IMI 2
5th Call for proposals

Indicative Call Topics Text

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Content

DISCLAIMER

All information regarding future IMI Call topics is indicative and subject to change. Final information about the IMI's future Calls will be communicated after approval by the IMI Governing Board.

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

The initiative should therefore seek to involve a broader range of partners, including mid-caps[2], from different sectors e.g. biomedical imaging, medical information technology, diagnostic and/or animal health industries (while ensuring gender 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 2015 scientific priorities 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.

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

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.

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

Topic 1: Patient perspective elicitation on benefits and risks of medicinal products from development through the entire life cycle, for integration into Benefit Risk assessments 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 should be involved in the determination of benefit-risk considerations during the development of medicines as well as during the approval and post-approval phases. Stakeholders recognize that the robustness and transparency of pharmaceutical development, regulatory approval deliberations and health technology assessments have been improved through patient involvement and input. In general such input is not necessarily restricted to preference elicitation on identified benefits and risks but could also include patient input across the 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 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 regulatory authorities (RA) and health technology assessment (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; i.e. in 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 health authorities (HA) 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 (e.g. children, cognitively impaired subjects).

Methodologies for patient value elicitation are available and have been used frequently in the market research area, in health economics and outcomes research to substantiate real-life evidence and more recently in patient readability (user) testing. However there are no well-accepted methodologies for systematic use in the regulatory and HTA processes. Such methodologies would include qualitative and quantitative approaches as referenced below, and a roadmap for incorporation into drug development activities (including discussions between industry and regulators).

What is missing to date is:

- An understanding of when and under what circumstances patient involvement in benefit-risk evaluation is most valuable, in particular:
  - A process analysis to confirm which stages of benefit-risk evaluation are most suitable for patient involvement and of highest value to the patient e.g. before/during/after the phase 3 program. 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 positive 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 RAs, HTA bodies and payers.
- An understanding of how patient involvement in benefit-risk evaluation can best be performed, in particular:
  - The appraisal of methodologies feasible for general use in industry (that are easy to understand and respond to by the patient) that allow gathering and documenting perspectives of a wide patient or subject group. These methods should be characterised based on reliability, required interfaces, analytical methods to evaluate the data as well as appropriate documentation of the results. 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 various preferences 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 risk/benefit assessments.
- Experience with applying methodology to collect patient preferences with respect to benefit-risk:
  - 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 level of patient input at each stage of the development and 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 patient, physician, health authority, academia and industry stakeholders:
  - Despite the strong consensus among stakeholders that patients should be involved in the determination of benefit-risk throughout the lifecycle, there are widely divergent views between and within stakeholders on how this should be done. Establishing 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 regulatory policy.

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 HA and HTA bodies 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. Instead the involvement of patients in the decision making process has been anecdotal and limited to individual or small groups of patients or patient representatives. It is indisputable that if patient input is to become an important element of the HA/HTA decision-making process, data regarding their preferences must also be robust and representative of the patient population.

To move from the era of individual patient testimony, we must develop the science of patient input. This evolution in science, practice, and processes represents a significant evolution within pharmaceutical, HA, and HTA bodies and patient communities. A precompetitive public-private partnership is necessary to develop and advance the science, since it is too large an endeavour for any one organization to effectively address alone. A public-private partnership also contributes to and helps maintaining 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 establishing a consensus among stakeholders, who currently have widely divergent views, on how patients should be involved in 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 regulatory policy.

Opportunities

Several regulatory, industry and public-private partnership 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, discussion with their leaders, and an assessment of the most critical next steps. This will provide an understanding of the existing infrastructure for integrating patient preference studies into regulatory decisions. A brief list of these efforts and the web references include:

- 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=873619EMA'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

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. 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. 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.

Overall objectives

The overall objective of the action is to establish recommendations supporting the development of guidance for industry, regulators and HTA bodies on how and when to consider patient perspectives in benefit-risk assessments. 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.

It is expected that in the Short Proposal the applicants address all the above objectives (within the available duration and maximum IMI 2 JU 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

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

It should aim to create synergies and complementarities with relevant projects, in particular IMI projects and H2020 related projects. The following IMI ongoing funded projects might be considered:

- European Patients Academy on Therapeutic Innovation (EUPATI).
- Accelerated development of vaccine benefit-risk collaboration in Europe (Advance).
- Coordination and support action: enabling platform on Medicines Adaptive Pathways to Patients. This activity will be structured as a public/private consortium under an IMI2 framework known as Adapt Smart. The action is planned to run for 30 months with planned initiation in June 2015.
- Close interaction with the IMI2 Call 3 action generated by the topic 'Knowledge repository to enable patient focused medicine development' (Stage 1 Short Proposals submission deadline 24-Mar-2015, Stage 2 Full Proposal submission deadline 22-Sep-2015) to evaluate synergies and avoid duplication of efforts.

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 which stage(s) of drug development such methods could be best applied.
- Define the objectives for case studies. Identify which public partner(s) and/or industry institutions will run 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 following criteria:
  - the value of the information obtained and its usefulness to the different stages of the drug development life-cycle.
  - the ease-of-use of the methodology by the patients.
  - the feasibility of applying such methodology in routine practice.
- An assessment of the level 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 the case studies,

- Recommendations to support the development of guidance for industry describing:
  - when and how to include patient preferences to assess benefit-risk in drug development and post-approval stages; and align with the IMI2 action generated from the Call 3 topic 'Knowledge repository to enable patient focused medicine development'.
  - a set of methodologies suitable for patient involvement, acceptable to RAs and HTA bodies.
- Recommendations to support the development of guidance for regulators and HTA bodies on use of patient preferences to support assessment and licensing decision making.

Industry Consortium

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.

Indicative duration of the action

The indicative duration of the action is 60 months.

Indicative budget

The indicative EFPIA in-kind contribution and the IMI2 JU contribution will be matched. Due to the global nature of the participating industry partners it is anticipated that considerable elements of the EFPIA contribution will be provided from non-EU/H2020 associated countries.

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 IMI 2 JU 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. regulatory agencies, HTA bodies, as a prerequisite for the success of this action - for instance 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

Already in their short proposal the applicant should come with their suggestion for such architecture taking in consideration the EFPIA 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 regulatory agencies/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 and ensure external awareness.

Work Package 2: Patient preference elicitation approaches

Building on the knowledge available in this area:

- Conduct a process analysis to confirm which stages of benefit-risk evaluation are most suitable for patient involvement and of biggest value for the patient.
- Review and critically appraise available patient preference research methodologies in terms of strengths, weaknesses and lessons learned.

- Identify a set of candidate methodologies to go forward for testing, and make recommendation as to which stage(s) these could best be applied.
- Define the objectives for case studies. Discuss and agree with public partner(s) and industry institutions which will run the case studies. The aim is to cover a good choice of therapeutic areas of relevance for patient preferences.

Stop criteria: if the candidate methodologies from Work Package 2 are not regarded as a feasible basis for sufficient case studies or if the number of case studies is too low to show the value of patient preferences in benefit-risk assessment.

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 following criteria:
  - the value of the information obtained and its usefulness to the different stages of the drug development life-cycle
  - the ease-of-use of the methodology by the patients
  - the feasibility of applying such methodology in routine practice
- Use the case studies to assess the recommended level of patient input at each stage of the drug development life-cycle.

Stop criteria: if the outcome of the case studies does not provide sufficient information to establish recommendations to develop guidance for industry, regulators and HTA bodies intended in Work Package 4.

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 assess benefit-risk in drug development and post-approval stages; and align with the IMI 2 project a knowledge repository to enable patient focused medicine development
  - a set of methodologies suitable for patient involvement, acceptable to regulatory authorities and HTA bodies
  - Establish recommendations to support the development of guidance for regulators and HTA bodies on use of patient preferences to support assessment and licensing 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 rate of a dialysis patient with DKD is less than 25 percent—worse than most cancers—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 markers (i.e. biomarkers) for (i) the identification of patients at high risk of progression, (ii) identify patient subpopulations that are likely to respond to candidate therapeutics and (iii) to provide early indications of potential safety issues linked to candidate therapeutic agents.

The proposed topic invites Applicant Consortia to launch a cross-functional research initiative with the objective of identifying and validating these critically needed biomarkers. The research plans should embrace a strong focus initially on:

- 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, define, and select appropriate preclinical model systems;
- Back-translating clinical database findings to develop improved in vitro and in vivo models of DKD, and
- 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 active participation from and 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 Health Technology Assessments, HTAs).

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.

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 somewhat slowed 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 2 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 (e.g. 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. 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)[4] 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 agencies, patients, nephrologists, and ultimately, payers.

Hence, a collaborative research plan 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.
Early, close and continued interactions with regulators within this consortium are highly desirable.

Overall objectives

Future successful development of therapeutics for DKD will depend in large part on the proper selection of patients for the evaluation of a novel therapeutic. These patients will be identified ideally through the application of highly accurate biomarkers, which can help to identify fast-progressing DKD patients, patients in whom the novel therapeutic is likely to be efficacious, and patients in whom the novel therapeutic is likely to be free of a particular adverse safety event the biomarker was designed to predict.

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 hypothesized 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 & 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 predictive biomarkers for both efficacy and safety, and identify new druggable target pathways for future drug development. The consortium should also 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 (e.g. companion diagnostics).

Applicants are expected to address all the above objectives in the Short Proposal (within the available duration and maximum IMI 2 JU 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.

[4] http://c-path.org/programs/pstc/regulatory-successes/

Potential synergies with existing Consortia

It is expected that this action will synergize 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 chronic kidney disease stage 3 rapid progressors. 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) and DIRECT (Diabetes research on patient stratification);
- FP7-funded projects like KIDNEYCONNECT, and DN CURE;
- US-Consortia like the Kidney Health Initiative and the Predictive Safety Testing Consortium (PSTC) at the Critical Path Institute.

Expected key deliverables

Through a network of DKD laboratories and clinical databases, several 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

- Validate (and possibly identify) 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
- Validate clinical biomarkers that can be used within (A) registration trials and (B) development of companion diagnostics
- Development of imaging technology/biomarkers/diagnosis
- Prognostic imaging biomarkers
- Read out predictive imaging biomarkers
- Identify ‘dynamic biomarkers’ that change with experimental therapeutic and/or SOC treatment
- Identify predictor biomarkers of safety (e.g. cardiovascular) outcomes 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
- Implement 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 in setting of diabetes
- Identify mechanisms and pathways that can be targeted to reduce the slope of eGFR/yr loss curves

- Back-translate clinical findings to select/improve preclinical (*in vitro/in vivo* models) which correlate with human DKD
- Back-translate clinical findings to identify predictor biomarkers of efficacy response (preclinical and clinical)
- Identify differences in pathway drivers for DKD between T1D and T2D patients.

Expected impact

The potential impact gained from the identification and use of new DKD prognostic, predictive 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 overall 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 standardised 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 by global payers, due to the evidence of a likely enhanced efficacy signal seen in biomarker-selected patients.

Industry Consortium & Associated Partners 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 the Innovative Medicines Initiative 2 (IMI 2) Joint Undertaking, if so foreseen in the applicable annual work plan, may publish at a later stage another Call for proposals restricted to those actions already selected under this Call 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. The detailed scope of the Call will be described in the relevant annual work plan.

In the context of this topic, the EFPIA companies envision the possibility of expanding Work Package 1 (WP1 - see below) in the future to support the construction and maintenance of a long-standing clinical data repository to serve as a future source of biomarker identification and/or validation. Leveraging any success the first and other WPs, as long as the results are positive, such further work would be the natural progression of the project. Building on these prior successes would maximise the long-term impact of the larger action, and engender continued future successes in making clinical development of new therapeutics, as well as their application in the clinic, both more fruitful and more efficient. This proposed extension would also take advantage of already established collaborations and networks forged in the overall action, thereby maximising efficiency on time and resources.

Indicative budget

The indicative EFPIA in-kind contribution and the financial contribution from IMI 2 JU will be matched 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.

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), basic researchers in field of *in vitro* and *in vivo* modelling of DKD, biomarker/diagnostics specialists (could be SMEs), investigators with access to biospecimens from longitudinal cohorts, bioinformaticians and big data analysts, regulatory health authorities, imaging specialists, translational medicine experts. Cross fertilization and demonstrated ability to collaborate well with the pharmaceutical companies also showcased in prior working groups/consortia will be critically important for all participants.

Subject to a succesful Stage One evaluation outcome, the selected applicant consortium will join the industry consortium to build a seamless, collaborative and fully-integrated final full consortium.

Such networks 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 samples are required. Cohorts and data may be retrospective and/or prospective in nature.
- Institutional/individual expertise with respect to animal and/or *in vitro* models relevant to DKD.
- Institutional/individual expertise with respect to serum, urine and/or imaging biomarker development. Included in this is large scale data management and computational expertise.

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

Suggested architecture of the action

Already in their short proposal the applicant should come with their suggestion for such architecture taking into consideration the EFPIA 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 cross-functional and cross-sector team members described above are advised to work together in dedicated work packages addressing the different aspects of the overall topic. Each Work Package team should consist of academic and industrial/biotech members, manifesting as multiple examples of inherently public-private collaborations, with regular interactions to ensure knowledge exchange between the different expertises. Inter-work package knowledge transfer should be ensured at all times via regular management board meetings.

In order to plan for interactions with RAs/HTA bodies, relevant milestones and appropriate resource allocation should be built into the action architecture as well as aspects related to dissemination and sustainability.

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

Please also note that the following outline of the architecture for the action is a suggestion; different innovative project designs are welcome.

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.

The suggestion is that this action should be organized into 6 major Work Packages:

Work Package 1:

Validate (and possibly identify) new biomarkers from and applicable to broad populations in order to differentiate fast from slow progressors of DKD. 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.

Work Package 2:

- Identify clinical predictor 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 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 DKD patients.

Work Package 3:

- Validate clinical biomarkers that can be used within (1) registration trials and (2) development of companion diagnostics.
- Implement specific personalised diagnostics in DKD by communicating value proposition to target audiences (i.e. regulators, patients, practitioners, payers).

Work Package 4:

Development of Imaging Technology / Biomarkers/Diagnosis: Prognostic Imaging BMs, Read Out Predictive Imaging BMs.

Work Package 5:

- Identify causal mechanisms and pathways for developing *de novo* DKD in setting of diabetes.
- 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

Neurodegenerative diseases such as Alzheimer Disease (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 characterized 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. Although preliminary evidence may point to decreased microglial activity being associated with AD, the ultimate causative link between inflammation or microglia activity and AD/ageing 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 activated T cells and macrophages may invade the AD brain and may 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 the increasing amyloid beta-plaque load in the course of the disease or the dysfunction of key players in microglial activity might trigger or accelerate AD.

Multiple Genome-wide Association Studies' (GWAS) studies 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, 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 frontotemporal 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 phagocytotic activity[17].

Thus, a working hypothesis may be that these genes confer increased risk of AD by reducing the phagocytotic activity of microglia leading to reduced clearance of Amyloid beta aggregates and cell debris, as indicated in the figure below from Malik *et al*., (2013).

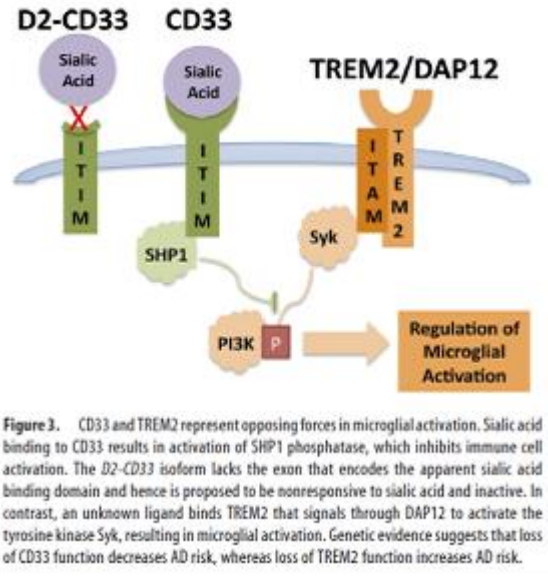

Figure 3. CD33 and TREM2 represent opposing forces in microglial activation. Sialic acid binding to CD33 results in activation of SHP1 phosphatase, which inhibits immune cell activation. The *D2-CD33* isoform lacks the exon that encodes the apparent sialic acid binding domain and hence is proposed to be nonresponsive to sialic acid and inactive. In contrast, an unknown ligand binds TREM2 that signals through DAP12 to activate the tyrosine kinase Syk, resulting in microglial activation. Genetic evidence suggests that loss of CD33 function decreases AD risk, whereas loss of TREM2 function increases AD risk.

Figure 1: taken from Malik *et al*. J. Neurosci. 33:13320, 2013

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 phagocytotic 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 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 e.g. 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[5] 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:
  a) and if so, at what stage in the progression of AD-related phenotypes
  b) and if modulation of microglia is able to delay progression of AD-phenotypes
  c) and what are the effects of activated microglial cells on T cells and B cells
  d) 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:
  a) determine what differentiates a tissue protective or even restorative microglial cell from a tissue destructive one.
  b) determine how this phenotype can be influenced.
  c) determine the relative roles of microglial-bound TREM2 and CD33 receptors versus their shed counterparts.
  d) 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.
- 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.

It is expected that applicants address all the above objectives in the Short Proposal (within the available duration and maximum IMI 2 JU contribution) and demonstrate a relevant strategy for achieving them, through partnership with the industry consortium.

[5] 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.

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 should take in 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. 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 for knock-down and over-expression of targeted genes, to confirm findings by gene knock-down or over-expression studies in disease relevant preclinical models and
- 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 expressing TREM2 +/- CD33 +/- DAP12
  - provision of a robust TREM2-dependent phagocytosis assay in cell culture
  - provision of a robust TREM2-signalling reporter line in cell culture
- Identify and characterize endogenous ligands of CD33 and TREM2

Industry Consortium

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. 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)

Indicative duration of the action

The indicative duration of the action is 60 months.

Indicative budget

The indicative EFPIA in kind contribution and the IMI 2 JU contribution will be matched 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.

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 IMI 2 JU contribution) and demonstrate a relevant strategy for achieving them, through partnership with the industry consortium.

This may require mobilising as appropriate, expertise in: Alzheimer's disease 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-inflammational processes/pathways from preclinical species to humans, IT (in particular data communication and data basing) and project management.

It may also require mobilizing 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 in their Short Proposal their suggestions for creating the Full Proposal architecture taking in 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.

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 (see details in the description of the industry consortium).

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

1. 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 amyloid (J20) and tau (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

2. 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).
3. Assays: phagocytosis assay using human AD tissue brain slices or macrophage/microglia-like cell lines.
4. Development of methods to knockdown CD33 *in vitro* and *in vivo* using antisense oligonucleotides.
5. High-content imaging devices and technology for quantitative assessment of inflammation status as well as AD pathology in the brains of animal models.
6. 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.
7. Small animal proton emission tomography (PET) imaging, including test tool compounds in vivo for microglial activity detection via translocator proteine ligands (TSPO)-PET.
8. Measurements of TREM2 in cerebrospinal Fluid (CSF) as a potential pharmaco-dynamic marker.
9. Development of antibodies against TREM2.

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:

- 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:

- '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:

- role of TREM2 and CD33 in development of AD-related phenotypes in rodent models.
- get insight into differences in immune response on AD pathology between human and rodents.
- Biomarkers.
- Neuroimaging.

Work Package 4:

Identification of small molecule modulators of microglia effects on progression of AD-related pathology.

Work Package 5:

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	Celebro 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 proteine ligands

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Topic 4: Understanding the role of amyloid 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 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 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 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, and

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, 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.

It is expected that applicants address all the above objectives in the Short Proposal (within the available duration and maximum IMI 2 JU 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

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://www.synapse-managers.com/epad/: 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 Joint Programming in Neurodegenerative Diseases (JPND) actions (http://www.neurodegenerationresearch.eu/initiatives/), other European research projects (e.g. PREDICTAD: http://www.predictad.eu/) and research infrastructure initiatives, as well as at national level with relevant actions.

To optimise impact of this research project 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 the utility of β-amyloid imaging in a clinically relevant population, such as subjective memory complainers (SMC) and 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 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 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 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 preclinical AD 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.
- 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

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 and the IMI2 JU contribution will be matched. 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.

Sufficient budget will have to be reserved for Scientific Advice at the European Medicine Agency (EMA).

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 IMI 2 JU 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

Already 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.

In their short proposal the applicant should come with their suggestion for such architecture taking in consideration the EFPIA contributions and expertise as indicated below. 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 (4) 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 A) Amyloid Diagnostic and Patient Management Study and B) 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, operationalization 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 deliverables as in section 6 part A. 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 Flutemetamol and 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 deliverables as in section 6 part B. 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 as in section 6. 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 Flutemetamol and 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 file sharing 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

References:

1. Beach TG *et al* (2012). J Neuropathol. Exp. Neurol. 71 (4) 266-273
2. Salloway S *et al* (2014). N Eng. J. Med. 370: 322
3. Curtis C *et al* (2015). JAMA Neurology. 72 (3) 287-294-333
4. Sabri O *et al* (*in-press*). Alzheimer's and Dementia.

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, 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 healthcare and community engagement practices in the AD healthcare and clinical trial environments to evolve the field toward maximisation of resources for patient and caregivers. In order to achieve these goals, several broad steps are required:

- Collect data on a new early paradigm for diagnostic and therapeutic advancements to help local decision makers.
- Broaden the understanding of the experience of AD beyond the last few years of its course.
- Increase the connectivity between AD thought leaders and AD clinicians.
- 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 tactics 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, and drive 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: see sections 9-11 below)

- 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.
- Assess key tools, mechanisms and processes for community engagement and patient identification for care and resource utilization in various communities.
- Compare and contrast various patient access models and how they contribute to improved detection, diagnosis, and clinical research in these communities.
- Based on findings, establish archetypes of patient access models for implementation in similar communities.
- 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 IMI 2 JU 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.

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.

- ADI – Alzheimer's Disease International has accepted the task of developing an AD clinical trial consumer campaign in conjunction with the OECD, CEOi and World Dementia Council. Such material could be leveraged/tested in these demonstration communities.
- ALCOVE – 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.
- 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.
- IMI-EPAD – 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, 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.

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 tactics and assessment metrics. Ideally some tactics would need to be implemented at multiple regional sites for comparison across regions.

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

- Resource availability: diagnostic expertise, specialized biomarker programs, genetics, counseling, 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 behaviors 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.
- 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.
- 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 counseling 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 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 enrolment in clinical trials.
- 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. Tactics 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. Archetype programs of patient access models will inform guideline development and implementation recommendations. This will be used to facilitate regulatory and payer discourse, as well as advise the 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 clinical trials programs.

Industry Consortium

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.

Indicative budget

The indicative EFPIA in-kind contribution and the IMI 2 JU contribution will be matched 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.

Future action Expansion

Potential applicants must be aware that the Innovative Medicines Initiative 2 (IMI2) Joint Undertaking may publish at a later stage another Call for proposals restricted to those actions already selected under this Call 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 2 would have a duration of up to 5 years and will only be initiated after a futility analysis of the progress of Phase 1, and contingent on certain milestones being achieved to justify a Phase 2. This Phase 2 extension would aim to provide opportunity to expand successful Phase 1 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.

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

In their short proposal the applicant should come with their suggestion for such architecture taking in consideration the EFPIA contributions and expertise as indicated below. The below suggested architecture is just an example and different designs are welcome, if properly justified.

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 tactics 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 tactics, 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 1 Call.

Potential Work Packages

- **Access/engagement Model development and assessment:**

  a) Establish multiple IMI2 key regional projects to identify and test models for efficient earlier identification of mild AD dementia and prodromal AD patients.

  b) Assess key tools, mechanisms and processes for local engagement and patient identification for care and resource utilization in various communities.

  c) Compare and contrast various patient access models and how they contribute to improved detection and diagnosis in these communities.

  d) Build and scale model programs for further implementation, look for systematic changes that can make the demonstration site experiment sustainable after IMI2.

  e) Evaluate whether certain healthcare systems or community archetypes have greater success with different tactics and/or activities.

- **Modelling economic and public health impact and Guideline development:**

  a) Work with regional experts to assess key impact on local economic health care and public access to resources.

  b) Based on findings, establish recommendations for archetypes of patient access models for implementation in similar communities.

  c) 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 TBD) 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 dialog.

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: 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 on-set 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 labs 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 proposal 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.

- 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 factors, such traumatic brain injury, diabetes, cardiovascular conditions, inflammation and genetic factors that influence the development of AD in homo- or heterozygous ApoE4 carriers.
- Examine processes relevant for neurodegeneration beyond theApoE4 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.
- 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 IMI 2 JU 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

Considering the envisioned timelines and budget of this proposal, 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 may share tools and knowledge with the relevant work-package of the IMI project STEMBANCC (http://stembancc.org/index.php/work-packages-in-detail/).

Furthermore synergies with relevant Joint Programming in Neurodegenerative Diseases (JPND) actions should be considered at the European level (http://www.neurodegenerationresearch.eu/initiatives/), other European research projects as well as research infrastructure initiatives, as well as with relevant actions at national levels.

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

The Research and Development organizations of the Pharmaceuticals section of the below 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 and the IMI 2 JU contribution will be matched. 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.

Applicant consortium

(to 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 on the defined deliverables in synergy with the industry consortium and complementing their contributions as in section 12.

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

Already 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 final architecture of the Full Proposal will be defined together with the industry consortium and should

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

- Drug discovery and development expertise
- 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

As a starting point it is suggested to consider organizing the work-plan in 4 major work packages (WP) however different innovative project designs are welcome, if appropriate:

Work Package 1:

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:

Activities towards analysis of information and achievement of scientific consensus towards a refined 'ApoE hypothesis of AD'.

Work Package 3:

Research into ApoE biology in models *in vivo/ex-vivo* with high relevance to AD.

Work Package 4:

Data management and statistics to allow integrated analysis of data set (please see guidelines in the General Conditions to our Calls for Proposals).

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

Applicants intending to submit a short proposal in response to the IMI2 Call 5 should read the topic text, above, the IMI2 Manual for submission, evaluation and grant award and the IMI2 Evaluation Criteria.

Call Identifier	H2020-JTI-IMI2-2015-05-two-stage
Type of action	Research and innovation action
Publication Date	30 June 2015
Stage 1 Submission start date	30 June 2015
Stage 1 Submission deadline	**29 September 2015** – 17:00:00 Brussels time

Eligibility and admissibility conditions

The conditions are described in parts B and C of the General Annexes to the work programme.[6]

Evaluation criteria, scoring and threshold

The criteria, scoring and threshold are described in the IMI2 Evaluation Criteria, with the following exception:

IMI2-2015-05-01 IMI2-2015-05-02 IMI2-2015-05-03 IMI2-2015-05-04 IMI2-2015-05-05 IMI2-2015-05-06	If a proposal fails to achieve the threshold for a criterion, the evaluation of the proposal will be stopped.

Evaluation procedure

The full evaluation procedure is described in the IMI2 Manual for submission, evaluation and grant award.

The procedure for setting priority order for proposals with the same score is given in the IMI2 evaluation criteria.

For research and innovation action topics, 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.

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.

[6] http://ec.europa.eu/research/participants/data/ref/h2020/wp/2014_2015/annexes/h2020-wp1415-annex-ga_en.pdf

Indicative timetable for evaluation and grant agreement

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

Consortium agreements

In line with the Rules for Participation and Dissemination applicable to IMI2 actions[7] and the IMI2 model grant agreement, participants in research and innovation actions are required to conclude a consortium agreement prior to grant agreement.

Submission Tool

Please note: The IMI electronic submission tool **SOFIA** (Submission OF Information Application) is to be used for submitting a short proposal in response to a topic of the IMI2 Call 5; no other means of submission will be accepted. SOFIA will be opened for submission of proposals on 30 June 2015. Updates of the proposals may be finalised until the Call submission deadline. Please note that the proposal must be finalised and then the submit button must be pressed by the Call submission deadline in order to submit the proposal for eligibility check and evaluation.

To access the IMI electronic submission tool SOFIA, applicant consortia wishing to submit a short proposal will need to complete a request for access to the tool.

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