (minority populations, age, etc.) of clinical patient population;
- change in social resource (support groups, social work services, etc.) utilisation;
- change in treatment (non-pharma/non-traditional treatments, neutriceuticals, SOC, CTs, other) utilisation;
- change in referrals to clinical trials (absolute #/HCP referring, number of HCPs referring);
- change in referrals to dementia specialist (relevant for PCP sites) (absolute #/HCP referring, number of HCPs referring);
- changes in perception about earlier diagnosis;
- improvement in reported caregiver burden;
- median number of years of follow up. Median number of follow up visits;
- change in the number of patients referred to the clinical site by general practitioners, geriatricians, neurologist or psychiatrists;
- evaluation and use of various diagnostic tools by general practitioners and specialists for improving timely and accurate diagnosis.

Overall action impact goals:

- The intention of this action is to initially assess key metrics and access models for prioritization applicability. Methods and metrics should be analysed to measure efficiency and efficacy, and categorized into archetype models customized for various community types. Once successful archetype programs of paradigm shift are identified in successful models, they can be replicated in similar communities. This will be used to facilitate further development of independent efficient care models that engage more patients, engage them earlier in the course of disease, and provide access to a wider array of resources and aimed at improving access and enrolment in clinical research programs.

Industry Consortium

Lilly, Astrazeneca

Potential in kind contributions could include (but are not limited to):

- project management
- data management
- scientific expert speakers
- communication and outreach expertise
- training resources/materials
- regulatory experts
- health technology assessment and economist experts.

Indicative duration of the action

The indicative duration of the action is 30 months.

Future action expansion

Potential applicants should be aware that the Innovative Medicines Initiative 2 (IMI2) Joint Undertaking may publish another Call for proposals restricted to those actions already selected under this Call at a later stage 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.

Phase two would have a duration of up to 5 years and will only be initiated after a futility analysis of the progress of phase one, and contingent on certain milestones being achieved to justify a phase two. This phase two extension would aim to provide opportunity to expand successful phase one programs with additional funding. This phased expansion would allow for timely building on the progress and outcomes of the initial deliverables.

As issues regarding access of resources, community outreach, awareness and engagement require individualization for each community, there is no expectation of a one-size-fits-all model. For this reason, the uniqueness of this project's goals and design justify and require an expectation of exploratory endpoints. There will be expected learnings in the initial phase of these projects that may likely inspire improvements in efficiency and methodologies moving forward. For this reason, launching this program with a built in opportunity to expand after the initial 30 months, increase resources and budgets, grow, change and/or add study sites offers an ideal model for addressing the aims of this program.

Indicative budget

The indicative EFPIA in kind contribution will be EUR 2 043 000. Due to the global nature of the participating industry partners it is anticipated that part of the EFPIA contribution will be provided from non-EU/H2020 associated countries.

The indicative IMI2 contribution will be a maximum of EUR 2 043 000.

Applicant Consortium

The Applicant consortium will be selected on the basis of the submitted Short Proposal.

The applicant consortium is expected to address all the research objectives and make key contributions to the deliverables in synergy with the industry consortium and complementing the contributions of the participating EFPIA partners.

Successful implementation will depend upon participation by institution involved in patient care, education, support, and community outreach, as well as those participating in active clinical research programs and patient organizations that have a focus in the countries of concern. In order to meet the key objectives of the project, an emphasis should be placed on variety of healthcare and patient population environments spread across key European countries.

This may require mobilisation as appropriate of a network of multiple partners that may include:

- academic basic, translational, clinical research scientists;
- regulatory expertise;
- economic or public health modelling experts;
- professional Project Management Organisations;
- local advocacy organisations.

Due to the structure of this phased expansion design, we encourage focused and concrete applications that can clearly correspond to the outlined objectives and that can demonstrate successful inclusion of the expertise outlined above.

Suggested architecture of the full proposal

The final architecture of the Full Proposal will be defined together with the industry consortium and should enable activities aiming at achieving all objectives and deliverables as indicated in the previous relevant sections and in collaboration with the EFPIA partners.

Project design should consist of establishing multiple varieties of key regional model demonstration sites that will employ proposed methods with the aim of improving patient access and engagement, to facilitate an earlier entry point for clinical care and research involvement. Projects may take a stepwise approach such as first identifying patient engagement programs across the EU, developing a framework for evaluation to include various methods, metrics, and socio-economic outcomes. Novel patient engagement programs may be based on successful features of existing AD and other chronic disease programs, or other patient engagement models, and tailoring programs to specific stakeholder (primary care, specialty, local, regional, etc.), influencing design and duration of projects. Initial programs staging for later scaling of successful models are expected for the current phase one Call.

Potential Work Packages

- **Access/engagement Model development and assessment:**
    - to establish multiple IMI2 key regional projects to identify and test models for efficient earlier identification of mild AD dementia and prodromal AD patients;
    - to assess key tools, mechanisms and processes for local engagement and patient identification for care and resource utilization in various communities;
    - to compare and contrast various patient access models and how they contribute to improved detection and diagnosis in these communities;

- to build and scale model programs for further implementation, look for systematic changes that can make the demonstration site experiment sustainable after IMI2;
- to evaluate whether certain healthcare systems or community archetypes have greater success with different methods and/or activities.

- **Modelling economic and public health impact and Guideline development:**
  - to work with regional experts to assess key impact on local economic health care and public access to resources;
  - based on findings, to establish recommendations for archetypes of patient access models for implementation in similar communities;
  - to share and distribute access models for broader application and for replication at the country-specific level.
- **Administration and management:**
  - in kind contribution of the EFPIA Industry participants would fund and host regular (timing to be confirmed) roundtable discussions for the Demonstration sites to come together and discuss ideas and share learnings. The goal is not to drive to one consensus position, but instead to encourage experimentation and transparent dialogue.

Additionally, the industry partners can and will provide project management support for the overall project management and universal metrics collection as well as writing resources, as appropriate. An additional goal is to ensure broad dissemination of the experiments and results such that countries that are not selected as demonstration sites will still be able to benefit from the learning.

Topic 6: From ApoE biology to validated Alzheimer's disease targets

Topic details

Topic code	IMI2-2015-05-06
Action type	Research and Innovation Action (RIA)
Submission & evaluation process	2 stages

Background and problem statement

Alzheimer's disease (AD) currently affects over 35 million people world-wide, and these numbers are expected to grow substantially over the next few decades. Current treatments treat the cognitive symptoms associated with AD with only modest efficacy and there are no medicines that slow the progression of the disease. Research over the past few decades has predominantly focused on understanding how beta amyloid (Aβ) formation leads to disease pathology based on autosomal dominant mutations of amyloid precursor protein, presenilin1 and presenilin2 that cause early onset Alzheimer's disease. Accordingly, drug discovery efforts to date have focused on these pathways. However, these mutations account for less than 5% of all AD cases.

In contrast to familial AD mutations, Apolipoprotein E (ApoE) ε4 is the most prominent risk factor for sporadic, late-onset AD (LOAD), which comprises over 95% of AD cases. At least one copy of the ApoE ε4 gene is found in approximately 60% of AD cases, with one ε4 allele conferring a threefold increased risk and two ε4 alleles conferring a twelvefold increased risk of developing the disease. Conversely, ApoE ε2 protects against the disease. ApoE ε4 (ApoE4) carriers have an earlier disease age of onset and the disease progresses faster.

While ApoE4 has been clearly established as the most prominent AD susceptibility gene, there has been comparatively little research into the link with disease pathology. Some have suggested that ApoE4 is less-protective than the other two ApoE isoforms ε2 and ε3, while others maintain that ApoE4 exerts a toxic gain-of-function. The molecular basis of ApoE4 pathology is also uncertain, with purported effects on lipid metabolism, beta amyloid formation, mitochondrial function, and poorer recovery from trauma, as well as other factors.

There is also no clear rationale how to modulate ApoE4 as a treatment approach for AD. One hypothesis suggests that AD pathology is the result of reduced ApoE function, particularly as it relates to toxic beta amyloid species. Proposed approaches based on this theory seek to directly or indirectly elevate ApoE levels or otherwise improve ApoE function, such as increasing lipidation. Some targets utilizing this approach include Liver X Receptor (LXR) agonists, Retinoid X Receptor (RXR) agonists, and ApoE mimetics. Others suggest that expression of ApoE, particularlyApoE4, is detrimental and seek methods to decrease ApoE function, such as an anti-ApoE antibody. Still others take an intermediate approach with the suggestion that ApoE4 can be structurally modified by small molecule drugs to take on the conformation of ApoE3. In this case the pathological aspects of ApoE4 are eliminated and increased healthy ApoE function can occur.

Need and opportunity for public-private collaborative research

The magnitude and complexity of the issue is such that it can only be addressed by a major public-private-partnership involving a variety of stakeholders. This is a program that cannot be accomplished by an individual research group or company and will require a strong collaborative effort to be successful.

Despite being identified as the single biggest risk factor for the most prevalent form of AD, LOAD, over 20 years ago, the number of published studies investigating ApoE is about one-tenth the number of Aβ studies and less than half the number of investigations into tau-related neurofibrillary tangles, the other hallmark of AD pathology. Currently ApoE research is being conducted by a relatively small number of academic laboratories and the mechanism by which ApoE4 increases the risk of developing AD remains to be elucidated. Most AD drugs that attempt to slow the progression of the disease that have been tested in clinical trials target specific aspects of Aβ formation and clearance. AD patients that are carriers of ApoE4 tend to show worse outcomes in these trials. The few drugs targeting ApoE-related mechanisms that have been identified did not reach advanced clinical trials.

A partnership between academic researchers with the knowledge on ApoE biology, small and medium sized enterprises (SMEs) with innovative technologies, and biopharmaceutical industry endorsing the approach and providing the competencies and capability for target and drug discovery and development to move from basic knowledge to new treatments, is necessary to clarify further the nature of the ApoE4-related liability in AD and identify novel methods for targeting this liability to more effectively treat the disease and achieve disease modification in this large patient population.

Overall objectives

The aim of the action to be generated from this topic is to identify critical mechanism(s) by which ApoE4 leads to the development of AD as a basis for new treatment approaches based on these basic research findings, and identify biomarkers in support of treating ApoE4-positive patients. An important component in this regard will also be to understand why ApoE ε2 plays a protective role. While it is important to build on the available knowledge, the goal of this topic is to understand the role of ApoE4 in the development of AD irrespective of previous hypotheses. Specifically, research will seek to understand how ApoE4 leads to AD and not how ApoE4 might fit into the Aβ hypothesis:

- to clarify the role of ApoE as a risk factor in the development of AD/LOAD. Increase understanding of how ApoE4 interacts with other AD risk and genetic factors that influence the development of AD in homo- or heterozygous ApoE4 carriers;
- to examine processes relevant for neurodegeneration beyond the ApoE4 interaction with Aβ, such as decreased synaptic integrity, brain atrophy, mitochondrial dysfunction and neuro-inflammation. Identify the time course of ApoE4 effects on neurodegeneration. Elucidate a ‘toxic gain of function’ vs. ‘loss of function’ for both of which evidence has been provided. Investigate the protective effects of ApoE ε2. Identify promising points of intervention for novel treatment strategies, and of equal importance, identify targets to be avoided;
- to provide evidence for the identification of biomarkers (biochemical, imaging, etc.) to more readily identify the ApoE4 carriers that will convert to AD or will have a more aggressive phenotype. This may also impact the decision of when and how to intervene with treatments.

Applicants are expected to address all the above objectives in the Short Proposal (within the available duration and maximum IMI2 contribution) and demonstrate a relevant strategy for achieving them, through partnership with the industry consortium.

This will have to be fully developed with the industry consortium in the Full Proposal.

Potential synergies with existing Consortia

Considering the envisioned timelines and budget of this action, the planned work will build and leverage as much as possible on available assets and resources to successfully achieve its objectives. 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. Collaboration by design should be a cornerstone of the proposed strategy.

In particular it is expected that this action will collaborate - including data leveraging and sharing - with the projects under the umbrella of the IMI Alzheimer's Research Platform (http://horizon2020projects.com/sc-health/imi-alzheimers-projects-launch-joint-platform/ and in particular EMIF (http://www.emif.eu/) and EPAD (www.ep-ad.org)) and may share tools and knowledge with the relevant work-package of the IMI project STEMBANCC (http://stembancc.org/index.php/work-packages-in-detail/).

Synergies and complementarities should be considered (e.g. see EU Joint Programming Initiative – Neurodegenerative Disease Research (JPND, http://www.neurodegenerationresearch.eu/about/) and ERA-Net NEURON (http://www.neuron-eranet.eu/)), building from achievements, and incorporating when possible, data and lessons learnt (e.g. from LIPIDIDIET http://www.lipididiet.eu/index.php?id=6644) while avoiding unnecessary overlapping and doubling of efforts. As a basis for the bioinformatics approaches, both the ADAMS GWAS project which includes an AD arm (http://cordis.europa.eu/project/rcn/93053_en.html) as well as the IMI project Aetionomy (http://www.aetionomy.eu/index.php?id=5263) are relevant.

To optimise impact of this research project collaboration and synergies with other relevant non-European initiatives (see for example the Alzheimer's pillar of the Accelerating Medicines Platform (AMP-AD: http://www.nih.gov/science/amp/alzheimers.htm) should be taken into consideration as well.

Expected key deliverables

- A refined 'ApoE Hypothesis of AD' that details i) the role of the ApoE4 isoform in the development of LOAD neuropathology - including a clarification of the 'toxic gain of function' vs. 'loss of function' discussion that has been ongoing - and ii) the protective role of ApoE ε2. These results are expected to inform critical decisions regarding new treatment strategies for AD and associated translational strategies comprising biomarkers.
- Generation/application of highly relevant model systems capitalizing on human induced pluripotent stem cell technology in conjunction with gene editing, and other mammalian and non-mammalian neurobiological systems to enable/support the investigation of ApoE biology, and for subsequent application in drug discovery for the configuration of 'screening cascades'.
- Identification of promising 'entry points' (targets) within ApoE biology for biopharmaceutical intervention. This may be through directly modulating ApoE, impacting its function through associated receptors, or affecting upstream/downstream components ('ApoE pathway targets'). Conversely, identified targets that are not optimal 'entry points' - or could even be deleterious - will be avoided.
- The improved understanding of ApoE as a risk factor for AD and its interactions with other risk factors is expected to support the identification of individuals at greatest risk for developing AD.

The successful achievement of the expected deliverables of this action will provide the basis for a follow-up action (to be launched as part of a future Call for proposals) aimed at:

- improved understanding of the disease biology progression and identification of the optimal treatment window;
- establish ApoE4/biomarker signature (preferably in plasma) to stratify MCI/AD patients for potential ApoE biopharmaceutical interventions.

Industry Consortium

AbbVie, Biogen, Janssen and Roche.

The Research and Development organisations of the pharmaceuticals sections of the above EFPIA companies will be participating and contributing to the action generated from this topic.

Indicative duration of the action

The indicative duration of the action is 36 months.

The successful achievement of the expected deliverables of this action is anticipated to be the basis of a follow up action building from the assets and results of this initiative and to be launched as part of a future Call for proposals.

Indicative budget

The indicative EFPIA in kind contribution will be EUR 3 510 000. Due to the global nature of the participating industry partners it is anticipated that part of the EFPIA contribution will be provided from non-EU/H2020 associated countries.

The indicative IMI2 contribution will be a maximum of EUR 3 510 000.

Applicant consortium

The applicant consortium will be selected on the basis of the submitted Short Proposal.

Applicants are expected to address all the above objectives in the Short Proposal (within the available duration and maximum IMI2 contribution) and demonstrate a relevant strategy for achieving them, through partnership with the industry consortium.

This may require mobilisation as appropriate of expertise in: Alzheimer's disease pathophysiology and disease progression, ApoE and ApoE protein function and biology and interaction with AD, induced pluripotent stem cells (iPSCs) methods and technology, translational medicine, IT (Data communication and data basing, bioinformatics), pre-clinical imaging and biomarkers and project management.

It may also require mobilising, as appropriate, the following resources: access to relevant preclinical models, ApoE relevant models with high relevance to AD, and complementary to those provided by the industry (e.g. post-mortem tissue), translational tools, access to state of the art *in vivo* facility and small animal imaging, biomarkers, bioinformatics tools, bio-banks and bio-samples, relevant clinical cohorts (directly or by engaging in collaboration with relevant pre-existing consortia), engagement of SMEs able to contribute relevant technologies.

The applicant consortium partners that will provide data and samples from existing clinical studies and repositories need to demonstrate in their application that those envisaged resources can be shared among all the partners. Thus the applicants have to document in their Short Proposal that applicable legal, ethical and data privacy laws allow sharing such data and samples within the consortium and with timelines compatible with the needs of the action.

Suggested architecture of the full proposal

In their short proposal the applicants should provide their suggestion for the project architecture, taking into consideration the industry contributions and expertise below.

The final architecture of the Full Proposal will be defined together with the industry consortium and should enable activities aiming at achieving all objectives and deliverables as indicated in the previous relevant sections and in collaboration with the EFPIA partners.

Expertise:

- drug discovery and development
- experimental medicine
- high content imaging
- research into ApoE biology in models with high relevance to AD, e.g. iPSCs-derived models and animal models
- statistics and data mining

Tools:

- human pluripotent stem cell genome edited ApoE allele series
- ApoE4 Ki mouse and liver-astrocytes immortalized lines
- ApoE antibodies and immunoassays
- ApoE lipidated protein
- generation of novel transgenic model :ApoE4-ki X APP-PS2 mice
- animal models of AD (know how, protocols) plus tools to investigate (antibodies, etc)
- APP/PS1 transgenic mice
- tauopathy *in vitro* and *in vivo* models
- relevant human studies & data

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

Work Package 1: Consortium management and governance

Consortium management and governance (including potential sustainability plans in case of a follow-up action), dissemination (please see guidelines in the General Conditions to our Calls for Proposals) and communication (including collaboration with other relevant initiatives).

Work Package 2: ApoE models

Activities should aim to establish and characterise highly relevant human ApoE models and technologies, including iPSC and transgenic models, enabling and supporting the systematic investigation of ApoE biology.

By the end of the third year this Work-Package should deliver a number of technologies/models which have been validated by the consortium for robustness, reproducibility and suitability to be used in the R&D process. Relevant intermediate milestones (at year 1 and year 2) will have to be suggested.

Work Package 3: APOE and neurodegeneration

Activities include bioinformatics, *in vitro* and *in vivo* as well as *post mortem* studies in highly relevant model systems to increase our understanding of how ApoE impacts neurodegeneration in AD as well as to identify and validate targets in the ApoE pathways.

By the end of the third year this work-package should deliver a number of validated targets for therapeutic intervention. Relevant intermediate milestones (at year 1 and year 2) will have to be suggested.

Work Package 4: ApoE and AD risk factors

Activities include bioinformatics, *in vitro* and *in vivo* as well as post-mortem studies in highly relevant model systems to improve understanding of APOE interactions with other AD risk and genetic factors to identify and validate targets in the ApoE pathways.

By the end of the third year this work-package – in close collaboration with WP3- should deliver a number of validated targets for therapeutic intervention. Relevant intermediate milestones (at year 1 and year 2) will have to be suggested.

Work Package 5: Data and knowledge management

Data and knowledge management including:

- data mining efforts for integrating in an unbiased manner knowledge from public sources (e.g. literature and public databases) to knowledge generated from WP2 to WP4;
- establishment of data format and content standards for data collection and data management in order to ensure interoperability to quality standards and optimal use of IMI resources (e.g. technical solutions for data storage, management, analysis or visualisation should always re-use existing solutions where possible in preference to the development of new resources);
- development and delivery of the data and knowledge management plan, illustrating clearly how the guidelines above are being adhered to (see details of expectations in the general conditions of the Call).

By the end of the third year this work-package should deliver an integrated knowledge base of ApoE biology in support of target discovery for therapeutic intervention and biomarker identification. Relevant intermediate milestones (at year 1 and year 2) will have to be suggested.

Glossary

Aβ	beta amyloid
AD	Alzheimer's disease
APP	amyloid precursor protein/
ApoE	Apolipoprotein E
EFPIA	European Federation of Pharmaceutical Industries and Associations
ki	knock-in
ko	knock-out
iPSCs	induced pluripotent stem cells
IT	Information technology
LOAD	Late onset Alzheimer's disease
MCI	Mild cognitive impairment
PS1	Presenilin 1
PS2	Presenilin 2
RXR	Retinoid X Receptor
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 (http://ec.europa.eu/research/participants/data/ref/h2020/legal_basis/rules_participation/h2020-rules-participation_en.pdf) and the Commission Delegated Regulation with regard to IMI2 JU http://eur-lex.europa.eu/legal-content/EN/TXT/PDF/?uri=CELEX:32014R0622&from=EN.

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

Applicants intending to submit a Short Proposal in response to the IMI2 Call 5 should read this topic text, the IMI2 Manual for submission, evaluation and grant award and the IMI2 RIA Evaluation Criteria.

Call Identifier	H2020-JTI-IMI2-2015-05-two-stage
Type of action	Research and innovation action
Publication Date	9 July 2015
Stage 1 Submission start date	9 July 2015
Stage 1 Submission deadline	**13 October 2015** – 17:00:00 Brussels time
Stage 2 Submission deadline	**15 March 2016** – 17:00:00 Brussels time

Indicative Budget	
From EFPIA companies and IMI2 Associated Partners	EUR 47 477 000
From the IMI2 JU	EUR 47 477 000

Call Topics

IMI2-2015-05-01	The indicative contribution from EFPIA companies is EUR 6 000 000. The financial contribution from IMI2 is a maximum of EUR 6 000 000.	Research and Innovation action. Two stage submission and evaluation process. Only the applicant consortium whose proposal is ranked first at the first stage is invited for the second stage.
IMI2-2015-05-02	The indicative contribution from EFPIA companies is EUR 13 235 000. The indicative contribution of IMI2 Associated Partners is EUR 1 851 000. The financial contribution from IMI2 is a maximum of EUR 15 086 000.	Research and Innovation action. Two stage submission and evaluation process. Only the applicant consortium whose proposal is ranked first at the first stage is invited for the second stage.

IMI2-2015-05-03	The indicative contribution from EFPIA companies is EUR 8 838 000. The financial contribution from IMI2 is a maximum of EUR 8 838 000.	Research and Innovation action. Two stage submission and evaluation process. Only the applicant consortium whose proposal is ranked first at the first stage is invited for the second stage.
IMI2-2015-05-04	The indicative contribution from EFPIA companies is EUR 12 000 000. The financial contribution from IMI2 is a maximum of EUR 12 000 000.	Research and Innovation action. Two stage submission and evaluation process. Only the applicant consortium whose proposal is ranked first at the first stage is invited for the second stage.
IMI2-2015-05-05	The indicative contribution from EFPIA companies is EUR 2 043 000. The financial contribution from IMI2 is a maximum of EUR 2 043 000.	Research and Innovation action. Two stage submission and evaluation process. Only the applicant consortium whose proposal is ranked first at the first stage is invited for the second stage.
IMI2-2015-05-06	The indicative contribution from EFPIA companies is EUR 3 510 000. The financial contribution from IMI2 is a maximum of EUR 3 510 000.	Research and Innovation action. Two stage submission and evaluation process. Only the applicant consortium whose proposal is ranked first at the first stage is invited for the second stage.

Technology readiness levels (TRL)

Part G of the General Annexes to the EC Work Programme shall apply mutatis mutandis for the actions covered by this Work Plan.

Evaluation

Part H of the General Annexes to the EC Work Programme shall apply *mutatis mutandis* for the actions covered by this Call for Proposals with the following exceptions:

This call text specify the Call for proposals is a two-stage Call, and it has a predefined submission deadline.

The proposals are evaluated against the specific IMI 2 evaluation criteria (Excellence, Impact and Quality and efficiency of the implementation)[7] according to the submission stage

Type of action	Excellence	Impact	Quality and efficiency of the implementation*
RIA and IA	The following aspects will be taken into account, to the extent that the proposed work corresponds to the topic description in the IMI2 annual work plan: **Clarity and pertinence of the objectives;** **Credibility of the proposed approach;** **Soundness of the concept, including trans-disciplinary considerations, where relevant;** **Extent that proposed work is ambitious, has innovation potential, and is beyond the state of the art;** **Mobilisation of the necessary expertise to achieve the objectives of the topic and to ensure engagement of all relevant key stakeholders.**	The following aspects will be taken into account, to the extent to which the outputs of the project should contribute at the European and/or International level: **The expected impacts of the proposed approach listed in the IMI2 annual work plan under the relevant topic;** Enhancing innovation capacity and integration of new knowledge; **Strengthening the competitiveness and industrial leadership and/or addressing specific societal challenges;** **Improving European citizens' health and wellbeing and contribute to the IMI2 objectives;**[8] Any other environmental and socially important impacts; Effectiveness of the proposed measures to exploit and disseminate the project results (including management of IPR), to communicate the project, and to manage research data where relevant.	The following aspects will be taken into account: Coherence and effectiveness of the project work plan, including appropriateness of the allocation of tasks and resources; Complementarity of the participants within the consortium (where relevant); Clearly defined contribution to the project plan of the industrial partners (where relevant); Appropriateness of the management structures and procedures, including risk and innovation management and sustainability plan.

The scheme above is applicable to a proposal in the second stage of a two-stage submission procedure. For the evaluation of proposals at first stage of a two-stage submission procedure, only the criteria 'excellence' and 'impact' will be evaluated, and withinthese criteria only the aspects in bold will be considered.

Scores must be in the range 0-5. Half marks may be given. For the evaluation of first-stage proposals under a two-stage submission procedure, the threshold for individual criteria is 3. There is no overall threshold. For the evaluation of second-stage proposals under a two-stage submission procedure; the threshold for individual criteria is 3. The overall threshold, applying to the sum of the three individual scores, is 10.

[7] http://www.imi.europa.eu/sites/default/files/uploads/documents/IMI2_CallDocs/IMI2_Evaluation-Form_RIA-IA_en.pdf
http://www.imi.europa.eu/sites/default/files/uploads/documents/IMI2Call4/IMI2_EvaluationForm_CSA.pdf

[8] 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)

These evaluation criteria include scores and thresholds. If a proposal fails to achieve the threshold for a criterion, the other criteria will not be assessed and the evaluation of the proposal will be discontinued.

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

The full evaluation procedure is described in the IMI2 Manual for submission, evaluation and grant award in line with the H2020 Rules for Participation[9].

Under the two-stage evaluation procedure, and on the basis of the outcome of the stage 1 evaluation, the applicant consortium of the highest ranked short proposal (stage 1) for each topic will be invited to discuss with the relevant industry consortium the feasibility of jointly developing a full proposal (stage 2). The applicant consortia of the second and third-ranked short proposals (stage 1) for each topic may be invited for preliminary discussions with the industry consortium if the preliminary discussions with the higher ranked proposal and the industry consortium fail. Such contacts should be done in priority order, i.e. the second ranked proposal should be contacted only after failure of pre-discussions with the first ranked, and the third after the second ranked.

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

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

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

List of countries and applicable rules for funding

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

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

(b) which fall within one of the following categories:

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

(ii) secondary and higher education establishments;

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

(c) the Joint Research Centre;

(d) international European interest organisations.

[9] http://www.imi.europa.eu/sites/default/files/uploads/documents/IMI2_Call1/Manual_for_submission_evaluation_grant%20award_2014.06.26.pdf

[10] 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

Admissibility conditions for grant proposals, and related requirements

Part B of the General Annexes[11] to the EC Work Programme shall apply mutatis mutandis for the actions covered by this Work Plan.

Eligibility criteria

Part C of the General Annexes to the EC Work Programme shall apply mutatis mutandis for the actions covered by this Work Plan.

Types of action: specific provisions and funding rates

Part D of the General Annexes to the EC Work Programme shall apply mutatis mutandis for the actions covered by this Work Plan.

Submission tool

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

Addititonal infomation

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/portal/doc/call/h2020/h2020-phc-2014-single-stage/1600139-essential_information_for_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 proposals to ensure that the proposed activities comply with ethical principles and relevant national, Union and international legislation. Any proposal that contravenes ethical principles or which does not fulfil the conditions set out in the H2020 Rules for Participation, or in the IMI2 Call for proposals shall not be selected. [12]

In order to ensure excellence in Data and Knowledge Management consortia will be requested to:

1) Disseminate scientific publications on the basis of open access[13].(see "Guidelines on Open Access to Scientific Publications and Research Data in Horizon 2020")

2) Include a Data Management Plan outlining how research data will be handled during a research project, and after it is completed, as part of the full proposal. (see "Guidelines on Data Management in Horizon 2020" providing guidance for the collection, processing and generation of research data). In order to ensure

[11] http://ec.europa.eu/research/participants/data/ref/h2020/wp/2014_2015/annexes/h2020-wp1415-annex-ga_en.pdf
[12] Article 19 of Horizon 2020 Framework Programme, and Articles 13 and 14 of the Horizon 2020 Rules for Participation
[13] 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

adherence to the legislation concerning protection of personal data, controlled access digital repositories and data governance will need to be considered.

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

4) Disseminate a description of resources[14] according to well-established metadata standards such as the Dublin Core (ISO15836) in order to make the resources included and generated by the IMI Actions discoverable for metrics and re-use.
Proposals shall contain a draft plan for the exploitation and dissemination of the results.

Indicative timetable for evaluation and grant agreement

	Information on the outcome of the evaluation (first stage of a two-stage evaluation procedure)	Information on the outcome of the evaluation (second stage of a two stage evaluation procedure)	Indicative date for the signing of grant agreement
Two-stage evaluation procedure	Maximum 5 months from the submission deadline at the first stage.	Maximum 5 months from the submission deadline at the second stage.	Maximum 3 months from the date of informing the applicants on the outcome of the full proposal evaluation.

Budget flexibility

Part I of the General Annexes to the EC Work Programme shall apply mutatis mutandis for the actions covered by this Work Plan.

Financial support to third parties

Part K of the General Annexes to the EC Work Programme shall apply mutatis mutandis for the actions covered by this Work Plan.

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[15] (e.g. IMI2 model Grant Agreement).

Consortium agreements

In line with the Rules for Participation and Dissemination applicable to IMI2 actions[16] and the IMI2 model grant agreement, participants in research and innovation actions are required to conclude a consortium agreement prior to grant agreement.

[14] Examples of Resources are (a collection of) biosamples, datasets, images, publications etc.
[15] http://www.imi.europa.eu/content/documents#calls_for_proposals_-_imi_2_programme

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