IMI2
7th Call for proposals

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Contents

Introduction

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

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

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

The IMI2 Strategic Research Agenda (SRA)[4] is the main reference for the implementation of research priorities for IMI2. The scientific priorities for 2015 for IMI2 have been prepared based on the SRA.

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

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

Before submitting a proposal, applicant consortia should familiarise themselves with all Call documents such as the IMI2 Manual for evaluation, submission and grant award[5], and the IMI2 evaluation criteria. Applicants should refer to the specific templates and evaluation procedures associated with the topic type: Research and Innovation Actions (RIAs) or Coordination and Support Actions (CSAs).

[1] The Council Regulation (EU) No 557/2014 of 6 May 2014 establishing the Innovative Medicines Initiative 2 Joint Undertaking (IMI2 JU).
[2] http://www.who.int/medicines/areas/priority_medicines/en/
[3] Under 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.
[4] http://www.imi.europa.eu/sites/default/files/uploads/documents/IMI2_SRA_March2014.pdf
[5] http://www.imi.europa.eu/sites/default/files/uploads/documents/IMI2_CallDocs/IMI2_SubmissionManual_Dec2015.pdf

Topic 1: Validation of translational imaging methods in drug safety assessment (TRISTAN)

Topic details

Topic code	IMI2-2015-07-01
Action type	Research and Innovation Actions (RIA)
Submission & evaluation process	2 stages

Specific challenges to be addressed

Evaluation of drug candidates, small molecules or biologicals, in terms of toxicity and absorption, distribution, metabolism and excretion (ADME) is a critical prerequisite for candidate progression. The ability to further improve on the quality of the data obtained would provide a more precise understanding of ADME processes. The utilisation of dedicated imaging biomarkers has the potential to even further improve the quality of pre-clinical data as well as the possibility for improved patient monitoring in phase I and II clinical trials. The development of imaging biomarkers both for the pre-clinic and the clinic has the potential to advance safety evaluation through a better understanding of longitudinal profiles associated with mechanisms of toxicity, as well as understanding the sites of on- or off-target effects. Although there are a number of published studies that attempt, for example, to use PET and MR imaging biomarkers both pre-clinically and clinically, there seems to be a lack of systematic validation in order for such technologies to be fully accepted by healthcare authorities and regulators. If properly validated, both modalities have the potential to significantly support not only efficacy readouts, but also drug safety evaluation. In order for imaging biomarkers to become more main-stream, impacting the drug discovery process more widely, there need to be technical advances, as well as a better standardisation across the imaging community to ensure protocols, biomarkers, analysis and data interpretation are well recognised and equivalent. If properly validated, imaging methods will support establishment of the ADME concept and estimation of toxic effects of drug candidates and could additionally strongly support efforts to identify the minimal (i.e. safest) dose providing useful therapeutic efficacy. In contrast to invasive methods, imaging has the potential to verify results from animal studies in phase I clinical trials, ensuring the validity of animal findings in humans.

A particular need for the use of imaging has been identified in the toxicological assessment of the liver, the lung and for investigation of a compound' s bio-distribution. The liver is involved in excretion of most drugs and is therefore a major target of drug toxicity. Liver toxicity is assessed by investigation of liver enzyme levels. Elevation of biochemical markers is regarded as a clear sign of non-tolerable side effects. However, the reason for liver enzyme up-regulation often is unknown. One aspect for induction of liver toxicity is the drug-mediated attenuation of liver-bile transporter function. Characterising the activity of these transporters is a priority for researchers. Monitoring their function over time by tracking excreted molecules utilising dedicated imaging methods will support the establishment of toxicity mechanisms. While some initial results are available from animal studies on Gadoxetate-enhanced MRI addressing MRP2 function, this imaging method still needs validation in humans.

Chronic inflammatory diseases of the airways remain areas of considerable unmet medical need. The failure to translate a number of promising drug candidates from preclinical assays and animal studies to humans has led to the demand for more predictive tools, especially for the preferred inhaled therapies. Pulmonary drug toxicity requires further elucidation with biomarkers that are readily available in the *in vivo* setting, without the need for biopsy. There are many drug classes and formulations, that produce histo-pathological manifestations including diffuse alveolar damage, pulmonary haemorrhage, non-specific interstitial pneumonia, oedema, hypertension, bronchiolitis obliterans organising pneumonia, phospholipidosis, and the development and relevance of a foamy macrophage population. Further understanding of the latter is required, not only in humans but in preclinical species used to evaluate dose and toxicity of new drugs.

The relevance of biologicals as drug candidates has increased dramatically over the last decade. Monitoring of bio-distribution and target/off-target concentration by means of imaging in order to understand the systemic distribution and the fate of the biologics and to support prediction and optimisation of dose and dosing intervals is of special value in designing bio-therapeutics (biologics) for sub-cutaneous application (SQ)[d]. The detailed characterisation, spatial distribution and if possible quantification of biologics in the various compartments of the dermis, the sub-cutis and the local draining lymphatic system are of critical importance to understand the biology of SQ application. One major drug-related adverse event of biologics is the formation of ADAs (anti-drug-antibodies). Imaging of biologics can help researchers to understand which role an optimal SQ[d] dose plays in this immunogenic response of ADA formation. The further fate of the SQ applied biologics is currently described by the PK/PD relationship in blood or plasma including evaluation of the degradation pattern into various fragments of complex formation with ADA. The detailed visualisation and quantification of a biologic in the different subsequent organs (liver, kidney, brain) is still at its beginning. Especially with the brain, biologics need to cross the blood brain barrier (BBB). Imaging of this important event is an essential step towards understanding if, where and how this transport takes place.

Need and opportunity for public-private collaborative research

Using imaging technologies like biomarkers holds not only the potential to revolutionise the evaluation of disease allowing a personalised therapeutic intervention, but also the possibility of improving the quality of clinical trials in drug development. However, strong scientific effort is needed in order to identify and validate appropriate imaging procedures. Coordinated work on standardisation of technical image acquisition, imaging procedure, image post-processing and analysis as well as data presentation is necessary to validate the imaging biomarker procedure pre-clinically and consecutively in humans. This can be achieved best by integrating the expertise of vendors of imaging equipment and software solutions with the academic scientific excellence in imaging methodology, the knowledge of toxicologists and healthcare professionals and the highly standardised and regulated toxicological and DMPK research environment of the pharmaceutical industry. An applicant consortium should thus include all relevant chemical and biological resources, multiple pre-clinical and clinical imaging research sites equipped with a relevant imaging infrastructure, partners providing image processing and analysis tools, as well as partners providing biochemical and histological biomarker validation assays, safety pharmacology, statistics and regulatory input.

Scope

The overall aim of the initiative is to leverage the potential of available imaging techniques in order to improve drug safety analysis and the translatability of findings from animals to humans by validating imaging procedures as biomarkers. Applicant consortia should provide clear evidence that state-of-the-art imaging techniques, when validated properly, can support pre-clinical and clinical drug development and improve safety for individual patients. This may also include stratification of patients for allocation to clinical trials or study sub-groups in order to improve trial outcome quality. It is expected that applicant consortia address all of the three focuses outlined above:

- establish assessment of liver-bile transporter function by means of dynamic imaging in animals and verify the results in humans, thereby creating a validated tool for translational liver toxicity and toxicity mechanism assessment;
- establish and validate imaging biomarker procedures to assess, characterise and quantify the extent of interstitial lung disease in order to introduce a tool for translational lung toxicity evaluation;
- develop and utilise methods to assess the bio-distribution of biologicals with long terminal half-lifes directly after sub-cutaneous injection and at later time points using invasive and non-invasive imaging methods with the aim of increasing the efficacy of pre-clinical safety assessment and improving the translatability of findings to humans.

Standardisation and technical validation of imaging procedures as biomarkers will essentially include:

1. standardisation of the entire imaging workflow, also for multi-modal approaches, in order to achieve a high level of robustness and reproducibility of results;
2. optimisation of single-modality imaging sensitivity and specificity for each envisaged imaging procedure;

3. creation of imaging biomarker-specific evaluation software packages allowing the extraction of key parameters or parameter maps in order to characterise the biomarker, in particular for multi-modal imaging;
4. standardisation of commonly-used formats for easy inter-laboratory exchange and understanding of imaging data and result reports.

After implementation and validation of highly-standardised imaging biomarker procedures across sites and imaging equipment vendors in animals, the translatability of results to humans shall be addressed in clinical studies. Healthcare authorities, patient organisations and health technology assessment specialists should be included in discussions on imaging biomarker validation strategies and feasibility early.

Expected key deliverables

Deliverable 1: Liver transporter assessment

It is envisioned that existing biochemical data on liver-bile transporter function (originating from animals and humans) will be collected from available sources to be matched to imaging results generated. A robust method for image acquisition, analysis and image data evaluation shall be established, building on previously published work, which can be used to quantify the functional impairment of mrp2. Introduction of a platform independent data evaluation tool is anticipated which facilitates standardisation but which would also offer a user-friendly data evaluation and work-flow guidance.

The pre-clinically established and validated imaging method shall then be applied to healthy volunteers treated with established drugs known to induce a transient functional impairment of MRP2. The established tools for image evaluation shall be able to evaluate both pre-clinical and clinical imaging data and to compare them. This methodology shall then be used to evaluate the translatability of a drug's influence on liver-bile transporter functional attenuation between different animal species and humans. It will also be used to identify the relevance of differences in baseline transporter function between individuals and its influence on drug toxicity development.

Ideally the drug-mediated functional impairment of other liver-bile transporters like BSEP shall be addressed in a similar manner by an imaging method to be established. Proof of mechanism of such a method in humans would be essential.

Deliverable 2: Pulmonary toxicity assessment

An imaging procedure capable of supporting the characterisation of drug-induced interstitial lung disease state shall be established and validated in order to overcome the perceived lack of standardisation of these approaches, which currently limits their utility in translational drug development. There are many drug classes and formulations, notably powdered delivery, that produce histopathological manifestations of pulmonary drug toxicity. Further understanding of foamy macrophage appearance, prevalence and consequence to other cells in the lung is required, in humans and in pre-clinical species, to evaluate the dose and toxicity of new drugs.

A comprehensive library of imaging biomarkers shall be provided that represent the breadth of lung disease from early stage through to the chronic condition. Imaging data of disease and toxicity shall be matched and analysed together with histo-pathological and functional parameters.

Imaging technologies shall be systematically exploited and validated against biological and biochemical measures to further our understanding of disease and toxicity identification and mechanism in the lung. Technologies may include UTE-MRI, hyperpolarised nuclei, both gas and metabolite, DW-MRI; DCE-MRI/-CT, smart contrast agents for cellular identification and specific disease biomarkers, as well as further MRI, CT, PET and optical approaches. Additionally, molecular biomarkers of disease and toxicity that can be utilised to generate contrast agents or tracers shall be assessed (e. g. cell surface markers to cells involved in toxicity development).

Deliverable 3: Bio-distribution of biologicals

The aim is to assess local as well as systemic distribution of biologics. For local application the particular challenges to be addressed are reduction of pain during injection, assessment of the degradation patterns at the injection site, degradation degree and time course and to optimise the sub-cutaneous bioavailability ratio in order to improve drug dose and dosing regimen. The systemic distribution and target/off-target concentration of biologics shall be monitored by imaging techniques in order to replace whole body auto radiography and to support safety evaluation of NBEs.

The advancement and validation of invasive and non-invasive imaging technologies that can be utilised for the identification and localisation of biologics in tissues at a broad range of spatial resolution is regarded essential to improve scientific understanding. *In vivo* fluorescence imaging in rats and pigs shall be matched to *ex vivo* (e. g. fluorescence, MALDI/MALDI 2, other) imaging, histology and classical biochemical analytics in order to assess bio-distribution on a microscopic scale. PET imaging shall be established and applied to analyse whole body bio-distribution on a macroscopic scale. Both shall be combined to investigate extra-cellular distribution, degradation, phagocytosis and correlation of sub-cutaneous to plasma levels. In addition ADA formation shall be addressed. PET imaging procedures validated in animal studies shall be employed in humans in order to verify the translatability of pre-clinical bio-distribution results.

The concept of 'appropriate' tissue exposure in healthy vs. diseased animals is still undefined. Thus methods shall be developed allowing for *in vivo* real-time quantification, tissue epitope quantification software and, potentially, modelling of local quantification data in animals. Additionally, FcRn biology, baseline foetal exposure properties, foetal exposure properties after GI delivery and understanding of potential different molecular mechanisms in FcRn role in barrier function or transcytosis and antibody half-life shall be assessed.

Deliverable 4: Standardisation and validation of image acquisition, evaluation and reporting

In order to provide a validated technology platform for imaging biomarkers, a focus of this project shall be the creation of an information technology based infrastructure which allows:

- configuration of the imaging performance of the used imaging modality(ies) to generate robust and extremely reproducible results with minimal efforts, inter alia by selecting and optimising scan protocols and image reconstruction routines;
- creation of a common data evaluation and analysis framework for the determination of biomarker-specific parameters or maps which can be derived from the scanned images and which are quantitative indicators addressing the key issues of the biomedical questions;
- use of appropriate software tools to compare, cross-validate and combine imaging results generated in a multi-modal imaging approach;
- the exchange, storage and archiving of imaging results in a common data format and that allows linkng imaging data to be linked to other relevant biological/biochemical data;
- the generation of reports about the imaging procedure and key results in a highly transparent and traceable manner allowing easy cross-laboratory exchange;
- the development, optimisation and validation of workflow-supporting software tools.

These tasks are common to all work packages and are essential to its overall success. Image format standards already established in the clinical domain shall be used. According to the objectives of the Small Animal Imaging DICOM Working Group and the DICOM-NEMA standards committee, the DICOM standard is the preferred candidate to share image datasets among the collaborators. The intention of the DICOM Working Group to extend DICOM to describe animal-specific aspects of the acquisition, to adopt DICOM for interchange of all forms of small animal imaging results and to bridge the gap between small animal and human research has to be supported.

Expected impact

The information and knowledge acquired through this program will be of utmost value for further improving the safety evaluation of novel drug candidates, including both small molecules as well as biologics. Appropriate imaging procedures used as imaging biomarkers have a strong potential to improve translatability of pre-clinical results to healthy volunteers and patients and thus help to avoid late stage attrition of development programmes. In addition, functional diagnostic imaging methods used as biomarkers would offer the opportunity of confirming drug toxicity mechanisms in humans, including the potential for determining drug-drug interactions. The opportunity to follow a drug's bio-distribution and its effect on tissues or molecules longitudinally by means of imaging intrinsically includes the potential to reduce animal numbers in pre-clinical studies. Hence the work in this programme strongly supports the 3R principle (refinement, reduction, replacement) in substantially reducing the number of animals needed in pre-clinical research.

Potential synergies with existing consortia

This consortium's goals perfectly complement the aims of the recently started Euro-BioImaging[6], a large-scale pan-European research infrastructure project on the European Strategy Forum on Research Infra-structures (ESFRI) Roadmap. Euro-BioImaging is funded by the EU and includes representatives of 12 countries and EMBL working together towards the implementation of the infrastructure. Since the effective use of the infrastructures depends upon the validation of biomarker imaging technologies there is also a need to explore synergies with imaging 'hardware' companies such as those organised in this initiative. Our topic will complement Euro-BioImaging by providing new validated biomarker imaging techniques that will be able to expand the use of such infrastructures. Furthermore, the consortium under this call shall seek close cooperation with patient organisations and other initiatives. The topic will build on achievements from all relevant European and Member State initiatives and will proactively search for synergies with other Horizon 2020 (H2020) projects and global initiatives. Of special interest for this consortium will be results achieved in the MIP-DILI project[7] under the IMI initiative as well as results of the liver sub-team of the "Imaging for translational safety assessment" initiative under the HESI[8] framework. Outcomes from the IMI consortium ABIRISK[9] will also be of interest. This project may also significantly benefit from results of the eTRIKS[10] consortium launched under IMI regarding data exchange and combined analysis of data from different sources and formats.

Industry consortium

The industry consortium will comprise pharmaceutical and imaging companies. Industry specialists from the areas of biologics, preclinical & clinical pharmacology, safety pharmacology, diagnostic imaging and clinical trials will actively participate in the project's work packages. The industry contribution will be to provide joint scientific leadership, coordination and project management expertise to optimise the consortium's efforts, as well as a sound track record and experience in toxicology and pre-clinical imaging. Industry contributions will support these efforts by contributing to all work packages.

- Bayer (coordinator)
- Abbvie (co-coordinator)
- Sanofi
- GSK
- Novo Nordisk
- Pfizer
- PMB Alcen

[6] http://www.eurobioimaging.eu/
[7] http://www.mip-dili.eu/
[8] http://www.hesiglobal.org/
[9] http://www.abirisk.eu/
[10] https://www.etriks.org/

- General Electrics
- Bruker

In detail, Bayer, Sanofi and GSK will contribute pre-clinical imaging expertise and resources (MRI & CT), PK modelling activities and MRI/CT contrast agents. Bruker will contribute to imaging technology validation, data acquisition and evaluation, image analysis including multi-modality approaches, image co-registration, workflow optimisation, and set-up of respective tools. Abbvie and Novo Nordisk will contribute relevant biologics as tool compounds as well as biochemical and biological analytics. PMB Alcen will contribute to PET-tracer development and support in radiochemistry. GE will contribute consulting for hyperpolarisation techniques. Pfizer will contribute consulting for clinical trial set-up and conduct. All industry partners are committed to contributing pre-clinical data and expertise to shaping precise needs for standardisation and workflow organisation.

Indicative duration of the project

The indicative duration of the project is 60 months. This duration allows in-depth systematic analysis and validation of biomarker imaging approaches in animals and humans.

Indicative budget

The indicative EFPIA and associated partners in-kind contribution will be EUR 12 000 000.

The indicative IMI2 contribution will be a maximum of EUR 12 000 000.

Applicant consortium

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

The applicant consortium is expected to address all the research objectives and make key contributions on the defined deliverables in synergy with the industry consortium which will join the selected applicant consortium in preparation of the full proposal for stage 2.To address the complex tasks of the topic adequately, the project is expected to build a network for translational imaging in drug safety assessment. Such a network shall be multidisciplinary and include experts from the fields of contrast agent / tracer chemistry, pre-clinical imaging and radiology, toxicology (especially liver and lung toxicology), disease biology, imaging technology and research information technology. The applicant consortium is expected to comprise:

- contribution with relevant animal models;
- relevant invasive and non-invasive pre-clinical imaging expertise at multiple sites;
- relevant non-invasive clinical imaging expertise at multiple sites;
- skills in biochemical and biological (including *in vitro* and *in vivo*) validation of imaging results;
- expertise in pharmacokinetic modelling of imaging data;
- ability to program data evaluation tools allowing for integration and concerted evaluation of very different types and formats of data (pre-clinical, clinical, biochemical, histological, imaging data);
- expertise in developing and deploying tools for storage and exchange of imaging data together with associated pre-clinical and clinical data;
- expertise in translating pre-clinical and clinical imaging research demands into standardised, user-friendly and work-flow oriented tools for image acquisition, evaluation and result reporting;
- expertise in tracer or contrast agent design and medicinal chemistry;
- radiochemistry expertise and infrastructure for synthesis and use of required PET tracers for pre-clinical and clinical use;

- experience in conducting clinical imaging studies.

On a successful stage 1 evaluation outcome, the selected applicant consortium will join the industry consortium to build a seamless, collaborative and fully-integrated final full consortium and make key contributions on the defined deliverables in full synergy with the industry consortium. Intense exchange within this team of experts will be key for the success of this initiative.

Suggested architecture of the full proposal

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

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

In addition a plan for interactions with regulatory agencies with relevant milestones and appropriate resource allocation should be built into the project architecture as well as aspects related to dissemination and sustainability, facilitating continuation beyond the duration of the project.

The final architecture of the full proposal will be defined by the participants in observance of IMI2 rules and in contemplation of the achievement of the project objectives.

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

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

Note: Data collection and data management should be conducted according to established data standards and/or in collaboration with a data standards organisation (e.g. CDISC), to develop new data standards if no established data standards exist and according to the Small Animal Imaging DICOM Working Group by the US National Cancer Institute supported by the DICOM-NEMA standards committee.

Suggested project structure

This project is suggested to be organised in 5 major work packages:

Work package 1: Project coordination

- 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;
- communicate with the project team as well as outside the project to ensure alignment with all stakeholders, collaboration with other relevant projects and initiatives and to ensure external awareness.

Work package 2: Liver transporter assessment

- Collect available pre-clinical and clinical data regarding liver-bile transporter function assessment and structure this data for alignment to generated imaging data. This data collection shall be used as basis for the validation of Gadoxetate enhanced dynamic MRI for function determination of the liver-bile transporter mrp2.
- Establish, standardise and validate a robust Gadoxetate enhanced dynamic MRI process for liver-bile transporter function assessment in animals against biochemical and biological measures utilising compounds known to impair liver transporter function. Then translate the method to humans and verify its robustness in human imaging studies across imaging sites and vendor platforms.
- Optional: assess further imaging based approaches for other relevant liver-bile transporters (e.g. BSEP) by means of PET, MRI, CT or US. Proof of mechanism in man would be essential.

Work package 3: Pulmonary toxicity assessment

- Collect available pre-clinical and clinical data from existing drugs regarding pulmonary toxicity assessment/drug-induced interstitial lung disease and establish a comprehensive library of imaging biomarkers; structure this data for alignment to generated imaging data.
- Develop and apply dedicated imaging methods and procedures (which may include MRI, CT, PET, SPECT and potentially optical imaging) for detection and characterisation of interstitial lung disease. Approaches to generate novel, valuable contrast agents or tracers shall be assessed. Methods may be employed in a multimodal fashion if applicable.
- Standardise and validate the developed imaging procedure pre-clinically against biochemical and biological measures applying drugs known to impair lung function.
- The pre-clinically validated imaging procedure shall be translated to humans and be verified across clinical imaging sites.

Work package 4: Bio-distribution of biologicals

- Advance, apply and compare dedicated invasive and non-invasive imaging methods and procedures for assessment of bio-distribution and degradation of biologicals. Methods may include MALDI/MALDI2 imaging, optical/fluorescence imaging, immune-detection, potentially OCT and PET and may be employed in a multimodal fashion; sensitivity issues with LC/MS of large molecules shall be assessed.
- Standardise and validate the developed imaging procedures pre-clinically against biochemical and biological measures applying biological tool compounds and compare results between healthy and diseased animals to verify their validity.
- Apply imaging of biologics to selected compartments like CNS, liver, kidney for a better understanding of their bio-distribution.
- Assess foetal exposure by comparative distribution/quantification & imaging studies; establish the baseline fetal exposure properties for NBE and ADC; measure foetal exposure properties in selected compartments after SQ delivery.
- Develop and validate tissue epitope quantification software, assess modelling of local quantification data for animals Assess therapeutic compartments vs. non-target related disposition. The pre-clinically validated non-invasive imaging procedure shall be translated to humans and be verified across clinical imaging sites.

Work package 5: Technical standardisation and validation of imaging procedures

- standardise the entire imaging workflow for single and multi-modal approaches, in order to achieve a high level of robustness and reproducibility of results regarding each applied imaging biomarker procedure;
- optimise sensitivity and specificity of single-modality imaging for each applied imaging biomarker procedure;
- create specific image evaluation software packages allowing the extraction of key parameters or parameter maps for characterisation of the imaging biomarker, in particular for multi-modal imaging;
- standardise formats for easy inter-laboratory exchange and understanding of imaging data and result reports;
- all tasks have to be closely interlinked with the remaining work packages.

Glossary

ADA	Anti-Drug Antibodies
ADC	Antibody-Drug Conjugates
ADME	Absorption, Distribution, Metabolism and Excretion
BBB	Blood Brain Barrier
CDISC	Clinical Data Interchange Standards Consortium
CNS	Central Nervous System
CT	Computed Tomography
DCE-MRI/-CT	Dynamic contrast-enhanced MRI / Dynamic contrast-enhanced CT
DICOM	Digital Imaging and Communications in Medicine
DMPK	Drug Metabolism and Pharmacokinetic
DW-MRI	Diffusion-weighted Magnetic Resonance Imaging
GI	Gastrointestinal tract,
LC/MS	Liquid Chromatography / Mass Spectrometry
NBE	New Biological Entity
MALDI	Matrix-Assisted Laser Desorption Ionization
MRI	Magnetic Resonance Imaging
OCT	Optical Coherence Tomography
PET	Positron Emission Tomography
PK/PD	Pharmaco Kinetic / Pharmaco Dinamic
SPECT	Single-Photon Emission Computed Tomography
SQ	Sub-cutaneous application
UTE-MRI	Ultrashort echo-time Magnetic Resonance Imaging

Topic 2: Identification of druggable targets modulating misfolded proteins in Alzheimer's and Parkinson's diseases

Topic details

Topic code	IMI2-2015-07-02
Action type	Research and Innovation Actions (RIA)
Submission & evaluation process	2 stages

Specific challenges to be addressed

The estimated population of patients with Alzheimer's disease (AD) and Parkinson's disease (PD) worldwide is currently about 44 and 10 million respectively and is expected to rise markedly over the next decades due to an aging population. Currently, only symptomatic treatments are available. Therefore a treatment with the potential to delay or halt disease progression is highly needed. The development of drugs towards neurodegenerative diseases has been especially challenging with a success rate in AD clinical trials of only 0.4% during the last decade which is among the lowest for any therapeutic area (Cummings et al., 2014[4]).

In AD, extracellular depositions of amyloid beta peptides (plaques) and intracellular filamentous inclusions of tau (tangles) constitutes a hallmark of the disease. The same type of inclusions is observed in both the sporadic and in familial cases linked to mutations in the amyloid proteins, substantiating a central role of this protein in the pathological process. Mutations in tau lead to frontotemporal dementia and other related types of dementias, but they are is still a hallmark of AD and a key pathological component. In PD, the neuropathology is defined by intracellular inclusions of alpha-synuclein (Lewy bodies and Lewy neurites). Rare familial cases have also been identified which link mutations in alpha-synuclein directly to PD (Polymeropoulos et al., 1997[8]). Thus, there is a strong rationale for these proteins as central players in the developing neurodegenerative pathology. Despite increased understanding of the aetiology of AD and PD, developing a therapy to prevent, delay or slow down the progression of these diseases has turned out to be exceptionally difficult. Years of research have only yielded therapies capable of relieving symptoms. Many of the drugs being used today are developed based on target pathways identified decades ago as exemplified by the current use of cholinergic and dopaminergic based therapies for AD and PD respectively. There are many reasons why this area of research has been so challenging for drug developers. For example, although progress has been made, scientists still do not fully understand the underlying mechanisms of these diseases, particularly when it comes to separating potential causes from effects of the disease. This makes selection of viable targets for new therapies very difficult. Also, the limited pathology and long experimental timelines required for current animal models of these diseases has been a large barrier in preclinical testing of drug candidates.

Recently, new scientific opportunities to identify druggable targets have arisen based on the spreading and seeding hypothesis of tau and alpha-synuclein protein as prion-like proteins. This hypothesis allows setup of *in vitro* and *in vivo* models based on tau or alpha-synuclein pathological material isolated from patients, animal models or recombinant fibrils seeded into cells or animals and with a resulting defined mechanistic readout (spreading or seeding) (Clavaguera et al., 2009[3]; Holmes et al., 2013[5]; Watts et al., 2013[12]; Prusiner et al., 2015[9]). Thus, it is envisioned that these models may be used in a screening set-up to identify new targets and later validate their druggability.

Need and opportunity for public-private collaborative research

For the project to be successful it requires a strong understanding of fundamental biological processes; cellular seeding and spreading mechanisms of pathological proteins in neurodegenerative diseases and protein turn-over. Both research areas are represented by intense and rapidly-advancing research activities

conducted in different academic and industrial research laboratories. Advancing and focusing the research discoveries to identify drug targets related to Alzheimer's and Parkinson's diseases requires multidisciplinary approaches including target identification screens, tool compound development, and validation in a wide range of experimental cell and animal disease models. The critical mass needed and availabilities of assay, models and reagents are only available through broad collaborations.

Scope

Neuropathologically, both AD and PD are defined by the presence of aggregated amyloid proteins. The appearance of alpha-synuclein aggregates and tau tangles in the brains of patients have been described to follow a very characteristic pattern (Braak, 1991 and 2003[1 & 2]). Also, a sequential spread of pathology has been suggested based on for example the observation that transplants of human foetal dopaminergic neurons into the striatum in PD patients developed Lewy-body like structures 12-16 years after transplantation (Li et al., 2008[7]; Kordower et al., 2008[6]; Clavaguera et al., 2009[3]). Hyperphosphorylated tau injected into the brains of rodents is taken up by the neurons and subsequently induces aggregation of endogenous tau. These and other findings suggest that tau and alpha-synuclein have prion-like properties, and that spreading and seeding constitutes a central pathological mechanism for Alzheimer's and Parkinson's diseases.

Therapeutic intervention in the spreading process may occur at different levels. Some approaches have focused on inhibiting the fibrillation process with small molecules (for example methylthioninium, a proposed tau aggregation inhibitor is in phase I clinical trials) (reviewed by Wisniewski et al., 2015[13]; Tran et al., 2014[10]; Vassar 2014[11]). More recently, work begun exploring immunotherapy targeting alpha-synuclein or tau. Antibodies will potentially be able to prevent both formation of pathogenic species and facilitate the clearance of already-formed species and shield pathogenic forms, thereby preventing them from mediating direct toxic insults. The first antibodies are currently in a phase 1 clinical trial (Roche/Prothena).

However, our understanding of the molecular mechanisms involved in the spreading, uptake, seeding, aggregation, impact on cell homeostasis, release and toxicity is still very sparse, hence limiting effective intervention strategies.

A key objective of the action will be to use the recent advances in setting up both *in vitro* and *in vivo* model systems for spreading and seeding processes. Genome-wide genetic screens and small molecule screens to identify targets and mechanisms involved in these processes should be performed. Based on the key mechanisms identified in these screens, targets will be chosen for further validation of drugabbility and therapeutic potential *in vitro* and *in vivo*.

Expected key deliverables

- A platform consisting of:
  - robust *in vitro* assays for tau and alpha-synuclein uptake and seeding/aggregation useful for target identification;
  - established model systems for *in vitro* and *in vivo* validation of targets modulating seeding and spreading of disease-associated forms of tau and alpha-synuclein proteins.
- Conducted genetic based screens on either seeding, spreading or clearance to identify targets in the relevant druggable genome. Eventually, a tool compound screen with annotated compounds could be considered as well.
- Established tools to knock-down and over-express targeted genes and identify suitable reagents to quantify knock-down or overexpression.
- Findings validated by gene knock-down or over-expression studies in disease (focus on AD & PD) relevant preclinical models *in vitro* and *in vivo*.
- Druggable targets reducing the pathological spreading of tau or alpha-synuclein.

Expected impact

Several outputs from the project may contribute to the research and development (R&D) process of developing new therapies against PD and AD. Establishing a common preclinical platform of assays based on the hypothesis of turnover / aggregation / spreading of misfolded pathological proteins is important to reach a consensus of how new treatment principles can best be evaluated and substantiated. Such a platform can form the basis for identification of new druggable targets which would open up the development of new innovative treatments against PD and AD.

Potential synergies with existing consortia

Applicants should take into consideration, while preparing their Short Proposal, relevant national, European (both research projects as well as research infrastructure initiatives), and non-European initiatives. Synergies and complementarities should be considered, building from achievements, and incorporating when possible, data and lessons learnt while avoiding unnecessary overlapping and doubling of efforts.

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

For example synergies with, and learning from, relevant JPND actions[11&12], Horizon 2020 (e.g. PROPAG-AGEING[13]) and FP7 (e.g. PROTEASYS[14], PRISITINE-PD[15], SKIPPERAD[16], MAMBA[17]) initiatives as well as the ERA-Net Neuron[18] should be considered at the European level, as well as any relevant actions at national level.

Synergies and leveraging should also be considered with ongoing IMI initiatives which might already been developing relevant platforms, tools and compounds libraries such as AETIONOMY[19], STEMBANCC[20] , ULTRA-DD[21] and EUROPEAN LEAD FACTORY[22].

To optimise the impact of this research project, collaboration and synergies with other relevant global initiatives (see for example AMP-AD[23]) should also be taken into consideration.

Industry consortium

- Lundbeck (lead company)
- J&J
- Abbvie
- Novartis
- Lili & Lilly

The indication addressed by this topic is AD and PD, with a focus on the role of cellular mechanisms regulating the processing of tau and alpha-synuclein. As described above, the topic will address several areas within the scope of basic research; e.g. setting up suitable assays to study uptake, seeding and spreading processes of tau and alpha-synuclein, identifying targets modulating these processes for validation and drug development, which are processes typical for the pharma industry. Academic research groups will

[11] http://www.neurodegenerationresearch.eu/initiatives/
[12] http://www.neurodegenerationresearch.eu/wp-content/uploads/2015/10/JPND_Call_2015_For-JPND-website.pdf
[13] http://cordis.europa.eu/project/rcn/193308_en.html
[14] https://erc.europa.eu/projects-and-results/erc-funded-projects/PROTEASYS?retain-filters=1
[15] https://erc.europa.eu/projects-and-results/erc-funded-projects/PRISTINE-PD?retain-filters=1
[16] https://erc.europa.eu/projects-and-results/erc-funded-projects/SKIPPERAD?retain-filters=1
[17] https://erc.europa.eu/projects-and-results/erc-funded-projects/MAMBA?retain-filters=1
[18] http://www.neuron-eranet.eu
[19] http://www.aetionomy.eu/index.php?id=5263
[20] http://stembancc.org/
[21] http://www.ultra-dd.org/
[22] http://www.europeanleadfactory.eu/
[23] http://www.nih.gov/science/amp/alzheimers.htm

be focusing on *in vitro* and *in vivo* methodologies, while industry contributions will support these efforts. In particular, the industry consortium will bring in expertise in later-stage activities like evaluating target druggability and small molecule identification and qualification.

Contributions will be on:

- assay development
- *in vitro* and *in vivo* pharmacology
- drug screening
- chemical support of compound tool generation and screening of chemical libraries
- ADME-T / PK
- Information technology (IT) (systems biology/bioinformatics).

Indicative duration of the project

The indicative duration of the project is 48 months.

The successful achievement of the expected deliverables of this project 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 and associated partners in-kind contribution will be EUR 4 685 000.

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

The indicative IMI2 contribution will be a maximum of EUR 4 685 000.

Applicant consortium

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

Applicants are expected to address all the above objectives in the Short Proposal (within the available duration and maximum IMI2 contribution) and demonstrate a relevant strategy for achieving them, through partnership with the industry consortium which will join the selected applicant consortium in preparation of the full proposal for stage 2.

This may require mobilising as appropriate:

- academic expertise in Alzheimer's disease and Parkinson's pathologies and disease progression;
- expertise in translational medicine;
- expertise in protein clearance, uptake/endocytosis/exocytosis mechanisms and cell responses to misfolded proteins;
- expertise in and application of relevant models, screening systems and tools (making them available for other members of the consortium as needed);
- integration of drug discovery expertise; project management;
- expertise in other neurodegenerative diseases beyond AD & PD with pathologies based on similar misfolded proteins (e.g. FTD and MSA), might be a further asset.

Suggested architecture of the full proposal

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

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

The final architecture of the full proposal will be defined by the participants in observance of IMI2 rules and in contemplation of the achievement of the project objectives.

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

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

Work package 1: Governance and project management

- grant administration
- project plan
- dissemination of scientific results.

For each work package it is suggested that a Work Package leader create a detailed project plan and engage with the project team as well as people outside the project to ensure alignment with all stakeholders, facilitate collaboration with other relevant projects, and take initiatives to ensure external awareness.

Work package 2: Establishing a collection of *in vitro* and *in vivo* assays for tau and alpha-synuclein uptake, seeding and aggregation and aggregate-dependent toxicity

- set up and validate different assays and model systems;
- reach an agreement/consensus of which assays should be used for target identification and/or target validation.

Work package 3: Identification of targets using genetic based and small molecule based screening in cellular assays established and selected from work package 2

Already available validated assays can also be used directly if agreed by the consortium.

- conduct genetic based screens by knocking down or modulating specific targets in cellular models with defined mechanistic or phenotypical endpoints;
- get insight into targets and mechanisms affecting uptake, seeding and aggregation.

Work package 4: Target validation and evaluation of target druggability using *in vitro* and *in vivo* assays

- validate effect of modulating or inhibiting selected targets and/or pathways *in vitro* and *in vivo* and study effects on alpha-syncuclein and tau and their affected biologies;
- investigate the druggability of targets and more broadly characterise the implications of modulating the target(s).

Work package 5: Data and knowledge management

- establish data format and content standards for data collection, data management and data sharing in order to ensure interoperability to quality standards and optimal use of IMI2 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);
- develop a data and knowledge management plan.

Glossary

ADME-T/PK	Absorption, Distribution, Metabolism, Excretion / Pharmacokinetik
AD	Alzheimer's Disease
Druggability	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 but has also been extended to include biologic medical products such as therapeutic monoclonal antibodies
PD	Parkinson's Disease

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Topic 3: Pathological neuron-glia interactions in neuropathic pain

Topic details

Topic code	IMI2-2015-07-03
Action type	Research and Innovation Actions (RIA)
Submission & evaluation process	2 stages

Specific challenges to be addressed

Neuropathic pain (NP) is a widespread disease affecting 6-8% of the population, causing great misery, and incurring huge costs to society. Often it is a chronic condition, lasting for months or even years. It arises after insults such as surgery, trauma, diabetes, chemotherapy or viral infections which can cause the peripheral and/or central somatosensory nervous systems to become dysfunctional and behave abnormally. Current therapies are inadequate because they address only the symptoms, not the causes, of the pain, and are therefore not curative. In fact, the aetiologies of the disease are poorly understood, hindering the development of new analgesics with improved efficacies.

It is clear that initiation and maintenance of NP is not dependent on neuronal activity alone. Glia – microglia, astrocytes, oligodendrocytes, Schwann cells and glial satellite cells - contribute directly to the modulation of neurotransmission, especially within the spinal cord, by the release and uptake of pro- and anti-nociceptive mediators and neuro-transmitters. The balanced interplay between neurons and glia is fundamental to healthy homeostasis in the nervous system. NP has many features of a neuro-inflammatory disorder in which activated glia play important roles. These are major sources of aggravating inflammatory mediators and of substances such as glutamate or ATP that sensitise neurons and enhance nociception. Indeed, the extent of glial activation parallels the intensity of NP.

Glial responses to tissue inflammation differ greatly in rodents and humans. As NP involves aberrant interactions between glia and neurons, it is not surprising that the *in vitro* and *in vivo* rodent test systems currently used to identify treatments, read-outs or biomarkers for NP frequently fail to translate into clinical use. A salutary example is propentofylline: its promising preclinical profile was not replicated in clinical trials because it suppresses proinflammatory reactions of rat, but not human, microglia. Clearly, in order to be validly predictive, the mechanism of drug action in preclinical assays must mirror that in humans. The dilemma is that this is often not known as human tissue experiments are fraught with ethical problems. However, it has now become possible to generate human neurons and glia cells by inducing pluripotent stem cells or by reprogramming cells such as fibroblasts. It is possible that their interactions in co-culture will be sufficiently similar to those in intact neuronal tissues that they will reflect the pathological alterations in intra- and inter-cellular signalling pathways which occur in NP states.

It is proposed that if these pathways are analysed in depth, the information will guide the discovery of effective analgesics and of clinically useful biomarkers, and help improve the healthcare of millions of patients.

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. Identifying pathological mechanisms behind the development and maintenance of NP, and identifying ways to restore these to healthy normality in order to not only relieve but to cure the pain, is a very ambitious and complex undertaking which is beyond the scope of any individual research group or company and will require a strong collaborative effort to be successful. Indeed, it will require the coordinated and dedicated efforts of a multi-disciplinary consortium which brings together

expertise from different complementary professional research areas in academia, small and medium-sized enterprises (SMEs) and pharma industries.

The industry partners will act as the project leads and provide expertise in preclinical models of neuropathic pain. The Applicants, whether academic laboratories or SMEs, will be skilled in complementary and innovative methodologies such as differentiation of human induced pluripotent stem cells (hiPSCs) or analysis of heterogenous cell populations by high content screening (HCS) microscopy. Such a consortium will be well-positioned to make significant progress towards understanding the development of neuropathic pain, and how to ameliorate it. Furthermore, the engagement of the industry partners will ensure that any innovative technologies or druggable opportunities identified by the consortium will be capitalised upon quickly.

Scope

The ultimate goal is to develop *in vitro* cell cultures which reflect the interactions between neurons and glia in healthy neuronal tissues and in NP states in both rats and humans, and to use these to discover new curative clinical therapies for NP. Initially the methods will be established and validated in rat tissues and cells; subsequently they will be applied to cultures and co-cultures of human neurons and glia derived from pluripotent human cells.The HCS technology will be applied as it enables a fast multiparametric screening of many conditions with a decent cellular and mechanistic resolution at the same time.

Intra- and intercellular signalling pathways will be analysed in samples of rat tissue (e.g. peripheral nerves (PNs), dorsal root ganglia (DRGs) and spinal cord (SC)) by a battery of techniques including transcriptomics, proteomics and immunohistology studies employing HCS microscopy, which allows thousands of cells to be monitored at a single cell level (e.g. dissociated neuronal cell types) for changes in their signalling. The tissue samples will be collected from naïve rats, and from rats developing or suffering from chronified peripheral neuropathy induced by chemotherapy or spinal nerve ligation (SNL). Changes caused by the NP state will be defined and compared. Rats will be subjected to behavioural tests, as well as to electrophysiological tests of the spinal cord and of peripheral nerves, and also to immuno-histochemical, neurochemical, transcriptomics, and proteomics analyses using samples obtained from tissue (e.g. PNs, DRGs, SC), plasma and cerebrospinal fluid (CSF). In parallel, this in-depth analysis could also lead to biomarkers for pathological neuron-glia cross-talk in rats.

The aim is to add to existing information about the changes in neuron-glia cross-talk *in vitro* and in tissue which occur during the chronification of pain after peripheral neuropathies in rats, and examine whether the *in vitro*, *ex vivo* and *in vivo* read-outs are congruent, and whether novel points of intervention can be identified. The effects of various pharmacological interventions on the observed changes will also be tested to examine whether they cause changes in the NP disease indicators.

It is hypothesised that under appropriate conditions, co-cultures of neurons and glia cells may possess properties which usefully reflect those of the neuron-glia axis within neuronal tissue. Such cells can be isolated from tissue of naïve and neuropathic rats, permitting the development of cell cultures of neurons, and glia, and co-cultures of both cell types. The battery of *in vitro* investigations used to characterise changes in signalling pathways during the development of neuropathies *in vivo* will also be applied to examine whether these differences are retained in (co-)cultures from the tissue of naïve and neuropathic rats. In addition, the abilities of various stressors (e.g. chemotherapeutics, glucose, reactive oxygen species, hypoxia, lack of trophic support) to induce neuropathic-like alterations in signalling, and the ability of drugs to modify such alterations, will be examined *in vitro*. Congruence between the properties of the *in vivo* and *in vitro* studies would support the hypothesis that neuron-glia co-cultures behave as a surrogate tissue that can usefully mimic *in vivo* responses, and provide a basis for reducing the need for animal experimentation during drug discovery.

As human functional nerve tissue is not available, neurons and glia cell cultures and co-cultures will be derived from appropriately induced human pluripotent progenitors. These will be examined with all of the *in vitro* methods employed to characterise the rat cultures. These studies are particularly ambitious, but of great interest should the analogous rat studies be promising. They could lead to a highly innovative shift in the research paradigm, not only for discovering new analgesics, but for neuro-regenerative drugs in general. Because they are so innovative, it is anticipated that it will only be possible to conduct preliminary

development work during the course of the current proposal, but that if this is promising, these requisite studies would be performed during a project extension.

The hope is that the proposed project will collect enough information to permit the definition of interventions which at least alleviate NP better than current treatments, or are even able to reverse the pathological chronic state, and are therefore truly disease-modifying and curative.

Expected key deliverables

The establishment of chronic peripheral pain in rats will involve an aberration of neuron-glia cross-talk. The key mechanisms behind this will be identified and characterised with a special focus on the reasons for the chronification or lack of resolution of this pain state. Alterations in signalling pathways in PNs, DRGs or SC will be examined not only by application of transcriptomic and proteomic approaches, but also using HCS microscopy, and performing neurochemical and electrophysiological analyses.

The effects on the signalling pathways of specific pharmacological interventions with tool compounds or combinations of tool compounds will be defined, and the information used to identify key mechanisms of action and potential novel biomarkers. In parallel, biomarkers representative of neuron-glia cross-talk in rats will be sought in tissues, plasma and CSF; such biomarkers would support efforts not only to discover new analgesic compounds, but also to repurpose known targets or drugs.

These studies will provide an information basis to define better the properties that cell co-culture models of the neuron-glia axis should have in order to be of use in investigating the translatability of preclinical to clinical studies. Co-cultures of neurons and glia isolated from rat, or developed from reprogramming human cells, will be established, and the nature of the interaction between the cells defined. The ability of the co-cultures to respond to known pain mediators will be compared with that of the cells in their native neural tissue environment. If similar, then HCS-based assays of a human nociceptive system will be established and validated in a HTS format. Predictive and robust screening assays of rat and human nociceptive test systems may be a game-changer in the search for novel curative analgesics.

In summary, the key deliverables would be:

1. in-depth analysis of neuron-glia cross-talk to identify key mechanisms involved in the development and maintenance of chronic NP;
2. development of *in vitro* rat screening assays based on high content screening (HCS) microscopy that resemble the *in vivo* situation, in particular, the complex neuron-glia relationship present in NP states;
3. identification of biomarkers of pathological neuron-glia cross talk in rats;
4. development of *in vitro* human screening assays based on human iPSCs and HCS microscopy.

Expected impact

It has been long recognised that chronic NP is a serious medical and societal problem for which no adequate therapies are available. Current therapies such as anti-depressives, anti-convulsives, serotonin noradrenaline uptake inhibitors, topical anaesthetics, opioids and cannabinoids, were originally developed for different indications, and are used because there are no alternatives. They target the symptoms, not the causes, of the neuropathies.

The search for better and curative treatments is hampered by the lack of understanding of the reasons for the sensitisation underlying NP, and to chronification; these knowledge gaps preclude definition of plausible new targets. This IMI2 topic will employ cutting-edge techniques and technologies in order to deepen understanding of clinical NP at the cellular and genetic levels.

Traditional preclinical paradigms will be dissected to delineate the reasons for altered signalling pathways and cross-talk within and between neurons and glia during the development of neuropathies in rodents. An *in vitro* assay which mirrors the changes occurring *in vivo* will be developed and is expected to offer an extremely

valuable addition to methods for investigating neuropathies, and for selecting drugs which reverse them. Because rodent and human neuronal cells differ in their responses to inflammatory stimuli, an equivalent *in vitro* assay will be developed using human neurons and glia cells derived from a pluripotent progenitor.

The knowledge gained will greatly improve the chances of identifying and developing curative analgesic therapies for chronic NP which would enhance the quality of life for millions of patients, and bring substantial cost savings in healthcare.

Potential synergies with existing consortia

Considering the envisioned timelines and budget of this proposal, the planned work will build on and leverage as much as possible available knowledge 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.

The current proposal will build on achievements and knowledge from other relevant IMI projects, in particular with projects under the umbrella of the Strategic Governance Group for Neurodegeneration (SGG-ND) of which the Pain Group is a satellite working group. The expected rat and human screening assays of indicators of pathological neuron-glia cross-talk could lead to a highly innovative shift in the research paradigm, not only for discovering new analgesics, but for neuro-regenerative drugs in general. Thus valuable interaction is expected and sharing of experiences will be sought with the planned project 'Inflammation and AD: modulation microglia function – focussing on TREM2 and CD33' (IMI2 - Call 5 - Topic 3)[24].

This action may share tools and knowledge with the relevant work packages of the IMI project StemBanCC[25].

The proposal will strongly build on achievements and knowledge from the IMI project 'Europain - Understanding and controlling pain'[26] that finished in September 2015.

Furthermore, synergies should be considered at the European level with relevant Joint Programming in Neurodegenerative Diseases (JPND) actions[27] , Horizon 2020 (e.g. DOLORisk[28]), FP7 initiatives (e.g. GLORIA[29], ncRNAPain[30], PAINCAGE[31], Neuropain project[32], other European research projects and research infrastructure initiatives, as well as with relevant actions at national level. In addition, applicants should take into consideration, and seek synergies with, relevant US-based activities.

Industry consortium

EFPIA participants: Esteve (coordinating) and Grünenthal.

The indication addressed by this topic is neuropathic pain. The focus is the investigation of neuron-glia interactions which should provide information to enable the definition of curative analgesic therapies. As described above, the topic will address several areas from preclinical and translational research, in particular the characterisation and identification of key mechanisms involved in chronic pain-related neuron-glia cross-talk, suitable for curative therapeutic intervention in neuropathic pain patients. Furthermore, the topic will address the provision of robust, validated and translatable test systems for selected targets or pathways.

Industry contributions will support these efforts by contributing to all work packages, but in particular by bringing in expertise in rodent pain models of peripheral neuropathic pain. Although neuropathic pain can be

[24] http://www.imi.europa.eu/content/stage-1-16
[25] http://stembancc.org/index.php/work-packages-in-detail
[26] http://www.imi.europa.eu/content/europain
[27] http://www.neurodegenerationresearch.eu/initiatives/
[28] http://www.ndcn.ox.ac.uk/research/neural-injury-group/research-projects/dolorisk
[29] http://gloria.helsinki.fi/?page_id=168
[30] http://www.ncrna-pain.eu/
[31] http://www.paincage.eu/
[32] http://cordis.europa.eu/project/rcn/111184_en.html

caused by a wide range of insults such as diabetes, viral infections and wounding, in order to remain within a realistic work frame, the industry consortium has intentionally decided to investigate only chemotherapy-induced neuropathic pain in this topic as it is highly reproducible in both rodents and humans, and its basis is still not understood. Should the working hypotheses of the approach prove valuable, and if funding is available, future studies would address other forms of NP. In addition, EFPIA's contribution will be to provide joint scientific leadership, coordination and project management expertise to optimise the consortium's efforts.

Indicative duration of the project

The indicative duration of the action is 36 months.

Future project expansion

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

The objectives of a project extension could include:

- the investigation of peripheral and central NP induced by other insults such as diabetes and spinal cord injury in preclinical models;
- further analysis of the relevance of chronic pain-related neuron-glia cross-talk in establishing and maintaining NP as well as generation and phenotyping of transgenic/knock-out/in mice for key selected genes;
- validation and upscaling of the human iPSC-derived neuron-glia cell co-culture assay for additional pain-relevant signal cascades;
- testing the predictive validity of identified potential biomarkers in these pain states, and in related clinical neuropathies.

To fully address these new goals it is expected that additional expertise from SMEs and academic groups which possess relevant cutting-edge technologies would be required.

Indicative budget

The indicative EFPIA and associated partners in-kind contribution will be EUR 1 500 000.

The indicative IMI2 contribution will be a maximum of EUR 1 500 000.

Applicant consortium

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

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

The applicant consortium should summarise their abilities to make assured key contributions to all the relevant expected deliverables in synergy with the industry partners of the consortium (within the framework of the project duration and maximum IMI2 contribution).

The applicant consortium should consist of academic groups and SMEs who bring in their expertise in HCS microscopy or human iPSC technologies. They are expected to be able to contribute to the following deliverables:

- analysis of changes of signalling pathways in *in vitro* rat neuron-glia test systems (tissue e.g. PNs, DRGs and SC from naïve and neuropathic animals) using HCS microscopy;
- establishment of test systems with neurons and glia derived from induced human pluripotent stem cells;
- analysis of signalling pathways in human neuron-glia test systems (iPSCs) using HCS microscopy;
- analysis of translatability between *in vitro* rat and human nociceptor systems;
- establish equivalent rodent and human neuron-glia test system suitable for investigating the etiology of neuro-degeneration in NP and for drug screening.

Suggested architecture of the full proposal

The final architecture of the full proposal will be defined by the participants in observance of IMI2 rules and in contemplation of the achievement of the project objectives.

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

The applicant should include in their short proposal their suggestions for creating the Full Proposal architecture taking into consideration the industry contributions and expertise below.

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

In summary, this Topic proposal can be deconvoluted into several work packages (WPs) which, in combination, will deliver valuable research results aiming at:

- characterisation and identification of key mechanisms of pathological neuron-glia cross-talk involved in the development and maintenance of chronic NP which are suitable for curative therapeutic intervention in NP patients;
- provision of robust and validated rat and human screening test systems of selected indicators of pathological neuron-glia cross-talk for discovery of clinically efficacious curative analgesics.

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

1) grant administration
2) communication (within the consortium and with relevant external collaborators)
3) dissemination of scientific results and research data (see details of expectations in the general conditions of the Call), communication with patient organisations
4) sustainability plan facilitating continuation beyond the duration of the action.

Industry contribution:

- grant administration, communication, dissemination of the results, and sustainability plan.

Expected applicant consortium contribution:

- communication and dissemination of scientific results.

Work package 2 – In-depth analysis of *in vivo rat* models of chemotherapy- and SNL-induced NP

1) Behavioural characterisation (e.g. mechanical hypersensitivity, cold allodynia, thermal hyperalgesia).
2) Immunohistochemistry and molecular biological testing (e.g. RT-PCR, Western blot, ELISA).
3) *In vivo* neurochemistry (SC microdialysis).
4) *In vivo* electrophysiology (PNs and SC).
5) Sampling of tissue (e.g. PNs, DRGs, SC), plasma and CSF of naïve and neuropathic rats in order to supply WPs 3 and 4.
6) *In vivo* testing of pain-modulating compounds selected in WP3 in order to compare with the results of the *in vitro* HCS microscopy and thereby support testing their translatability (see WP3.5): Behavioural, immunohistochemical, molecular biological, neurochemical and electrophysiological testing. In addition, the rat *in vivo* data will also be compared with those generated in the human neuron-glia co-cultures (see WP6).

Industry contribution:

- In principle, the industry consortium is able to complete WP2 independently. However, as it is anticipated that interaction with the capabilities of the applicant consortium would enrich the quality of the results, such interactions will be sought.

Expected applicant consortium contribution:

- The applicant consortium could conduct relevant assays of tissues and other samples which are beyond the resources of the Industry Consortium.

Work package 3 – Characterisation neuron-glia cross-talk and development of a screening assay in rat nociceptive tissue using high content screening (HCS) microscopy

1) set up cell cultures of rat tissue (e.g. PNs, DRGs, SC) for HCS microscopy;
2) broad analysis of NP-induced changes to signalling pathways and parameters on neurons and glia (e.g. the expression level of kinases in PNs, DRGs or SC, translocation of signalling kinases during pain chronification, degree of phosphorylation of kinase regulatory subunits, alterations in mitochondrial function indicated by changes in morphology and membrane potential, as well as transcriptomics and proteomics);
3) establish markers suitable for subsequent establishment of assays for drug screening;
4) test appropriate analgesic compounds and modulators of changed signalling pathways and parameters which are identified in 2, with the aim of selecting parameters suitable for future screening activities;
5) translatability of results from HCS microscopy *in vitro* to the *in vivo* situation: based on the knowledge generated in 4, compare effects of selected analgesic compounds and modulators of changed signalling pathways in the *in vitro* HCS microscopy studies and the *in vivo* NP model (see WP2.6.).

Industry contribution:

- supply of tissue (e.g. PNs, DRGs, SC) of neuropathic and naïve rats, supply of reference compounds.

Expected applicant consortium contribution:

- set up cell cultures and HCS microscopy, broad analysis of changes in signalling pathways and parameters using a battery of techniques (e.g. investigate G-protein coupled receptors, receptor tyrosine kinase (RTK-), cytokine-signalling, mitochondrial functioning as monitored by e.g. analysis of their morphology and membrane potential, transcriptomics and proteomics), select parameters suitable for future screening activities.

  It depends on the expertise of the applicants which of the tissues (e.g. PNs, DRGs, SC) will be selected for setting up the rat cell cultures and which parameters will be investigated in the HCS microscopy. These aspects will be defined jointly during the Full Proposal submission.

Work package 4 - Identification of biomarkers relevant to analysis of neuron-glia cross talk in rats

1) transcriptomics and proteomics in tissue (e.g. PNs, DRGs, SC), plasma, and CSF collected from neuropathic and naïve rats (see WP2.5.).

Industry contribution:

- transcriptomics and proteomics.

Expected applicant consortium contribution:

- transcriptomics and proteomics in a complementary and synergistic way together with the industry consortium.

Work package 5 – Generation of human induced pluripotent stem cells (iPSCs) derived neuron-glia co-cultures

1) Generation of human iPSCs: sensory neurons (‘human nociceptors’):
   - establish protocols for differentiation of human iPSCs and maturation to neurons;
   - characterise sensory neurons (immuno-histochemistry, gene expression analysis);
   - HCS microscopy to identify test parameters suitable for subsequent assay development based on HCS analysis.
2) Functional characterisation of ‘human nociceptors’:
   - HCS-based analysis of markers and functional profile in comparison to rat data obtained in WP3;
   - characterisation of pain-relevant targets (using e.g. electrophysiological recordings, neurochemistry, FLIPR assays (using Calcium ion and voltage dependent dyes), GTPγS assays, binding assays, ELISA);
   - characterise effects of analgesic reference compounds (using e.g. HCS microscopy, electrophysiology, neurochemistry, FLIPR assays, Western blotting, immunohistochemistry).
3) Standardised generation of human glia cells for the co-culture with human sensory neurons:
   - establish a protocol for differentiation of glia cells (e.g. Schwann cells);
   - test myelination capabilities of human Schwann cells on ‘human nociceptors’;
   - establish a neuron-glia co-culture;
   - HCS-based analysis of the co-culture.

Industry contribution

- characterisation of ‘human nociceptors’ using electrophysiological recordings, neurochemistry, FLIPR assays (using Calcium ion and voltage dependent dyes), immunohistochemistry, GTPγS assays, binding assays, ELISA, gene expression analysis, and Western blotting; supply of reference compounds.

Expected applicant consortium contribution:

- generation of 'human nociceptors' and their co-culture with glia cells, their characterisation using a battery of techniques mentioned above in a complementary and synergistic way together with the industry consortium.

  It depends on the expertise of the applicants whether neuron-glia co-cultures reflecting the characteristics of PNs, DRGs, or SC will be generated. These aspects will be defined jointly during the Full Proposal submission.

Work package 6 – Use of HCS assays based on human iPSCs derived neuron-glia co-cultures

1) Establishment of HCS-based screening assays for analysis of pain-relevant signal cascades and drug effects in human neuron-glia cultures:
   - establish an HCS-based assay of a human neuron-glia system in a HTS format.
2) Proof of concept of the established and validated human neuron-glia assay system using selected analgesic compounds:
   - test analgesic compounds targeting different mechanisms and pathways in a pilot study;
   - assess assay quality and optimise test parameters as needed;
   - analyse the translatability between *in vivo* rat, *in vitro* rat and *in vitro* human 'nociceptive' neuron-glia systems.

Industry contribution

- supply of reference compounds.

Expected applicant consortium contribution:

- establishment and validation of a screening assay system in human 'nociceptive' neuron-glia systems using HCS microscopy, analysis of translatability between rat and human assays based on HCS microscopy.

Glossary

ATP	Adenosine Triphosphate
CSF	CerebroSpinal Fluid
DRGs	Dorsal Root Ganglia
ELISA	Enzyme Linked Immunosorbent Assay
FLIPR	Fluorescence Imaging Plate Reader
GTPγS	Guanosine 5'-O-[gamma-thio]triphosphate
HCS	High Content Screening
HTS	High Throughput Screening
iPSC	induced Pluripotent Stem Cells
NP	Neuropathic Pain

PNs	Peripheral Nerves
RT-PCR	Reverse Transcription Polymerase Chain Reaction
SC	Spinal Cord
SMEs	Small and Medium Sized Enterprises
SNL	Spinal Nerve Ligation

Topic 4: Dry age-related macular degeneration: Development of novel clinical endpoints for clinical trials with a regulatory and patient access intention.

Topic details

Topic code	IMI2-2015-07-04
Action type	Research and Innovation Actions (RIA)
Submission & evaluation process	2 stages

Specific challenges to be addressed

Age-related macular degeneration (AMD) is a chronic progressive disease and among the leading causes of legal blindness worldwide. AMD includes early, intermediate and late AMD (Ferris et al., 2013)[1]. Impairment of visual function starts in early AMD and progresses to late AMD with vision-threatening complications like neovascularisation (referred to as neovascular AMD) or irreversible 'geographic' atrophy (GA) of the retina. GA affects up to 10% of all AMD patients with prevalence in the UK alone of 276 000 patients it is estimated that this figure will rise to about 400 000 by 2020 (Owen et al., 2012, Rudnicka et al., 2012)[4&5].

Currently no effective treatments exist to address the major health problems of the transition from intermediate AMD to GA and progression of GA. The prerequisite for successful drug development in this disease area is the development of appropriate clinical endpoints with high sensitivity and specificity. Such endpoints need to be meaningful to patients and need to measure visual dysfunction beyond best-corrected visual acuity (BCVA), which is currently the only generally accepted functional clinical endpoint in retinal diseases. BCVA only captures central visual function, which may stay normal in intermediate AMD with imminent GA and even in advanced stages of GA, with extended retinal loss sparing the fovea. Only recently, for a subset of dry AMD patients with GA, the assessment of progression of GA was found to be acceptable for some regulators as an anatomic surrogate endpoint (biomarker) for disease progression.

Measures of visual function beyond BCVA, e.g. contrast sensitivity, dark-adaptation, and visual field deficits, are abnormal in intermediate AMD and GA (Holz et al., 2014)[[3] and have therefore been suggested as endpoints in clinical trials. Candidate clinical endpoints need to be systematically validated in adequate patient populations to be acceptable for regulatory authorities, health technology assessment (HTA) bodies, and payers. For future clinical research in dry AMD, there is a need for both structural (e.g. drusen volume and characteristics) and functional clinical endpoints that are highly correlated and would desirably respond early to disease progression and/or conversion to late AMD. Such assessments could contribute to the establishment of subphenotypes of intermediate AMD with a high risk of developing complications in late stage AMD.

Of equally high importance as the correlation of structural and functional clinical endpoints is the demonstration of patient relevance of impaired visual function beyond BCVA. For this purpose, existing or newly-developed measures of patient-reported health need to be validated to comprehensively cover disease-specific aspects of dry AMD.

Need and opportunity for public-private collaborative research

Only a combination of expertise from different areas of clinical research is expected to be able to address the complex challenge of validating functional and structural endpoints and measures of patient-reported health in dry AMD. A close collaboration of stakeholders across the following sectors will be required:

Pharmaceutical companies have expertise in clinical drug development as well as experience in requirements for clinical endpoints acceptable to regulatory agencies, HTA bodies, and payers.

Academic institutions have expertise in methods to assess visual function, structural pathologies and patient-reported health (including patient-reported outcomes) that may correlate with impaired visual function beyond BCVA.

Academic or contract research organisations have experience in a lean and efficient set-up and conduct of clinical trials fulfilling global requirements for clinical trial including GCP, ICH, Declaration of Helsinkiand ethical requirements to deliver high class clinical data.

Imaging and medical device companies have expertise in the development and application of contemporary examination methods, which could be used in a clinical trial setting.

Patients/ patient organisations, users and caregivers play an important role in establishing the utility, acceptability and value of new clinical endpoints, especially for measures of patient-reported health.

Scope

The applicants' proposals should differentiate between the two following categories:

- **Endpoints** are defined as dynamic measures of a disease state. Clinical endpoints in this Call topic (sometimes also referred as clinical outcomes or biomarkers) need to be assessed in the categories functional, anatomical, and patient-reported health.
- **Risk factors** are traits defining subpopulations with specific disease features or different rates of disease progression. They can be used, e.g. for definition of a clinical trial population or for subgroup analyses of trial data. Research on risk factors is not considered the main focus of this topic but may be a side product of clinical endpoint validation.

The main objective of this topic is development of **clinical endpoints** in dry AMD beyond BCVA. Research work should be focused around functional impairment in intermediate AMD and progression to late stage AMD complicated by GA as assessed with state-of-the-art methodologies and measures of patient-reported health. It is expected that structural imaging biomarkers will also be developed as surrogate markers of functional impairment of vision. Such biomarkers would also have the potential to predict progression of intermediate AMD to late stage AMD complicated by GA.

Functional, structural and patient-reported endpoints need to be validated in clinical trials with appropriate patient populations. Applicants are required to provide a detailed outline and justification of their clinical trial strategy including trial design (e.g. cross-sectional, longitudinal, combined, other), characteristics and availability of trial population(s), assessment methodologies (including performance characteristics as known from completed research) and time points for the interim and main assessment of clinical trial endpoints (e.g. time point for primary assessment, duration of follow-up period).

Applicants need to thoroughly delineate how the proposed clinical trial programme will be operationalised. The proposal needs to be put into the perspective of the overall duration of the grant (five years) and with the goal of delivering tangible trial results, e.g. a clinical study report covering all endpoints assessed, which should be used in the context of a regulatory qualification procedure for novel clinical trial endpoints/methodologies.

Acknowledging that these tasks may be extensive and time-consuming, applicants are recommended to use marketed or market-ready assessment technologies as compared to *de novo* development of technologies. If applicants propose the development of novel assessment devices, they are required to provide a detailed and thorough justification of timelines for device development and clinical validation within the five year time frame of this project.

Not in the scope of this topic is the *de novo* development of devices for functional assessments and imaging and the work streams aiming at the detection of novel molecular biomarkers.

Expected key deliverables

The key deliverables of this topic are the development (i.e. establishment and validation) of clinical endpoints in dry AMD based on clinical trial data. It is the responsibility of an applicant consortium to delineate how the proposed work packages will jointly work to achieve the deliverables of the project:

Deliverable 1: Development of clinical endpoints for impaired visual function beyond BCVA

This key deliverable comprises the validation of functional clinical endpoints as measures of functional visual impairment beyond BCVA in patients with intermediate AMD, and endpoints assessing progression from intermediate AMD to late stage AMD with GA. To allow for use in health economic models, utility measures based on the functional impairments observed need to be developed.

Deliverable 2: Development of measures of patient-reported health

This deliverable includes the development of measures like patient-reported outcomes, but also other approaches for covering patient-reported health, e.g. observer-reported outcomes, tests of visual function in virtual realities or other tests would be considered, if the scientific rationale and potential for regulatory acceptance of such measures would be sufficiently justified. Measures of patient-reported health need to be established and at least content validated. It is expected that for this specific deliverable, not only patients with intermediate AMD but also with the neighboring disease states, i.e. early AMD and manifest GA, will need to be included.

Deliverable 3: Correlation of functional assessments of impaired vision with structural deficits assessed with state-of-the-art imaging methodologies

The aim of this deliverable is to develop structural/imaging endpoints as surrogate markers of current or future functional deficits, which could be used as endpoints in clinical trials. Assessment of structural deficits by multimodal imaging is encouraged.

Expected impact

Currently the development of novel pharmaceutical compounds to modify the disease course of intermediate AMD to late stage AMD with GA is mainly limited by the lack of validated functional and structural clinical endpoints.

Whereas the functional consequence of impairment of central vision as documented by low BCVA scores is considered to be self-evident and generally undisputed with regulators and payers, other measures of impaired visual function beyond BCVA have as yet received neither similar attention nor acceptance as clinical endpoints by regulators and payers.

This project aims to establish and validate correlations between functional endpoints, structural endpoints and patient-reported health in dry AMD.

An extended toolbox of validated clinical endpoints will enable the development of therapeutics for dry AMD. It will greatly facilitate future trial designs in dry AMD, in early clinical trials, which aim to show proof of new therapeutic concepts in patients, as well in late stage development targeting confirmation of efficacy and safety of novel therapeutic approaches in larger patient populations.

For a successful completion of this project it is considered indispensable to seek interactions with regulatory bodies (e.g. the European Medicines Agency, EMA) but also with key HTA bodies and patient organisations to increase the chance of a wide acceptance of the novel clinical endpoints under investigation.

Potential synergies with existing consortia

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

This may include validation of functional and imaging methodologies established in previous work by existing research initiatives and groups. The proposed project should use accessible data from other projects as appropriate, e.g. for the planning of the clinical trial design. Any unnecessary overlap or doubling effort should be avoided. This should be especially considered for research tasks like genotyping of established risk genotypes, which are considered ancillary to the objective of this Call topic, which is development of clinical endpoints.

For example, synergies should be considered at the European level with relevant Horizon 2020 (e.g. EYE RISK[33], RETOXY[34]) and FP7 initiatives (e.g. MICROGLIA AND AMD[35]).

Applicants should include considerations in their proposal how the interactions with ongoing consortia are envisaged.

Industry consortium

The industry consortium will comprise the following pharmaceutical companies and Zeiss as imaging company:

- Bayer Pharma AG (Leader)
- Novartis (Novartis Pharma (Deputy leader), Alcon, NIBR)
- Janssen-Cilag Ltd
- Roche
- Zeiss

Specialists from the industry consortium in the field of clinical endpoint development, patient-reported health, health economics, clinical trial design and drug regulatory procedures will actively participate in all project work packages.

Indicative duration of the project

The duration of the project will be 5 years to allow for recruitment, follow-up and analysis of clinical trial data.

Indicative budget

The indicative EFPIA and associated partners in-kind contribution will be EUR 8 025 000 (including an expected EUR 6 500 000 in cash). The EFPIA cash contribution is intended to support achieving the deliverables of the work packages described in this Call topic including the conduct of clinical trials (WP1).

The indicative IMI2 contribution will be a maximum of EUR 8 025 000.

[33] http://www.eyerisk.eu/the-project.html
[34] http://cordis.europa.eu/project/rcn/196514_en.html
[35] https://erc.europa.eu/projects-and-results/erc-funded projects/MICROGLIA%20AND%20AMD?retain-filters=1

Applicant consortium

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

For a successful project, the applicant consortium needs to be multidisciplinary and have a proven track record in the following fields of expertise in research on dry AMD (i.e. intermediate AMD and/or late stage AMD with GA):

- strong practical expertise in the successful conduct of international multi-centre trials in ophthalmology (including e.g. access to appropriate patient populations, set-up, recruitment, monitoring, and data management and analysis);
- strong clinical expertise in ophthalmology with a focus on AMD;
- strong expertise in assessment methodologies for functional impairment other than BCVA;
- strong expertise in state-of-the-art ophthalmological imaging techniques including approaches of multimodal imaging;
- strong expertise in the establishment and validation of measures of patient-reported health, e.g. patient-reported outcomes in ophthalmology;
- expertise in successful interactions with regulators and/or payers, e.g.in conduct of an EMA qualification procedure for novel methodologies in clinical research;
- health economics expertise;
- expertise in project management in the context of IMI grants.

The size of the applicant consortium should reflect the necessary expertise needed to achieve the proposed objectives within the budget while ensuring the 'manageability' of the consortium and an efficient and effective team work. Therefore, the number of members of the applicant consortium needs to be thoroughly justified in the proposal.

Suggested architecture of the full proposal

The final architecture of the full proposal will be defined by the participants in observance of IMI2 rules and in contemplation of the achievement of the project objectives.

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

The below architecture for the full proposal is thought to reflect the organisational and scientific needs of this Call topic for clinical endpoint research in dry AMD. Any suggestion for a different organisational set-up needs a thorough justification by applicant consortia as to why such deviations would be more advantageous as compared to the proposed outlined architecture for achieving the overall goals of this topic and why this alternative structure would have a positive impact on the project's budget.

The consortium is expected to have a strategy in place for the translation of the relevant project outputs into regulatory, clinical and healthcare practice. A plan for interactions with regulatory agencies and HTA bodies with relevant milestones and resource allocation should be proposed to ensure this, e.g. by conducting

qualification advice jointly with the involved EFPIA partners on the proposed methods for novel methodologies for drug development and to finally receive an EMA qualification opinion by the end of the grant period.

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

While the detailed governance would be established jointly by the full consortium, the applicant consortium is recommended to consider a governance structure such as:

- Coordination Team (From applicant consortium: leader and deputy leader, from EFPIA consortium: leader and deputy leader, and lead of WP Project Management as non-voting member);
- Management Board (members of Coordination Team plus WP leads);
- General Assembly (representative (1 each) of all members of the public and EFPIA consortium as voting members).

The contribution and role of each of the members of the applicant consortium must be convincingly explained, including the individual contribution to the development strategy, e.g. development of clinical trial strategy and clinical trial protocol, or development of evaluation strategy and algorithms for functional and/or structural assessments.

For this topic, research units/sites/organisations only planned as investigational sites for the clinical trial(s) may be involved as third parties or subcontractors rather than members of the applicant consortium. It is expected that such sites will be subcontracted by a member of the public consortium for their activities. If the applicant consortium does not include CRO capabilities (either an ARO or CRO), then the entire conduct of the clinical trial(s) is subcontracted to an academic or contract research organisation

It also needs to be secured that there is accountability for a successful coordination and conduct of proposed clinical trials across work packages.

The proposal should be built to ensure coherence and interaction of all work packages, and for each work package it is expected that final key deliverables and at least one interim deliverable would be described.

Suggested work packages

It is expected that WP leads of all WPs (1-4) should work jointly together in the set up and conduct of the clinical trial(s) of this project to fully recruit the trial(s) in the given time, to generate data of sufficient quality for meaningful analyses, and to crosslink findings especially of WPs 2-4. In particular, it is expected that results of functional assessment (WP1, 2) will be correlated:

- with anatomical/structural findings to establish and validate biomarkers with the potential to substitute for functional assessments and vice versa (WP2, 4);
- with patient-reported health to support and confirm that abnormalities in tests of functional deficits are meaningful to patients (WP2, 3).

Work package 1: Clinical trials (1 WP lead from applicant consortium and EFPIA consortium each. The lead investigator(s) for the intended clinical trial(s) may be lead of WP1 or additional person(s) qualified for this role).

Platform for clinical trial conduct including:

- Trial set-up (feasibility, site equipment, basic training and certification).
- Monitoring (site, data, GCP conform conduct).

- Electronic Case Report Forms (eCRFs) and clinical database set-up and data management. A data management plan to be developped as required by IMI2. The eCRF/clinical database needs to be linked to the databases for functional assessments, imaging, and if applicable to patient genotypes.
- It is expected that the applicant consortium will address how the consortium will make clinical trial data available for WPs 2-5 for their analyses. Also it needs to be secured that data from this project will be accessible for further explorative analyses beyond predefined statistical analysis plans.
- Clinical trial statistics to develop and perform analyses of clinical trial data according to a statistical analysis plan (SAP) plus exploratory analyses.

Regulatory:

- Regulatory Interactions will be jointly prepared with partners from the EFPIA consortium using their expertise. It is expected that regulatory interactions are performed at the stage of clinical trial planning to get regulator feedback on the appropriateness of the clinical trial concept for regulatory acceptance of the proposed endpoints.
- The regulatory interactions should include the EMA and if possible the US FDA to get feedback on the potential acceptability of the planned endpoint strategy also outside Europe.
- It is required to provide a plan on how the proposed clinical endpoints could result in an EMA qualification procedure to support these methodologies for future regulatory trials.
- Interactions with HTA bodies and payers also need to be planned.

Genetic risk factors and biobanking in the clinical trial(s):

- The main focus of this Call topic is the development of clinical endpoints. However, the field of identifying genetic risk factors for AMD (including dry AMD) is continuously advancing. As such it is expected that patient collectives may be tested for known genetic factors of disease and that also correlation to specific functional impairments may be assessed. Genotyping may also include results of markers only recently identified. However, a *de novo* search for novel genetic risk factors is not in the scope of this project.
- Due to the extensive phenotypic characterisation of patients in this project it is however supported to propose a comprehensive strategy for the biobanking of patient specimens (e.g. DNA, RNA, serum) to potentially allow the establishment of cooperation with existing genetic AMD consortia. The extent of the proposed biobanking should be put into perspective with the overall budget and needs to have no meaningful negative budget impact on the other WPs.

Work package 2: Functional endpoints (1 WP lead from applicant consortium and EFPIA consortium each)

- Local evaluation of functional assessment results plus evaluation of these assessment data by a central evaluation unit. The central evaluation unit for functional assessments will have the role of providing quality control and standardisation of local assessments.
- Optional: to develop automated or semi-automated assessment algorithms on top of existing analysis software based on existing data or data from the clinical trials to further facilitate use of the functional endpoints in clinical practice.
- It is expected that the applicant consortia will provide a detailed list of the functional endpoints intended for evaluation.
  For each endpoint a thorough justification for their use must be provided (including available data on performance characteristics in previous studies). If possible, members of the applicant consortium should already have published peer-reviewed papers on the evaluation of the proposed functional methodology and their use as clinical trial endpoints.
  The description should already contain a justification of the scientific priority of each suggested endpoint and also cover practical aspects of administration in an expected elderly population and availability at participating sites.
- Structure-function relationships should be explored together with WPs 3 and 4.

- *De novo* development (devices not yet successfully used in normal controls and/or patients) of functional assessments is not in the scope of the proposed project.

Work package 3: Patient-reported health and health economics (1 WP lead from applicant consortium and EFPIA consortium each)

- establishment and content validation of patient-reported health in dry AMD;
- correlation of measures of patient-reported health with functional assessments;
- it is expected that research in this WP will follow existing regulatory guidance for the development of measures of patient-reported health, e.g. the US-FDA guidance on patient-reported outcome measures. (US FDA, 2009);
- establishment of utility measures jointly with WP2 to allow for health economic modelling beyond BCVA.

Work package 4: Anatomical and imaging endpoints (1 WP lead from applicant consortium and EFPIA consortium each)

This work package is expected to contain the following main work streams:

- Analysis of images from clinical trials using established standard imaging modalities plus novel, innovative technologies.
- Analyses should be done at experienced central reading centers (CRCs). If more than one CRC would be proposed as a member of the consortium, the rationale and overall impact (positive, negative) on budget and probability of project success needs to be justified.
- It is expected that the imaging devices used are either already commercially available or are market-ready prototypes which will be commercially accessible in the near future. Any technology used in this context should have the potential to be commercially available for future clinical trials.
- Multimodal image correlation is encouraged.
- *De novo* development (i.e. technical development, use in normal collectives and initial trials in patients) of imaging devices is not in the scope of this project.
- Forrelation of imaging pathologies with the outcome of functional assessments is mandatory.
- Optional: if applicable for the respective imaging modality and following correlation of the individual imaging parameter with a functional outcome, the proposal may contain a work stream for semi-automated or automated imaging analysis within the framework of the overall project.

Work package 5: Project management

Lean project management to fulfil requirements of IMI2 in respect to distribution and reporting of funding.

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[4]: Owen CG, Jarrar Z, Wormald R, Cook DG, Fletcher AE, Rudnicka AR (2012) The estimated prevalence and incidence of late stage age related macular degeneration in the UK. Br J Ophthalmol 96:752-756.

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[6]: U.S. FDA (2009) Guidance for Industry - Patient-Reported Outcome Measures: Use in Medical Product Development to Support Labeling Claims. 1-43.

Topic 5: A comprehensive 'paediatric preclinical POC platform' to enable clinical molecule development for children with cancer

Topic details

Topic code	IMI2-2015-07-05
Action type	Research and Innovation Actions (RIA)
Submission & evaluation process	2 Stages

Specific challenges to be addressed

Despite significant advances over the past 20 years in treatment and survival, >20% of all paediatric cancer remains incurable. In the western world, cancer remains the leading cause of disease-related death in patients under the age of 19. Due to advances in diagnosis, treatment, and supportive care, 80% of children diagnosed with cancer are expected to survive >5 years, compared to <50% during the 1970s. However, long-term side effects associated with treatment remain unacceptable for nearly 2/3 of these survivors. In many cases, 15 year survival rates are unacceptably low and there is often an increased risk of death up to 30 years after diagnosis. Childhood cancers are often the result of gene changes that occur very early in life and are not strongly linked to lifestyle or environmental risk factors. Most paediatric tumours have fewer mutations than adult tumours and therefore may be prime candidates for molecular targeted therapy, though this does not obligatorily result in reduced disease complexity or increased treatability. At the time of diagnosis, cancer is often much more advanced, i.e. metastatic, in children than in adults and therefore effective and safe treatments are urgently needed.

The prospect of molecular targeted therapies represents an unprecedented opportunity to potentially realise cures for many intractable paediatric tumours, and promises safer, less harmful treatment options for those children whose tumours are responsive to conventional therapy but will likely suffer debilitating long-term side effects. Unlike research for adult cancer, paediatric research is severely limited by a lack of disease-relevant preclinical models capable of generating effective patient-tailoring hypotheses to guide the clinical development of paediatric drugs. Paediatric drug development is in dire need of broad translational platforms, especially well-characterised tumour cell panels and broad *in vivo* models (which are often at the core of indication and molecular biomarker discovery). Currently, *in vivo* testing is limited to a variety of poorly-characterised, cell-derived xenograft models of arguable importance, and a handful of commercially available patient-derived xenograft (PDX) models. This underrepresentation of research tools in the fight against paediatric cancer, and the incomplete nature of their level of characterisation necessary to identify translational opportunities, limit the predictability of preclinical testing of potentially promising new agents and are clearly hampering clinical development. Furthermore, this paucity of tools all but eliminates potential patient tailoring approaches as the diversity of models within any given histology is simply too limited to propel meaningful biomarker development. Therefore, the aim of this programme is to establish a preclinical testing platform of direct patient-derived *vivo* and *vitro* models in 'saturating' numbers for 10 high-risk paediatric solid tumour types, and implement analyses of target patterns in clinical paediatric series and a quality-assured methodology for preclinical single and combination drug testing.

Need and opportunity for public-private collaborative research

The magnitude of the issue is such that it can only be addressed by a major public private-partnership involving a variety of stakeholders, including those primarily involved in understanding molecular mechanisms of disease, biopharmaceutical companies which endorse the approach and have a complementary experience and expertise, as well as regulators. This is a programme which cannot be successfully administered by an

individual research group or company but will require a broad consortium to be successful and to maximise its benefits for paediatric cancer patients and society.

There are two key elements to building an effective preclinical paediatric testing network:

1. identification and development of biologically relevant paediatric tumour models;
2. developing an informatics infrastructure capable of effectively parsing complex biological datasets with the ultimate goal of patient selection.

Academia is ideally suited to, and is indeed at the forefront of identifying and developing relevant tumour models due to the focused nature of their research and their close ties with research hospitals. SMEs often arise as a result of these activities which then allow academic researchers to further develop and expand their histology- and biology-based expertise. Industry on the other hand is often preoccupied with large and small molecule discovery, in particular with an adult disease focus and, due to limited access to paediatric disease models, may be limited in its ability to develop paediatric medication due to the existing challenges. It is these capabilities, applied to complex paediatric data sets that will lead to significant advances in treatment. As a result paediatric drug development in industry may be conducted in a somewhat disconnected fashion due to lack of tools and know-how. A consortium would open doors to paediatric development that are currently only partially open.

Scope

The objective is to build a comprehensive translational network of PDX models (>40 tumours per histology), matching cell lines/organoids and genetically modified mouse models (GEMM; >2 per histology) with complete molecular characterization and proven relevance to the following, major solid paediatric tumours:

- neuroblastoma;
- rhabdomyosarcoma (RMS);
- synovial sarcoma;
- malignant peripheral nerve sheath tumor (MPNST);
- Ewing's sarcoma;
- osteosarcoma;
- atypical rhabdoid tumours;
- medulloblastoma;
- high grade glioma (HGG), incl. diffuse intrinsic pontine glioma (DIPG);
- ependymoma.

The successful identification of promising clinical therapeutic molecules requires a broad and deep understanding of the molecular make-up and genetic determinants of paediatric tumours. This genetic and molecular diversity needs to be mirrored in the paediatric preclinical space including *multiple* genetically and molecularly characterised models per tumour histology. The project will build the infrastructure whereby promising clinical candidates are identified (as single agents and in combination) for paediatric development using patient-centric cutting edge translational approaches. The focus will be the development and validation of orthotopic PDX models (where possible, if not flank models will be incorporated) with parallel primary cell cultures (e.g., organoids) and GEMM models, complete with molecular characterisation (e.g., whole exome, RNA-seq including fusion analysis, SNP6, reverse phase proteomic array). In addition, access to the latest molecular targeted therapies either on the market or under development will enable SOPs for interrogating the molecular genetic diversity through HTS and mouse n=1 trials (including the associated bioinformatics infrastructure development). A key component of this project is the breadth and depth of tools across each histology, coupled with the powerful translational opportunity afforded through a comprehensive understanding of the genetics and proteomics of each disease. Primarily for mechanistic follow-up and, if necessary *in vitro* prioritisation for *in vivo* modelling, cell lines are envisioned to be derived from the same samples as the PDX models and similarly molecularly characterised. Cell line experimentation will be

important for following up detailed compound mechanism of action experiments not easily or quickly undertaken in the *in vivo* setting. In addition cell lines derived from treatment resistant tumour models will aid in the understanding and overcoming of both acquired and intrinsic resistance. The paediatric preclinical proof of concept (POC) platform will also provide the basis for effective biomarker-driven paediatric drug development in support of patient tailoring i.e. the right drug for the right patient based on the tumour's molecular profile. The incorporation of GEMM models will allow for testing of drugs in tumours within their microenvironment and 'naturally' occurring within their primary location. The data would then extend knowledge on how those tumours would acquire genetic modifications that would promote metastatic properties, what role the immune system plays in disease progression and ultimately lead to a better understanding of disease progression. The possibility of using humanised mouse models remains open, but currently the cost of such models may preclude an in-depth analysis of a wide range of paediatric tumour types. We plan to incorporate humanised immunological mouse models, but currently the costs, selection of the appropriate animal age and impact on paediatric drug development of such models will likely limit the extent and depth of analyses of a wide range of paediatric tumour types. Ultimately this network will benefit paediatric patients by accelerating targeted paediatric drug development and supporting regulatory filings in the EU and eventually the US through the development of comprehensive preclinical data packages necessary to move drugs into eventual clinical testing.

Expected key deliverables

The primary goal for this project is the development of a comprehensive preclinical paediatric testing platform with a panel of >400 well-characterised models (PDX, machting cell lines, and GEMM) of high-risk paediatric solid tumours (see 'scope') for the identification of molecules that are suitable for paediatric clinical cancer drug development. To achieve this goal the following deliverables are anticipated:

1) Definition of minimally-required preclinical data packages for 'Target Actionability' (see table 1 for modular components).
2) Systematic literature reviews of paediatric 'target actionability' for >20 drug targets matching the pipelines of the pharma partners (see figure 2 for example). (Sub-deliverables: improve and implement methodology, perform reviews, score in target actionability heatmap matrix, publish in scientific literature, update regularly, set up and maintain database).
3) Target aberration/activation patterns in clinical paediatric tumour series:
    - '*In silico*' target patterns in paediatric clinical series by leveraging existing tumour profiling data in public databases (e.g. TCGA, NCI-TARGET, AMC-R2, Paediatric Cancer Genome Project, Cell Line Encyclopedia), institutional research databases of academic partners and internal databases of EFPIA partners;
    - 'Wetlab' biological characterisation of a reference series of patient samples for the 10 high-risk paediatric solid tumours in the scope of this programme to allow assessment of 'clinical saturation' by 'mapping' of the PDX, cell line and GEMM models on the biological disease spectrum. At least 100 FFPE samples per tumour type analysed by the same technology as the models (NGS, RNA-Seq, CNVs, IHC, epigenetics, proteomics).
4) Comprehensive panels of precompetitive preclinical models; PDX models (> 40/disease type), with matching cell lines (10 cell lines/organoïds), and GEMMs (>2/disease type) for the following major paediatric solid tumours (as listed under 'scope'): neuroblastoma; RMS (alveolar and embryonal); synovial sarcoma; MPNST; Ewing's sarcoma, osteosarcoma; rhabdoid/ATRT; medulloblastoma, HGG (incl. DIPG); ependymoma; humanised immuno mouse models for a limited set of diseases.
5) Complete histopathological, clinical, pharmacological (standard-of-care (SOC) drugs) and molecular characterisation of models (NGS, RNA-seq., CNVs, IHC, epigenetics, proteomics) to enable adequate matching of tumour biology and compound mechanism-of-action. Facile and complete access to the cancer model network for all participants. Tumour tissue blocks must be available for future analyses from the primary tumour and the corresponding PDX models, and from the GEMM models.
6) Explore possibilities for '*in vitro'* and *'in vivo'* modeling of cancer immunotherapy drugs using the established series of PDX and GEMM models or generation of immunotherapy-specific models such as humanised mouse models within the budget limitations.

7) Testing of compounds from all consortium members (academic and industrial) in a limited number of approved and validated testing sites by a quality-assured methodology, including single drugs with readouts of 'biological efficacy' (i.e. target binding andinhibition, pathway modulation, biological effect), analyses of resistance mechanisms and testing of rational drug combinations. Implementing a focused *vitro* testing approach to limit unnecessary *vivo* testing. Coordinated testing of 'open' (i.e. company specific but unshielded, SOC, marketed drugs) and subject to agreement with the contributor on transfer of and access rights to results generated on such compounds, 'shielded' (i.e. company-specific) compounds at predefined times throughout the year.

8) Centralised data repository including certain results of the project such as precompetitive model characteristics (i.e. all data associated with model molecular and pharmacological characterisation using commercially-available agents) and SOC testing data with custom informatics tools to visualise and analyse data. There will be an agreement on the conditions under which the data included in the centralised data repository will be shared with the other beneficiaries and with third parties, taking into account the IMI2 legal and intellectual property (IP) framework.

9) Integration with EMA/PDCO paediatric investigation pan (PIP) process → framework for interaction with EMA/PDCO to gain understanding as to the applicability of this network to the PIP preclinical data generation process and ultimately provide an accepted translational framework for the initiation of paediatric clinical trials.

10) A plan for the sustainability of the functional results of the project which will preferably entail the grant of rights to an entity/organisation to be made responsible for such sustainability.

It is expected that a number of compounds that are controlled by certain of the beneficiaries, including industrial companies, will be used in the project. Under IMI2 rules, results, including those derived from such compounds or constituting direct improvements, are owned by the beneficiary that generates them. The IMI2 rules allow the consortium to establish that the ownership of such results, when solely owned by a specific generating beneficiary, can be transferred to the owner of the initial background / asset. Therefore, when the contributor of a compound would request a transfer of results derived from such compounds or constituting direct improvements to such compounds, and to ensure the viability of the action, the applicant consortium shall try to do the necessary to accommodate such request for instance by including an appropriate transfer of ownership mechanism in the consortium agreement. This is specifically the case for shielded and/or proprietary compounds, the contribution of which may be dependent on an agreement with the contributor regarding transfer of and access rights to results generated on such compounds in accordance with the IMI2 IP policy

Expected impact

The expected impact is speeding up the development of the next generation of medicines to combat paediatric cancer by providing a comprehensive, translational research platform specifically designed to identify medicines for childhood cancer patients. This approach will result in

1) increasing the number of cures across a wide range of paediatric cancer histologies (more lives saved);

2) potentially mitigating the long-term health effects typically associated with conventional chemotherapeutic approaches to treating childhood cancer (better quality of life for those who are saved due to potential targeting of the *disease* rather than attacking *general biological processes* important to both tumor and normal cells).

It is estimated that by 2020 across the US and EU there will be more than 1.5 million childhood cancer survivors whose long-term health effects due to survival therapies will create a heavy personal, economic and societal burden. The promise of targeted therapies specifically working in 'sensitive' tumours may one day allow the medical community to move away from a complete reliance upon toxic therapies. With this network in place industry will have a direct route into paediatric cancer research allowing for rational decisions on which tumours to treat and with which combination of agents. Paediatric drug development will be elevated from that which is required but minimally supported to a fully functional research paradigm that rivals approaches created for adult malignancies. By working with EU thought leaders it is anticipated that such a network will go hand in hand with EMA preclinical PIP requirements and will directly lead to more rational, and ultimately successful, paediatric clinical trials. In addition the data generated regarding underlying

mechanisms of paediatric cancer development and progression, along with potential treatment advances related to the genetics of paediatric disease, will be an unparalleled resource for researchers worldwide and will pave the way for future discovery and collaboration in this medically unmet space.

Potential synergies with existing consortia

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

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

Potential synergies with existing consortia include a variety of for-profit and non-profit groups engaged in paediatric research and clinical development.

- ITCC Biology (the biological laboratory consortium of the 'Innovative Therapies for Children with Cancer' network, whose research encompasses a subset of what is proposed in this document) http://www.itcc-consortium.org/ (Prof.S.Pfister, chair)
- a number of SMEs are in place across the globe and are in possession of a limited, but growing number of paediatric PDX models and are well versed in the operation of so-called avatar research studies using PDX mouse models[36 & 37]
- ENCCA (European Network for Cancer research in Children and Adolescents)[38]
- European infrastructures for translational medicine EATRIS[39]
- EU-related translational research, INFRAFRONTIER[40]
- The German Cancer Consortium (DKTK[41];) along with its core centre, the German Cancer Research Center (DKFZ[42])
- Biobanking and Biomolecular Resources Research Infrastructure, BBMRI[43]
- the Cancer Drug Development Forum (CDDF) based in Austria (common platform to improve drug development for children with cancer, encompassing academia, patient advocacy groups, health authorities and pharmaceutical companies[44])
- the Preclinical Paediatric Testing Consortium (PPTC) administered by the US NCI[45]

Industry consortium

- Eli & Lilly (Project Leader)
- Roche (co-Project Leader)
- Bayer
- PharmaMar
- Pfizer

[36] http://www.oncotest.com/
[37] http://www.epo-berlin.com/index.html;
[38] http://www.encca.eu
[39] www.eatris.eu
[40] www.infrafrontier.eu
[41] http://www.dkfz.de/de/dktk/
[42] www.dkfz.de
[43] www.bbmri.eu/about
[44] http://cddf.org/
[45] http://www.ncipptc.org/about

The industry consortium expertise includes:

- research scientists
- data management experts
- information technology experts
- regulatory experts
- PDX, GEMM and other models as appropriate
- existing relationships with and access to contract screening SMEs and PDX providers.

The in-kind contribution expected from industry consists of:

- cell line testing capabilities (mechanistic follow-up; not random compound screening)
- chemotherapy formulation and dosing expertise
- available paediatric cell line and PDX models
- development and validation of new paediatric models
- informatics capabilities – data visualization and analysis tools
- regulatory expertise
- deep cell line and in vivo model characterization including whole exome sequencing, RNA-seq (including fusion analysis), SNP6 array and reverse phase proteomic array
- compounds for POC testing subject to agreement with the contributor on transfer of and access rights to results generated on such compounds with IMI2 IP Policy.

Indicative duration of the project

The indicative duration of the project is 60 months.

Future project expansion

Potential applicants must be aware that the Innovative Medicines Initiative 2 (IMI2) Joint Undertaking may, if exceptionally needed, publish at a later stage another Call for proposals restricted to the consortium already selected under this topic in order to enhance and progress their results and achievements by extending their duration and funding. The consortium will be entitled to open to other beneficiaries as they see fit. The detailed scope of the restricted Call shall be detailed in the relevant Annual Work Plan. Future expansion may include optimisation of sustainability models and compound testing as well as expansion of the model types and entities and further translation into clinical relevance.

Indicative budget

The indicative EFPIA in kind contribution will be EUR 7 370 000.

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

The indicative IMI2 contribution will be a maximum of EUR 7 370 000.

Applicant consortium

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

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

This may require mobilising but is not limited to, the following expertise:

1) *in vivo* pharmacology expertise
2) proven surgical expertise → for cell line and PDX generation; histopathology; tissue block creation
3) pathology expertise (for tumour histological determination)
4) proven primary cell-line generation
5) informatics expertise including; data storage and retrieval (infrastructure), and custom applications for data visualisation and analysis
6) medical advice on current best practices for treating paediatric malignancies (advisory role only)
7) centralized testing capabilities
8) regulatory interactions
9) professional project ,management organisation for the day-to-day project management of the entire public private consortium
10) proposal for project sustainability;
11) proven access to existing PDX models and cell lines to be accessible for research integration into this project.

Suggested architecture of the full proposal

The final architecture of the full proposal will be defined by the participants in observance of IMI2 rules and in contemplation of the achievement of the project objectives.

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

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

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

The comprehensive ‘paediatric preclinical POC platform’ to enable clinical molecule development for children with cancer project is broken down into a series of seven quantifiable work packages. Each work package is envisioned to have an industry and academic leader. See also Figure 1.

Work package 1: Consortium management, administration and communication

- Industry contribution – Dedicated professional(s) tasked with overseeing the entirety of the project from a logistics standpoint.
- Applicant consortium contribution – local professionals to work closely on logistics with the industry-provided administrator(s).

Work package 2: Target actionability in paediatric cancers (deliverables 1, 2 and 3)

- Industry contribution – Contribution of expertise to define the content of preclinical POC data packages for 'target actionability' in paediatric disease contexts (see table 1). For systematic literature reviews of 'target actionability', EFPIA partners will contribute novel methodology (review checklists, matrix heatmap for target actionability scoring; see figure 2 for example), literature search and text-mining capacity, join in performing reviews and support publication. They will contribute IT and bioinformatic resources to develop an 'aggregated target pattern database'.
- Applicant consortium contribution – Joint process to define the content of preclinical POC data packages. Joint performance of literature reviews of 'target actionability' by contributing methodological expertise, performing and publishing reviews. Contribute access and expertise for *in silico* target pattern analyses in existing tumour profiling data in public databases and additional institutional research databases. The ideal situation would be a close match between the target pattern analyses from clinical samples with those of the various PDX models, i.e. PDX faithfully replicating what is observed in patients.
-

Work package 3: Paediatric cancer model development and characterisation (deliverables 4, 5 and 6)

- Industry contribution – EFPIA partners expect to contribute standardised mutually agreed upon assay/model validation criteria. In addition, and if within the scope of the indicated tumour types, EFPIA partners expect to contribute internal paediatric cancer models and immuno-modelling expertise. EFPIA partners will be responsible for full histopathological and molecular characterisation of the paediatric models including NGS, RNA-seq., CNVs, IHC, epigenetics, proteomics. The goal is at least 40 unique PDX models/tumour type with matching cell lines (10 cell lines/organoids) and at least 2 GEMM models per tumour type. For histologies where tumour heterogeneity is less of a concern i.e. translocation-driven tumours such as Ewing's and synovial sarcoma, 40 models may be unnecessary/unwarranted and resources may be diverted to capturing diversity in other areas. EFPIA partners will contribute immune-modelling expertise and work with applicant consortium members to generate immunotherapy-specific models directly from patient tissues or derived from the established series of PDX, organoid and GEMM models. The extent and depth of these models will be determined in the full condortium based on factors like cost, selection of the appropriate animal age and impact on paediatric drug development.

  Continuous monitoring of tumour acquisition and tumour characterisation is required. The matching (and/or PDX-derived) primary cell lines will primarily be used for in-depth mechanistic follow-up studies and also for *vitro* prioritisation to limit the amount of *vivo* testing. At the end of each year, model procurement progress and heterogeneity will be evaluated as part of an interim analysis, and the number of models indicated for any given tumour type may be adjusted. If model procurement moves at a swift rate and/or additional biological models (i.e., zebrafish or circulating tumour cell-derived xenografts) come on line during the course of project development, the possibility remains open to developing these non-traditional models should the industry consortium agree on their importance and utility.
- Applicant consortium contribution – Development and validation of PDX and GEMM models (and cell lines from the PDX models) and ensuring that patient consent is in place. Model characteristics should be mapped back to data from clinical series to assess tumor homo/heterogeneity, which will directly lead to adjustments in the number of tumours generated/histology (see above). Members will provide the samples necessary for model characterisation. The validated models will then form the basis for development of a limited number of centralised testing facilities to enable drug testing across the EU. Tissue blocks from initial tumour and PDX samples will also be generated and stored in a central repository. We estimate this repository to house about 1 000 samples overall..

Work package 4: Regulatory consensus on disease models and POC data package for PIP requirements (deliverable 9)

- Industry contribution – EFPIA partners will be responsible for interacting with EMA/PDCO representatives, at a minimum within the established framework of qualification advice/opinions for novel methodologies, academia and patient advocacy groups to ensure that the preclinical data generated by this platform is acceptable and appropriate for ultimately advancing compounds into clinical testing while simultaneously fulfilling the preclinical needs for molecule-specific PIPs.
- Applicant consortium contribution – Members from academia (including paediatric oncologists) and patient advocacy groups will contribute expertise and leverage existing public-private partnership networks to provide guidance on project scope and implementation with the ultimate goal of identifying molecules potentially suitable for clinical testing in pediatric cancer.

Work package 5: Testing of shielded and open compounds (deliverable 7)

- Industry contribution – Baseline characterisation of all models (PDX, matching cell lines and GEMMs) using accepted standard-of-care is a necessity prior to testing of EFPIA and academic partner molecules. Contribution of shielded and/or proprietary compounds is subject to agreement with the contributor on transfer of and access rights to results generated on such compounds in accordance with IMI2 IP policy. EFPIA partners will provide technical input for the implementation of a quality-assured methodology, including single drug testing with readouts of biological efficacy, specific immunotherapy molecule testing approaches, analyses of resistance mechanisms and testing of rational drug combinations. The use of focussed testing *in vitro* models will be explored for early identification of compounds with a low *vivo* efficacy to limit the number of *in vivo* experiments. EFPIA partners will then assess if it can provide clinical or nearly clinical molecules (single and in combination), i.e. development candidates, for testing within the network with the expressed goal of moving promising molecules into paediatric clinical development. Determination of test agents as shielded vs open is left to the discretion of each EFPIA partner with the following important exception:

  > 'Pathway' evaluation – As a pilot project to develop a common methodology for drug development and prioritisation within pathways, the EFPIA partners intend to conduct open compound testing of molecules against targets in the RAS/MEK/ERK pathway in tumours where pathway activation is indicated. Each company will assess if it can provide inhibitors against individual targets within the pathway in order to gauge the relative efficacy of target shutdown at different nodes, to assess resistance mechanisms and to develop rational drug combinations. This activity is expected to highlight the power of this network in identifying (combinations of) molecules suitable for potential clinical development, as well as informing the importance of inhibition along a pathway deemed crucial to tumorigenesis. Based on these results it is envisaged that other pathways may be analysed and (combinations of) drugs prioritised in a similar fashion.
- Applicant consortium contribution – Members will test the compounds (from all consortium members) across the various model systems and where applicable and appropriate assist in eventual clinical development. Members will contribute scientific expertise to analyse single drug 'biological efficacy' (target binding and inhibition, pathway modulation, biological effect), to assess single drug resistance mechanisms and to design and test rational combinations. Testing is envisioned to occur once models are in place, validated for consistent growth and tested using disease-relevant SOC.

Work package 6: Information technology infrastructure and data analysis (deliverable 8)

- Industry contribution – EFPIA partners will lead the design and operation of database storage and retrieval systems. EFPIA partners will also lead the design of custom data analysis and visualisation tools (an example of potential tools can be found here: http://www.nature.com/nm/journal/v21/n5/abs/nm.3850.html).
- Applicant consortium contribution – Consortium members will contribute to the development of the IT infrastructure using available expertise and existing infrastructure as warranted.

Work package 7: Establishment and implementation of sustainability model to ensure the paediatric testing infrastructure (models, testing scheme, data, etc.) continues post-IMI2 (deliverable 10).

- Industry contribution – Identification of milestones and continuous evaluation of the development of a sustainable entity/process. At the end of the project there must be an entity/process in place to allow for 1) access to data generated during the project and 2) for continued testing and data generation moving forward. Exactly how this work package evolves will depend in large part on the make-up of the applicant consortium and the progress towards the overall goal of the project.
- Applicant consortium contribution – The consortium will bring forward a plan to ensure that the sustainability goal is met. A close relationship amongst all consortium members is critical to achieving this goal.

Preclinical target actionability data package	
Module 1	**Target activation patterns in clinical series**
Module 2 *	**Target dependence in *in vitro* models** *(molecular validation)*
Module 3 *	**Target dependence in *in vivo* models** *(molecular validation)*
Module 4	**Molecule sensitivity patterns *in vitro***
Module 5	**Molecule PoC efficacy *in vivo***
Module 6	**Biomarkers; predictive and biological efficacy (PD)** *(confirmation)*
Module 7	**Resistance mechanisms**
Module 8.	**Rational combinations**

Table 1 Preclinical datapackages for 'target actionability'

***** It is envisaged that molecular determination of 'target dependence' (modules 2 and 3) is out of scope for this project. Only target expression and activation within the context of in vitro and in vivo samples is considered in scope **.**

A Comprehensive 'Paediatric Preclinical POC Platform' to Enable Clinical Molecule Development for Children with Cancer - Flowscheme

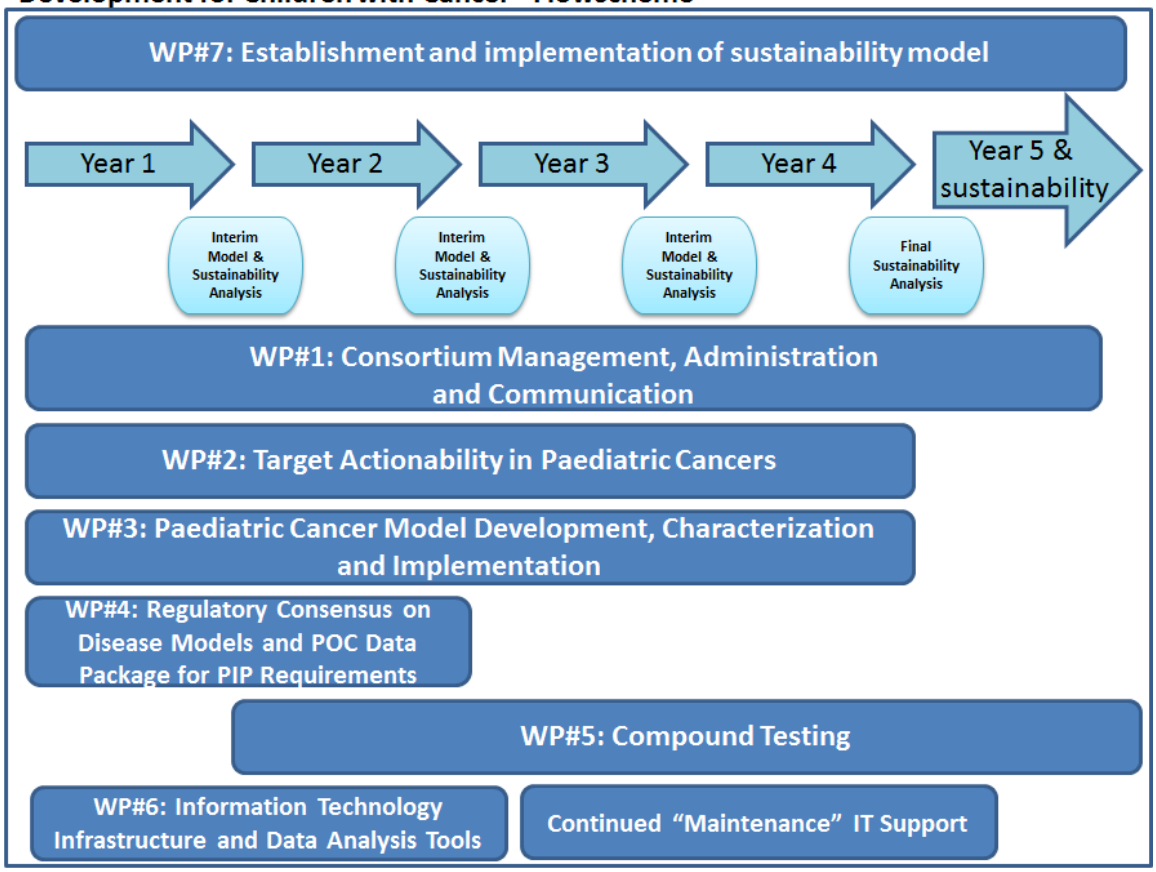

Figure 1

- Year 1 – Model development and characterisation; model implementation as models come on line, i.e., SOC testing, can occur in parallel if sufficient resources are available. Begin EMA/PDCO discussions. Begin sustainability discussions.
- Year 2 – Continued model development, characterisation and implementation. Assess success rates of model development and adjust focus and resources as determined by clinical need and opportunity. Continue qualification discussions with EMA. Implement common methodology and quality assurance. Limited drug testing should occur. Pilot project on pathway profiling (RAF/MEK/ERK) to begin. Continue to develop sustainability process and adjust as necessary.
- Year 3 – Continued model development with an increased emphasis on implementation and drug testing. Completion of pathway profiling project. Continue to develop sustainability process and adjust as necessary.
- Year 4 – Continued model development with an increased emphasis on implementation and drug testing. Methodology and quality-assurance of drug testing in place (based on # of models, and their availability).
- Year 5 – Drug testing in full force and final transition to the sustainability model. The number of drugs tested, and the frequency of testing, is in large part dependent on the available budget.

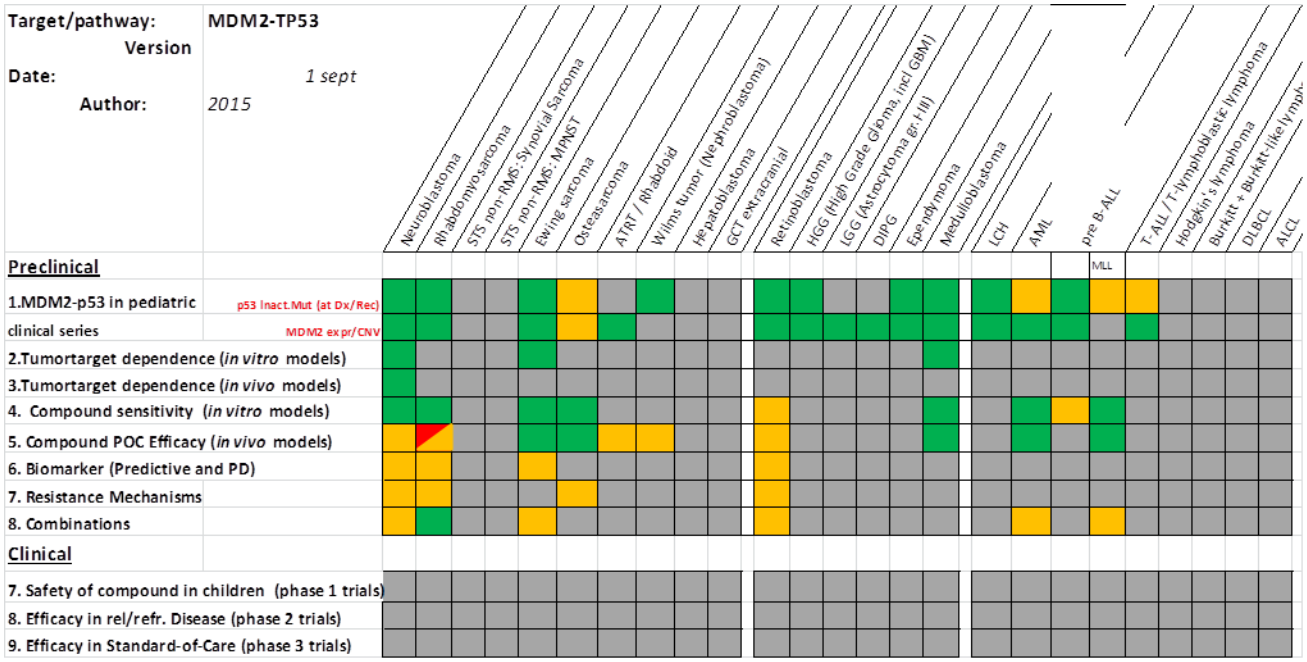

Figure 2

Systematic Literature review of target actionability; MDM2-p53 heatmap score, as an example

Glossary

GEMM	Genetically Modified Mouse Model
OPEN COMPOUND	A compound where testing data will be made available to all parties without costs
SOC	Patient Derived Xenograft Mouse Model
PIP	Paediatric Investigation Plan
SHIELDED COMPOUND	A molecule wholly (co-)owned or (co-)controlled by an EFPIA partner, for which testing data will not be made available to all parties without costs.
PDX	Standard-of-care

Introduction to the IMI2 Big Data for Better Outcomes Programme (BD4BO)

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

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

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

Programme structure

The programme will be composed of several topics which will address key enablers for the transition of healthcare systems towards more outcomes transparency, including an over-arching coordination structure (through a Coordination and Support Actions (CSA)), key structural and technology components (European Distributed Data Network) and several disease/therapeutic area (TA) topics focusing on a specific disease, population, therapeutic area or technology. Only one proposal under each topic will be selected.

In this Call, the BD4BO Coordination and Support Actions (CSA) is launched. The BD4BO Alzheimer's disease and haematologic malignancies topics were launched under IMI2 - Call 6. The European Distributed Data Network (DDN) and other disease-specific topics will be launched in future Calls.

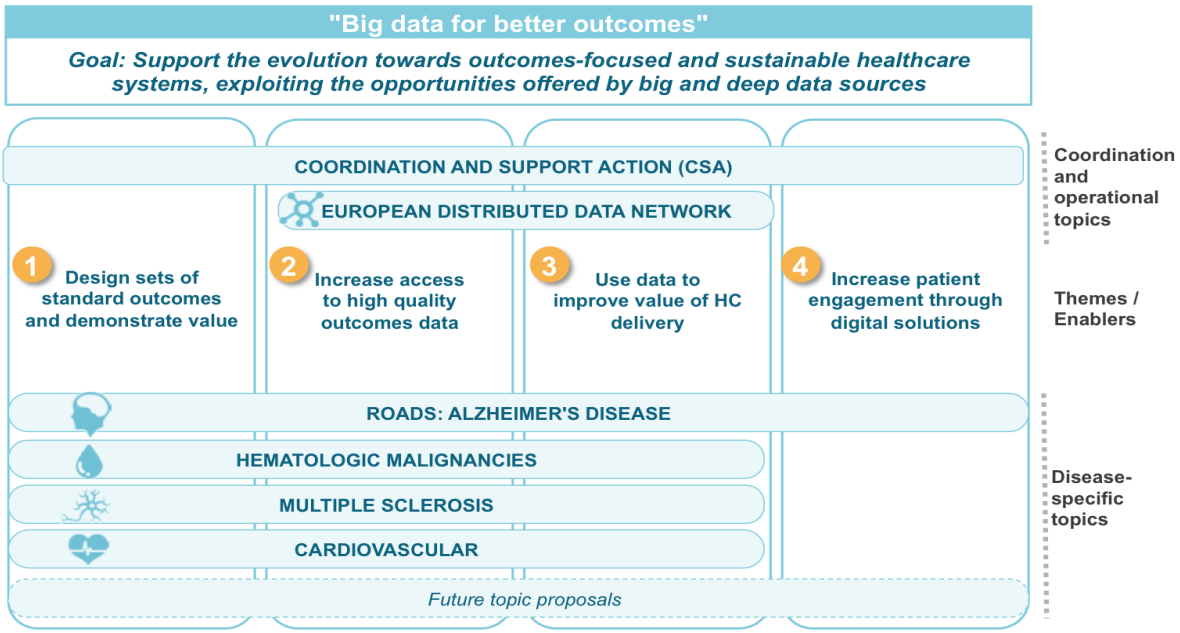

Figure 3: Programme structure, themes / enablers and CSA

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

Two projects, this Coordination and Support Actions (CSA), and forthcoming European Distributed Data Network Project (DDN) will therefore offer services to and complement activities of disease/therapeutic area related projects through:

- a central repository of knowledge/information
- a common ethical and personal data protection review and advice
- common standards for the collection, analysis and management of personal level data/knowledge
- assistance on the implementation of common data models and in the aggregation of data from different sources.

The distribution of tasks with responsibilities across different project teams within the programme (subject to adjustments as projects evolve) is summarised in figure 2:

	CSA	DDN	TA projects
Consistency & quality	• policy/direction, objectives, call texts • facilitate interactions and learnings between projects	• Standards for data and knowledge	• Contribute to Data Standards • Define TA specific Data Standards • Implementation
Knowledge integration	• Policy principles (programme level) • Gap analysis and recommendations for projects		• TA specific recommendations
Knowledge repository/platform	• Processes for collection, use and exploitation of knowledge and active process management	• Repository infrastructure	• Generate and manage TA specific contents
Engagement with HC stakeholders & communication	• Branding (templates, guidance) • Programme comms material • Programme website • Stakeholders engagement	• Recommendations on data formats and standards	• TA specific interactions with stakeholders (+reporting to CSA) • Communication (project level)
Data protection & integrity	• Legal & ethical standards • Code of practice • Common ethics Board • Templates/guidance	• Technical data security and privacy solutions • Common minimum data standards	• Operational interactions with competent authorities
Data sustainability & growth of networks		• Data sustainability mechanisms (including quality of data and adequate use)	

Figure 2: Allocation of tasks between Coordination & Support Action, Distributed Data Network and therapeutic area focused projects

Collaboration agreements

To ensure the interactions between the projects under the BD4BO programme, the therapeutic area/disease (TA) projects are expected to actively contribute key horizontal results to the Coordination and Support Actions (CSA) and the forthcoming European Distributed Data Network (DDN) projects which will provide direct advice and support to the TA projects. Therefore all grants awarded for the TA projects will be complementary to the Grant Agreements under the CSA and DDN topics. The respective options of Article 2, Article 31.6 and Article 41.4 of the Model Grant Agreement will be applied.

The TA consortia will conclude collaboration agreements with the Coordination and Support Actions consortium and the forthcoming European Distributed Data Network consortium. The collaboration

agreements are expected to include details of the services provided by the CSA and DDN to the TA specific projects such as the provision of data collection standards and processes, an interim repository for knowledge storage and management, data privacy standards, compliance and ethics regulations, including templates and other operational support.

The TA-specific projects are expected to contribute to the CSA knowledge repository and integration of learnings, and also participate in joint advisory boards and coordination boards to align on strategic programme elements such as definition of health outcome measurements, operational standards including data and knowledge collection and aggregation standards, common usage of IT infrastructures, communication of programme results and operational issues indicated in figure 2. All TA projects should ring-fence resources for these activities (approximately 5% on average, for example, experts to participate in central programme boards, participate in the adoption, adaptation and/or definition of common data standards, and/or cash that will cover the cost of operationalising e.g. central ethical and data protection boards and maintenance of the common IT infrastructure).

Need and opportunity for public-private collaborative research

The Big Data for Better Outcomes programme aims to provide high quality information that may provide decision makers with evidence on the enablers of value-based healthcare systems focusing on health outcomes. This healthcare system transformation would encompass payments, consider value and support aligned incentives between primary and secondary care moving towards the common goal of superior healthcare delivery and high quality data being made available. Therefore the engagement of patient organisations, regulators, payers, providers and other public stakeholders throughout the BD4BO programme is essential to ensure findings from those projects have appropriate buy-in and ultimately deliver real impact in transforming healthcare systems.

Expected impact

The expected impact of the programme would be a comprehensive plan for the development and implementation of key enablers to support the evolution towards value-based and more outcomes-focused and sustainable healthcare systems in Europe, exploiting the opportunities offered by big and deep data sources. The programme will also enable evolution and management of R&D portfolios and prioritisation of research methodologies in line with an outcomes focus.

Applicants should also refer to the ‘expected impact’ sections under each of the BD4BO topics.

Topic 6: Coordination and Support Actions (CSA) for the Big Data for Better Outcomes programme

Topic details

Topic code	IMI2-2015-07-06
Action type	Coordination and Support Actions (CSA)
Submission & evaluation process	2 stages

Specific challenges to be addressed

Several projects will be developed within the Big Data for Better Outcomes (BD4BO) programme to work on key enablers for the transition of healthcare systems towards more outcomes transparency, focusing on a specific disease, population, therapeutic area or technology. The development of different projects with common themes and related goals, the involvement of many actors and the generation of large amounts of information will result in relatively high complexity which will be critical to manage to secure success.

Coordination and expert support for the programme, through a Coordination and Support Actions (CSA), is required to aggregate and broaden the impact of individual projects within the Big Data for Better Outcomes programme. Through this coordination, the programme will support healthcare systems transformation to help focus on value and more outcomes transparency in collaboration with all relevant healthcare systems stakeholders.

In addition, the Coordination and Support Actions addresses data privacy issues in connection with human samples and data which are not only crucial for the BD4BO programme, but also for the healthcare sector in general where technological advances allow the use of increasing amounts of human samples and data for the development of personalised medicine. Such use requires a balancing of interests of patients on the one hand and research interests on the other hand. Accordingly, a focus of the Coordination and Support Actions is to create transparency when it comes to the application of data privacy laws in connection with human samples and data, to develop uniform standards, and to provide guidance in connection with patient informed consent forms and related data privacy aspects.

The success of the overall programme will rely on a coordinated approach across projects to ensure strategic alignment and consistency and to define new business and health funding models (including incentive models) that will allow for healthcare systems transformation. In addition, integration of areas of expertise which are common to most projects (such as data privacy and related legal considerations, sustainability or collaboration with payers/HTAs) will bring better results, consistency, and lower risk for the programme while managing resources more efficiently by avoiding duplication of work.

Collaboration between healthcare stakeholders and alignment with existing national and international projects is also needed to define a governance framework in relation to sharing and accessing part of the data and findings generated by projects. Since public entities hold valuable regulatory/supervisory expertise, their advice will be needed to facilitate the sharing of relevant project information with CSA members, while ensuring that privacy and confidentiality are protected. To the same extent, the expertise and perspective of academic institutions, SMEs (e.g. SMEs involved in the handling of human samples and data), patient organisations and medical associations as well as ethics committees acting in the realm of data protection in the healthcare sector are crucial for a successful outcome of the project.

The Coordination and Support Actions for Big Data for Better Outcomes is an opportunity to bring together, under a neutral collaborative framework, relevant stakeholders from the public and private sectors to foster discussion and coordinate activities of projects within the programme towards a shared end goal.

More background information is available in the IMI2 Big Data for Better Outcomes consultation paper[46].

Scope

The overall scope of this CSA is to establish an enabling platform with relevant stakeholders to support the quality and consistency of the individual projects in line with the overarching programme objectives and facilitate collaboration among projects within the Big Data for Better Outcomes programme. Thus, the CSA will be disease-agnostic, while most projects within the programme may have a disease focus.

The CSA will therefore:

- drive the health outcomes strategy of the programme;
  - define the strategy of the programme to support the transition of healthcare systems towards increased healthcare value focus with outcomes transparency through the programme;
  - operationalise a strategy to ensure quality and consistency across projects, identification of synergies and sustainability of results achieved;
  - identify opportunities for additional research action projects to address gaps;
- integrate knowledge from the projects and synthesise key learnings to provide a body of evidence to support healthcare systems transition to value-based healthcare and increased health outcomes focus;
- act as centre of excellence to exchange knowledge and learnings across projects;
- disseminate/share aggregated learnings among all stakeholders to complement the activities of the disease specific projects within the Big Data for Better Outcomes initiative, stakeholders to include patient organisations, regulators, payers, providers and other public stakeholders including relevant EFPIA and IMI2 groups;
- develop standards and guidance for the use of human samples and data in context of data privacy and related legal aspects;
- help address common issues.

This CSA should foresee mechanisms to ensure alignment with the forthcoming Distributed Data Network (DDN) project, which will include programme resources to set up systems for knowledge sharing within and across all BD4BO and give expert advice on data management.

Leaders of the individual Big Data for Better Outcomes projects are expected to participate in coordination meetings organised by the CSA and share project results with the CSA. Expertise within the CSA is not planned to replace required expertise within specific projects. The role of the CSA will be to coordinate, offer general advice, provide links to deep expertise when needed and disseminate integrated findings and learnings across projects. Its purpose is to enhance the likelihood of healthcare systems impact, while specific project management, advice and communications should be managed through the project consortium. To facilitate this participation, members of the individual disease specific projects are also expected to set aside and ring-fence resources (usually 5% of project budgets) in order to support the CSA and DDN activities in areas of overlap with project specific objectives.

Although research project participants will have access to a greater amount of data and results, a governance model will be defined to facilitate the sharing of relevant data and findings from projects with CSA members. Furthermore, members of the consortium will be involved in the shaping of recommendations to support healthcare systems' evolution in collaboration with multiple healthcare systems stakeholders.

[46] http://www.imi.europa.eu/sites/default/files/uploads/documents/Events/SF%202015/BigData_Concept_29May2015.pdf

Expected key deliverables

Deliverable 1: Strategic drive and coordination of projects within Big Data for Better Outcomes

- strategy definition;
- rigorous programme management and coordination of projects:
  - consistency, quality and synergies between projects;
  - mapping and collaboration with relevant projects within and outside IMI2;
  - approaches to ensure sustainability of results of projects within the programme;
  - coordination with IMI2 Strategic Governing Groups and EFPIA;
- where appropriate, recommendations for new research action projects.

Deliverable 2: Integration and management of knowledge from projects

- interim easily accessible and searchable repository of knowledge and knowledge management (the final infrastructure will be developed in cooperation with the foreseen Distributed Data Network project);
  - definition of knowledge domains that are critical to build;
  - reporting formats, key success factors for projects, mapping of data sources (scope, quality, and access), standardisation of methodologies (outcomes definitions and selection, measurement tools, analytical / IT solutions), key results and reports;
- distillation of findings and synthesis of key learnings across the programme and other non-IMI related initiatives, including identification of outcomes-focused pathways and access models.

Deliverable 3: Communication and collaboration with healthcare systems stakeholders

- dissemination of programme findings across all Big Data for Better Outcomes projects to leverage successes and learnings across the Big Data for Better Outcomes initiative;
- preparation of materials for internal and external communication, including white papers;
- public dissemination of recommendations and conclusions of the programme, including use of social media and training activities. In particular the documents and strategies developed in the frame of deliverables 2 and 4 should be made publicly available.
- forums, symposia, meetings with HTAs, HTA network[47], regulators, eHealth network[48], payers, providers, patients, national associations;
- identification of win-win solutions for private and public healthcare systems stakeholders;
- these communication channels may be used by disease-specific projects within the programme.

Deliverable 4: Standards and guidance for the use of human samples and data

- development of minimum standards (templates) for patient informed consent forms (ICFs) for clinical studies and other research studies;
- development of guidance documents to facilitate work with ICF templates, including their terminology and application, and guidance on related aspects of data privacy laws and regulations (e.g. concept of anonymisation) for Big Data for Better Outcomes, IMI/IMI2 projects and non-IMI related addressees;

[47] http://ec.europa.eu/health/technology_assessment/policy/network/index_en.htm
[48] http://ec.europa.eu/health/ehealth/policy/network/index_en.htm

- development of standards, training and educational guidance on some aspects of data privacy laws and regulations, data protection mechanisms and consequences of their application for Big Data for Better Outcomes, IMI/IMI2 projects and non-IMI related addressees (e.g. patients).

Expected impact

The expected impact would be:

- A comprehensively implemented plan for the development of key enablers to support the evolution towards value-based and more outcomes-focused sustainable healthcare systems in Europe, exploiting the opportunities offered by big and deep data sources. The projects will also optimise the exploitation of the outputs of other IMI data-related projects for the BD4BO objectives.
- Optimisation of investment in individual research actions under the programme.

Potential synergies with other consortia

The proposal will build on achievements and learnings from relevant IMI projects and specifically from all projects to be launched within the Big Data for Better Outcomes programme, starting with 2 topics in Call 6 published in October 2015.

The project is also expected to leverage and build on efforts of other real world evidence data or big data related IMI projects such as GetReal[49], EMIF[50], EHR4CR[51], OpenPHACTS[52] and eTRIKS[53].

The proposal should also consider other initiatives both at EU level (e.g. PARENT[54], Bridge[55], Big Data supporting Public Health Policies, Big Data PPP[56], EuDEco[57] and BigDataEurope[58]) as well as globally (e.g. OHDSI[59]).

Synergies will also be sought with ADAPT SMART[60] as far as standards and use of real world evidence is concerned.

With regard to data privacy, it will be crucial to align with data protection initiatives like the EFPIA Data Protection Working Group, TransCelerate BioPharma Inc. (TransCelerate)[61], the Clinical Trials Transformation Initiative (CTTI) Informed Consent Project[62], the Industry Pharmacogenomic Working Group (I-PWG) and others to develop consistent standards. These consistent standards will facilitate commercial and non-commercial R&D but even more so collaborations in the healthcare sector and cross-border projects.

[49] http://www.imi-getreal.eu/
[50] http://www.emif.eu/
[51] http://www.ehr4cr.eu/
[52] https://www.openphacts.org/
[53] https://www.etriks.org/
[54] http://patientregistries.eu/
[55] http://www.bridge-health.eu
[56] http://ec.europa.eu/newsroom/dae/document.cfm?doc_id=9488
[57] http://www.data-reuse.eu
[58] http://www.big-data-europe.eu
[59] http://www.ohdsi.org/
[60] http://adaptsmart.eu/
[61] http://www.transceleratebiopharmainc.com/
[62] http://www.ctti-clinicaltrials.org/

Industry consortium

- Novartis (lead)
- Bayer (co-lead),
- Janssen (co-lead)
- Eli & Lilly,
- Sanofi
- Pfizer,
- MSD
- Celgene
- GSK
- Health IQ
- Menarini
- EFPIA
- Servier
- Boehringer
- Intersystems
- ABPI
- Farma Industria
- UCB
- Novo Nordisk
- Amgen
- BMS
- Biogen
- Roche
- Vifor Pharma
- VFA

The industry consortium will contribute knowledge and expertise in the following areas:

- project and meeting management
- HEOR, Health outcomes definitions, value-based healthcare, RWE
- measurement tools and analytical
- regulatory/supervisory, HTA, payers, providers, patient groups
- benefit/risk assessment, pricing and reimbursement
- data privacy law and related legal aspects
- medical affairs and health care communication
- website management
- data/knowledge management, repository of knowledge
- public policy and governmental affairs
- patient engagement via digital solutions.

The industry consortium will also provide their expertise in the conduct and follow up of management tasks to secure this overall programme platform (including any IT system to help the work of the platform and the communication between partners) as well as provide the necessary resources for programme management, e.g. from defining strategic priorities to the organisation of meetings / workshops / teleconferences.

Indicative duration of the project

The indicative duration of the Coordination and Support Actions is 24 months.

Future project expansion

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

The objective of an expansion would be to ensure that the CSA project covers the full duration of the BD4BO programme, with the flexibility to adapt to resource requirements depending on the number of topics being

launched within the programme as well as the scope and ambition of the new topics. Therefore, the future Call will be open to other beneficiaries bringing additional expertise to the CSA project.

Indicative budget

The indicative EFPIA in-kind contribution will be EUR 3 550 000.

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

The indicative IMI2 contribution will be a maximum of EUR 3 550 000.

Applicant consortium

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

The applicant consortium is expected to address the objectives and make key contributions in synergy with the industry consortium which will join the the selected applicant consortium in preparation of the full proposal for stage 2. This may require mobilising:

- knowledge and expertise in healthcare systems including definition of validated outcomes metrics and measurement tools to support value-based healthcare;
- knowledge and expertise in real world evidence (RWE) and outcomes measurement within regulators, HTAs, payers, providers, patient associations, etc.;
- knowledge and expertise in legal, ethics and data privacy aspects on the management of sensitive personal level data (ideally one participant from the following interest groups) from an academic perspective as well as from the perspective of groups of academic research organisations, from the perspective of healthcare SMEs, in particular biobanking SMEs or health-IT companies, as well as from the perspective of national and international supervisory/regulatory authorities dealing with data protection in the healthcare context on a regular basis; understanding of patient and physician concerns such as in patient organisations and medical associations; ethical considerations as relevant in ethics committees;
- ability to develop outreach and communication strategies, on the role and challenges of using big data to improve outcomes, to the stakeholders and public at large;
- ability to develop effective communication tools, platforms to create awareness of the programme and disseminate findings;
- expertise to create training and communication materials based on results of the programme;
- proven expertise in rigorous programme management for projects of this complexity and scale, including risk management and sustainability of results.

The applicant consortium is expected to be multidisciplinary and to enable effective collaboration between key stakeholders (e.g. regulatory agencies/supervisory authorities, HTA, payers, academia, hospitals, SMEs, and patient organisations) and have the ability to engage with extended audiences within the above stakeholder groups.

The size of the consortia shall be carefully considered by the applicants who will balance multidisciplinarity and impact with the operational efficiency of the CSA.

Suggested architecture of the full proposal

The final architecture of the full proposal will be defined together with the industry consortium in observance of IMI2 rules to ensure the full achievement of the project objectives.

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

The Coordination and Support Actions for Big Data for Better Outcomes is expected to address multiple themes that focus on the key activities and capabilities required to coordinate and to provide support to all projects launched within the programme. In their short propsoal the applicants are expected to suggest an architecture for the full proposal to set up the platform that addresses the scope and the expected impact of this CSA, as well as incorporating and complementing the industry consortium contribution.

The below architecture for the full proposal is a suggestion; other project designs are welcome.

Programme strategy and coordination (including sustainability):

Deliverables to define and operationalise a strategy to develop concepts of value-based healthcare:

- synchronise BD4BO and CSA activities, liaise with IMI2 strategic governance groups (SGGs) and appropriate EFPIA groups;
- coordinate cross-project activites to ensure agreement with overall BD4BO objectives, and identify synergies;
- identify and engage with relevant projects outside the programme (both IMI and non IMI);
- design approaches to ensure sustainability is implemented consistently across projects;
- identify opportunities for new research projects.

Industry consortium contribution:

- strong programme management skills
- expertise in value-based healthcare, RWE
- network with leaders of IMI projects (BD4BO and others)
- governmental affairs and public policy.

Expected applicant consortium contribution:

- strong programme management skills, including roadmapping tools
- experience in coordinating projects of similar complexity / scale / sustainability
- expertise in initiatives related to health outcomes and value-based healthcare.

Integration of knowledge:

Deliverables:

- Knowledge repository: In year 1 of the CSA, this work package will be responsible for the management of knowledge across all the BD4BO projects. The CSA work will deliver an easily accessible and searchable repository of information and knowledge (not raw patient data), using a relatively simple and easily implemented off-the-shelf document management technology. It will be critical to define the various knowledge domains that will be captured, the reporting formats and some standardisation of methodologies early in the CSA, in collaboration with all the BD4BO projects. In year 2, the CSA will

produce a guidance document to allow the forthcoming DDN project to build on this knowledge repository as the BD4BO program increases in scope.

- In addition, in year 1, the work package will scope out a longer term, more scalable technical knowledge management solution, the requirements for which will also be provided to the forthcoming DDN project. This will need to be designed to meet the knowledge management needs for all BD4BO projects in the long term.
- A piece of work that will need to be done towards the end of year 1 of the theme will be to distill learnings from the success of the work of this theme itself. This piece will be included in the package of information that will be handed over to the forthcoming DDN project when the projects start.
- Distillation of findings: The CSA is expected to distill and aggregate findings from the different projects. They will identify best practices from different projects to standardise methodologies across the programme and synthesise key learnings from projects to support healthcare systems transition, including identification of outcomes-focused pathways and new funding and business models (e.g. incentive models).

Industry consortium and applicant consortium contribution

- The types of resource will be similar from both sides of the consortium since we anticipate that there will be need for a variety of specific roles, including information/knowledge management skills, project management, business analysis, healthcare systems expertise, expertise on outcome definition, measurement tools, etc. for standardisation of methodologies across diseases, HEOR expertise, knowledge about health funding models and various coordinating activities.

Communication and collaboration with healthcare systems stakeholders:

Deliverables:

Activities will aim at creating the necessary visibility and transparency about BD4BO activities to facilitate engagement and align understanding of concepts, principles, standards developed in the project, and reach out to relevant stakeholders to inform policy discussions. In addition, this theme is to establish communication channels with relevant healthcare systems stakeholders (patients, HTAs involving also HTA Network[47], regulators involving also eHealth Network[48], payers, medical societies, providers, and others as applicable) to collaborate with key stakeholders and give advice to all projects and how to support healthcare systems transition though the projects. The consortium will also be expected to keep the European Commission informed of the activities of the CSA, in particular the responsible unit of the Directorate General (DG) Health & Food Safety.

To achieve this, the proposed work theme will:

- align dissemination and communication strategies across the programme;
- create materials for internal and external communication;
- set up social media platforms and an inventory of communication opportunities (including communication to EFPIA members;
- support the publication and other dissemination of findings of BD4BO projects, including through training activities;
- coordination & communication - Coordination and integration of stakeholder engagment and ensure two-way sharing and embedding of insights and learnings, both in Member States and other stakeholders. There will be a need to identify and develop communication platforms for stakeholders (website , communication kit);
- develop evolving narrative - Develop a clear and customer-friendly narrative that explains the importance of outcomes-focused and sustainable healthcare systems, including the role of big data, this project and its evolving findings, and the potential impact of the final recommendations, covering the two year CSA project period;

- conduct a 'horizon' scan - This will be research work that will identify existing and best practices of related project initiatives from approximately 10 Member States and other perspectives in the field of policy, concrete projects, stakeholder engagement and communication strategies;
- disease action projects – Identify the learnings from disease action IMI projects in collaboration with healthcare system stakeholders;
- engage with stakeholders - Targeted outreach with stakeholders from approximately 10 Member States and other stakeholders to share insights from the project and feedback insights and advice from stakeholders to the project.

Industry consortium contribution:

- communication (communication strategies, media, social media);
- web set-up and management;
- science writers;
- event organisation;
- stakeholder engagement expertise at national and EU level with all relevant stakeholders, including but not limited to HTAs, regulators, payers, patients, medical societies, and providers;
- organisation of multi-stakeholder meetings, workshops or forums to foster stakeholder engagement.

Expected applicant consortium contribution:

- communication strategies and tools;
- science writers;
- creating communication materials;
- creating training materials and delivering training;
- appropriate resources and expertise from HTAs, regulators, payers, providers, patient organisations, medical societies and other appropriate stakeholders;
- organisation of multi-stakeholder meetings, workshops or forums to foster stakeholder engagement, especially with additional healthcare systems stakeholders beyond the consortium.

Standards and guidance for the use of human samples and data:

Deliverables:

Creating transparency, developing uniform standards for informed consent forms (ICF) and related legal data privacy aspects as well as providing guidance and training regarding legal data privacy aspects in connection with the use of human samples and data is the aim of this work package. It includes:

- development of minimum standards (templates) for ICFs for clinical studies and other research studies;
- development of guidance documents to facilitate the work with the generated ICF templates, including their terminology and application, and provision of guidance on related aspects of data privacy laws and regulations (e.g. concept of anonymisation) for Big Data for Better Outcomes, IMI/IMI2 projects and non-IMI related addressees;
- development of standards, training and educational guidance on aspects of data privacy laws and regulations, data protection mechanisms and consequences of their application for Big Data for Better Outcomes, IMI/IMI2 projects as well as non-IMI related addressees (e.g. patients).

Industry consortium contribution:

- legal expertise in connection with data privacy and related legal matters.

Expected applicant consortium contribution:

- knowledge and expertise in legal, ethics and data privacy aspects on the management of sensitive personal level data (ideally one participant from the following interest groups) from an academic perspective as well as from the perspective of groups of academic research organisations, from the perspective of healthcare SMEs, in particular biobanking SMEs or health-IT companies, as well as from the perspective of national and international supervisory/regulatory authorities dealing with data protection in the healthcare context on a regular basis; understanding of patient and physician concerns such as in patient organisations and medical associations; ethical considerations as relevant in ethics committees.

Glossary

BD4BO	IMI2 Big Data for Better Outcomes programme
CDISC	Clinical Data Interchange Standards Consortium
CSA	Coordination and Support Actions
EFPIA	European Federation of Pharmaceutical Industries and Associations
EHR4CR	Electronic Health Records Systems for Clinical Research
EMIF	European Medical Information Framework
eTRIKS	European Translational Information & Knowledge Management Services
HTA	Health technology Assessment
ICF	Informed Consent Forms
IMI	Innovative Medicines Initiative
OHDSI	Observational Health Data Sciences and Informatics
OpenPHACTS	The Open Pharmacological Concepts Triple Store
PARENT	PAtients REgistries iNiTiative
RWE	Real World Evidence
SME	Small and Medium Enterprise

Topic 7: Increase access and use of high quality data to improve clinical outcomes in heart failure (HF), atrial fibrillation (AF), and acute coronary syndrome (ACS) patients

(Part of the IMI2 Big Data for Better Outcomes Programme)

Topic details

Topic code	IMI2-2015-07-07
Action type	Research and Innovation Actions (RIA)
Submission & evaluation process	2 stages

Specific challenges to be addressed

Non-communicable diseases play a major role in the global burden of disease. By 2020, heart disease and stroke will become the leading causes of death and disability worldwide, with the number of fatalities projected to increase to more than 24 million by 2030.[63]

Three common cardiovascular diseases - heart arrhythmias (primarily atrial fibrillation or AF), heart failure (HF) and acute coronary syndrome (ACS) – cause much of this disability. While major advances in the management of these diseases have been achieved, medical management of these cardiovascular patients remains challenging.

The need to improve awareness, risk assessment, diagnosis, and treatment is measureable. Current treatment guidelines are often not followed, leaving many patients not or undertreated. Many patients have risk factors and comorbidities which complicate the assessment of interventions. Improving our knowledge about the role of risk factors and comorbidities should advance patient care by identifying risk markers that can guide therapies.

Guideline committees call for more data to inform management recommendations. Ultimately, these data should aid the development of new medications, interventions and targeted management recommendations that improve outcomes in all patients but in particular in pertinent patient subgroups. Likewise, healthcare providers should have new and improved diagnostics to select the right course of treatment. Such data should also help delay these diseases to more advanced ages.

The tool by which we will do that is data. But not data aggregation in the abstract, rather data aggregated and analysed to create specific algorithms useful for stratifying subtypes of the disease, predicting relevant outcomes, understanding underlying biology, and assigning a specific therapeutic regimen to the right patients at the right time. By the end of this project, new or improved tools and surrogate markers that can be used for patient selection and as benchmarks for therapeutic response should be identified. Improved understanding, prediction and assessment of cardiovascular outcomes should also facilitate clinical trials of therapeutic drugs.

Although current technology has led to the collection of massive amounts of healthcare data including medical records, claims information and patient-reported data, wide scale exploitation of these data sources has yet to be achieved. This is mainly due to obstacles in the linkage of data, which results in fragmented and isolated datasets (e.g. data in primary care and hospital or specialised care with no single database having complete information on the patient).

[63] Circulation. 2011;123:1671-1678

Also, disease registries capturing incident cases are rare as many patient registries are designed for healthcare administration purposes. Information on incident cases is crucial for studies of the aetiology and for studies of baseline characterisation of patients.

Powerful insights could be generated from the combination or linking of inpatient and outpatient hospital data, prescription data, sociodemographic data, clinical trial data from pharmaceutical companies and data from newer technologies and 'omic measurements. However, current systems are not ready to allow this. Due to the sensitivity of the information involved, a solid data governance framework is required that addresses privacy concerns and sets up mechanisms to ensure that only the right stakeholders have access to the relevant data.

Need and opportunity for public-private collaborative research

Stakeholders agree that large cardiovascular data sources should be tapped for this effort. However, neither the pharmaceutical industry nor individual public companies or organisations can solve this daunting problem alone. Rather public-private partnerships can provide the right setting to achieve this task by combining different skill sets and data sources. These partnerships should identify best how to link and analyse existing data. They should also identify and collect data that are not currently available, and integrate these new data into clinical management and drug development strategies that improve our ability to address the challenges of cardiovascular disease. These partnerships should ensure that adequate governance is provided to deal with the ethical and legal issues related to such an undertaking.

Both public and private organisations need to collaborate in defining what is required from the partnership. Private and public organisations can provide different kinds of expertise. While both can provide data, specifically public organisations (such as HTAs, regulators, payers, providers and medical societies) can provide the credibility that is required to establish a governance framework. The involvement of patients and/or patient organisations is also crucial to the success of the partnership. Since the goal of the initiative is to improve patient outcomes, patient input into the governance, use of data, definition of meaningful outcomes, design of studies and the unique viewpoint of what is acceptable and important to patients is essential. No public health initiative can succeed without the acceptance and ‘buy-in’ of patients so their input will be critical.

The timing of this initiative is ideal as it builds on many past and ongoing public-private cardiovascular initiatives such as EUR Observational Research Programme (EORP[64]), International Consortium for Health Outcomes Measurement (ICHOM[65]); disease-related initiatives such as the ESC[a] Global Heart Failure Awareness Programme and Heart Failure Association (HFA[66]). Initiatives in other areas of medical research offer relevant insights into study design and data capture/combining techniques such as GetReal (IMI)[67], EPAD[68], EMIF[69], ADAPT SMART[70], DDMORE[71] and OHDSI.

Scope

The main goal of this initiative is to improve AF, HF, and ACS patient outcomes through better access and use of data. This will require:

1. defining and prioritising relevant patient outcomes in collaboration with key healthcare system stakeholders and patients;
2. accessing and analysing relevant morbidity and mortality data from large population-based healthcare databases and patient data sources;

[64] https://www.eorp.org/
[65] http://www.ichom.org/
[66] http://www.escardio.org/The-ESC/Communities/Heart-Failure-Association-(HFA)/Heart-Failure-Association-HFA-of-the-ESC
[67] http://www.imi-getreal.eu/
[68] http://www.imi.europa.eu/content/epad
[69] http://www.imi.europa.eu/content/emif
[70] http://adaptsmart.eu/
[71] http://www.imi.europa.eu/content/ddmore

3. collecting and analysing data from clinical studies, genotyping, protein biomarkers, advanced imaging, or quality-of-life information directly from patients;
4. exploring algorithms that combine traditional and newer sources of data to improve our ability to assess the risk of a patient or population for relevant cardiovascular outcomes, diagnose the subtype and biological drivers of those risks, prescribe effective treatments, and monitor for progression or regression of disease;
5. translating the insights from these analyses into disease management concepts and guidelines, and innovative drug development to improve patient outcomes.

The key activities will include:

- align on key operational definitions of AF, HF, and ACS and corresponding operational clinical outcome definitions to be used in real world studies;
- identify data sources and a data strategy across multiple geographies;
- identify best practices in linking data sources;
- ensure data privacy and respect patient confidentiality;
- collect new clinical data, as well as genomics, proteomics, advanced imaging, life style factors, and quality of life aspects;
- improve the descriptive epidemiology of these diseases including time trends, variation between countries/regions, and inter-individual characteristics;
- understand how patients with diseases of interest are treated, geographical differences in treatment, and the levels of treatment adherence;
- improve knowledge about established and emerging risk factors and protective factors for AF, HF and ACS, including comorbidities, and results from genomic and proteomic characterisation;
- improve knowledge about risk factors and protective factors of defined outcomes of interest including results from genomic and proteomic analysis;
- establish systems to study new onset of disease to better understand and predict disease progression;
- identify and provide a data governance framework addressing concerns such as data privacy, quality, ownership and access rights to support future research;
- build on existing technologies for conducting advanced analytics including predicting health outcomes and modelling disease progression using traditional and new sources of data;
- pilot patient evaluation and treatment strategies based on these new predictive analytical tools;
- identify which risk factors are most amenable to individual and population management;
- provide recommendations or guidance documents on the appropriateness of different approaches based on feasibility examinations/pilot studies explored during the project;
- consideration of ethical and patient/healthcare professional communication in relation to differing treatment paths, and complex risk space.

Expected key deliverables

Final deliverables will be determined by the consortium in collaboration with public partners and are likely to include the following:

1) defined set of target diseases and outcomes that include both clinical operational definitions and definitions to be applied to existing registers including real world outcomes meaningful to patients and caregivers:
    - including alignment of key stakeholders (including patients) on the relevance of the outcome metrics for different uses (e.g. reimbursement, assessments, screening, etc.);

- including relevant process metrics and patient factors linked to outcomes of interest;

2) identification of data sources for required outcomes measures:
   - consider creating a searchable web tool;
3) strategy to access and combine quality outcomes data:
   - including a data governance framework to address data privacy, quality, ownership and access rights leveraging other IMI efforts;
4) data curation of data sources to be used in the project;
5) protocols, processes and tools to capture data addressing unmet needs;
6) collection of new data deemed to be relevant for the purposes of the study such as advanced imaging, life style factors including genomic and proteomic characterisation;
7) advanced analytics development:
   - quantification of risk factors and protective factors, using data from providers, registries and optionally data from patients, including:
     - impact of medicine adherence and drug switching;
     - link of occurrence measures of diseases and endpoint of outcomes;
     - understanding of differences across geographies;
     - insight into the impact of genetics and biomarkers based on proteins;
   - development of methodologies to predict outcomes based on risk factors, symptoms, including genetic and proteomic characterisation to better target treatments to patients who would benefit the most from interventions - this will also include modelling disease progression:
     - including effect of emerging risk factors such as iron deficiency;
     - including impact of comorbidities such as diabetes;
8) writing of a guidance document endorsed by key stakeholders.

Expected impact

The expected impacts of the proposed project are better and safer treatment paradigms for patients with AF, HF, and ACS. This impact should be achieved by providing evidence which will make it easier for healthcare providers (HCPs) and other stakeholders to *provide the right treatment to the right patient at the right time.*

To achieve this we expect this proposed project to:

- improve understanding of the risks of serious outcomes in these patients compared to the general population;
- improve knowledge on how these patients are treated in the real world and what affects outcomes with more efficient surveillance of safety and effectiveness in real world settings;
- improve information of the importance of adherence to treatment, the role of risk factors, comorbidities, genetics and lifestyles;
- improve awareness of quality of life aspects that are important for patients;
- evaluate and test tools that may be useful for predictive analytics and surrogate markers for cardiovascular outcomes;
- develop strategies to use these predictive analytic tools and surrogate markers to improve clinical care pathways and support innovative drug development that provide relevant improvement of outcomes that are important for patients.

Potential synergies with existing consortia

We expect to utilise synergies with the EMIF[72], EHR4CR[73], OHDSI[74] and other IMI and non-IMI initiatives, especially related to database techniques. The project will also build on work conducted by the European Society of Cardiology (ESC)[75], such as the World Heart Failure Alliance work and ERA-CVD[76], the ERA-NET on cardiovascular diseases to implement joint transnational research projects and set up international cooperations.

Synergies with other Big Data for Better Outcomes programme projects will also be ensured; these include the Coordination and Support Actions (CSA) and the Distributed Data Network (DDN) projects.

Industry consortium

- Bayer (lead)
- Vifor Pharma (co-lead)
- Novartis
- Servier
- Somalogic

The industrial participants will contribute expertise, data and resources to map the treatment pathway, understand drivers of outcome and cost variation and identify and pilot implementation of best practices.

Indicative duration of the project

The indicative duration of the project is 60 months.

Indicative budget

The indicative EFPIA in-kind contribution will be EUR 9 672 000 including access to placebo data from existing and concurrently collected clinical trial data capped to a maximum of EUR 4 000 000.

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

The indicative IMI2 contribution will be a maximum of EUR 9 672 000.

Applicant consortium

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

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

The applicant consortium is not expected to include data providers with information on subjects with HF, AF, or ACS, but it will be expected to collaborate with relevant data providers during the proposed project. Ideally research should be conducted in countries with sufficient good quality data, a well-established data access framework respectful of data privacy, and political willingness to establish such a framework.

[72] http://www.emif.eu/
[73] http://www.ehr4cr.eu/
[74] http://www.ohdsi.org/
[75] http://www.escardio.org/
[76] http://cordis.europa.eu/project/rcn/198784_en.html

Academia, researchers and data analytics experts will be relevant for the analysis of drivers of outcomes and the use of big data to identify best practices and methodologies to target care.

Payers, HTAs, governments, patients and physician organisations like the ESC have to also be engaged during the project, even if not necessarily as part of the applicant consortium, to align on outcomes that matter to patients and help identify and promote best practices identified in the projects.

Finally, media organisations might also be engaged to publish sources of outcome information and best practices identified through different projects in an EU-wide or world-wide report.

Suggested architecture of the full proposal

In their short propsoal the applicant is expected to have a strategy for the translation of the relevant project outputs into regulatory practices and clinical and healthcare practice. A plan for interactions with regulatory agencies/health technology assessment bodies with relevant milestones and resources allocated should be proposed to ensure this e.g. implementation of set of relevant outcomes in measurement and evaluations.

The final architecture of the full proposal will be defined together with the industry consortium in observance of IMI2 rules and in contemplation of the achievement of the project objectives.

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

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

Work package 1: Project coordination

The overall objective for WP1 is to establish a framework for collaboration and ensure minimisation of duplicative work and maximisation of sharing across the various work packages as well as to ensure strategic alignment of efforts. It has also has to coordinate with other projects within the Big Data for Better Outcomes programme through the CSA and the Distributed Data Network.

- project design and charters with clear accountabilities;
- set-up of joint governance structure:
  - joint senior steering committee as clearly visible decision making body;
  - define work expectations of different work streams, deliverables, dates, activities;
- provide coordination and support to project teams:
  - including organisation of annual general assemblies with all partners;
- ensure key cross-functional partners are engaged:
  - define project interdependencies, stakeholders and risks;
  - coordination with Big Data for Better Outcomes programme as per the planned collaboration agreements in BD4BO;
- provide a consistent, project-wide view of progress, issues, and interdependencies;
- project level communication of key information throughout change effort (e.g. timelines, updates, directives, etc.):

- including creation and management of a shared repository of documents, meeting minutes, etc.

Industry contribution

WP co-leaders to participate in CSA and DDN meetings for coordination within the Big Data for Better Outcomes programme and support with project design and day-to-day operation.

Expected applicant consortium contribution

Ensuring the implementation of the coordinating tasks and running the day-to-day operation, such as project tracking and reporting, meetings, internal communication, budget management, etc.

Work package 2: Disease understanding and outcomes definition

- specify operational and applicable definitions of AF, HF and ACS for use in data generation;
- specify operational and applicable definitions of outcomes of interest per disease mentioned above. The outcomes should include hard clinical study outcomes (which may include the disease itself, its complications or complications of treatment of the disease of interest), patient reported outcomes (PRO), outcomes relevant for healthcare provider/payers/regulators as well as biomarker-defined outcomes based on proteomics assays, pharmacogenomics, and imaging;
- define a core standard outcome data set that is applicable for the diseases listed above. These could be supplemented by specific outcome measures, for each of the specific diseases, that are expected to improve testing efficacy/ effectiveness and safety of novel therapies and better understanding of the nature of the disease and its clinical course;
- publication of white paper consensus documents on the issues described above, including recommendations for how best to combine randomised controlled trial data with observational study data to achieve a holistic data package for key decision-makers, healthcare providers and payers;
- produce a guidance document.

Industry contributions

- clinical and safety expertise;
- real life evidence generation expertise;
- study/trial management and operational expertise;
- expertise from HEOR including PRO and epidemiology;
- medical writing and project management;
- e-health industry companies (e.g. remote monitoring, imaging, biomarkers and pharmacogenomics expertise etc.);
- future technology companies.

Expected applicant consortium contribution

- literature review on outcomes and definition of relevant outcomes in collaboration with key opinion leaders (KOLs), clinical experts, patients, providers/payers, registry experts, etc;
- alignment of a core standard outcome set with KOLs, patients, providers/payers, registry experts;
- clinical expertise in the key diseases areas;

- experience in conducting population-based research in the key diseases areas;
- public e-health services and coordinators;
- data repositories / biobanks / registries targeting AF/HF and ACS;
- patient organisation representation;
- coordinating expertise to consolidate stakeholder outcome suggestions.

Work package 3: Mapping, selecting and curating existing data

1) Data mapping

   a) identification of data sources will be achieved through a pre-specified search strategy, described in a protocol. The protocol will detail databases, search strings, and inclusion/exclusion criteria. The design of the study protocol will be informed by the result of WP2;

   b) steps to identify potentially relevant data sources:

      i) searches of bibliographic databases (e.g. MEDLINE and EMBASE) and commercially available database catalogues[77] as well as through the ENCePP register hosted by EMA;

      ii) internet search:

         (1) use of common internet search engines (e.g., Google) to search for condition-specific data sources identified in the literature review;

         (2) websites of academic/public/private institutions;

         (3) websites and abstracts submitted to particular conferences (e.g. ICPE, ISPOR, ESC);

      iii) survey of internal resources: e-mail survey enquiring about our colleagues' experience with databases, targeting:

         (1) industry partners;

         (2) clinical research organisation (CRO) selected to execute WP2 activities;

      iv) data abstraction: The list of data sources derived from the literature review, internet search and the internal surveys will be compiled and shared for the selection of the most relevant data abstraction form. Data will be abstracted from articles and official websites. Each data source will be assessed based on the following criteria:

         (1) accessibility;

         (2) size (lives covered);

         (3) spectrum of data captured (type of observational research and level of data available);

         (4) duration of follow-up; overall and patient-level (mean);

         (5) record linkage; existing internal and external linkage, plus ongoing linkage activities;

         (6) medical ethics requirements;

         (7) overall data quality and quality assurance activities;

         (8) information on licensing fees (if available);

      v) direct contact of database holders and/or corresponding authors: should all information needed to populate the data abstraction form for a specific database NOT be found in the public domain, contacts with the database holders or corresponding author will be made to obtain the relevant information;

   c) the primary deliverable will be a report including cost considerations to access the database. Information retrieved from the search may also be synthesised on a programmable spreadsheet or an application to be made available to all partners.

[77] http://www.bridgetodata.org/

2) Data selecting and curating:

   a) Present data in a standardised format using a common data model that will transform the data to be amenable for easy analytics. Major activities undertaken to achieve the delivery of standardised data are detailed below.

   b) Standardisation of diverse sources: the data identified will be in diverse formats with little or no standardisation. Some of the data will also be inconsistent and erroneous. For primary data collection activities, we will identify disparate data and attempt to resolve the discrepancy by communicating with associated investigators or owners of the data. Data for clinical variables will be subjected to necessary reconciliations, de-duplication, cleansing and transformation to render the datasets ready for data integration. Standardisation will be implemented using ontologies for diseases, tissues, compounds, etc.

   c) Establish framework:

      i) select structured, controlled information models and biomedical ontologies suitable for standardisation and normalisation of disparate data sources used in this project. Linked data technologies may be appropriate in the context;

      ii) establish well-defined guidelines to promote consistency during curation activities such as mapping variables and review;

      iii) perform data curation:

         (1) interpret and establish the context for each study and variable within the study;

         (2) standardise variables and normalise values to the selected framework;

         (3) ensure validity through established peer review system and/or automated quality control;

         (4) for primary data collection activities, direct contact with study authors when necessary to resolve issues around consistency or conflict of data;

         (5) enable data citation as a reward and incentive mechanism.

Industry contribution

- expertise from HEOR, epidemiology, clinical, safety and PROs
- literature search, review and assessment
- database information and assessment
- biostatistics/programming
- data management
- provide databases.

Expected applicant consortium contribution

- medical: clinical expertise in the key diseases areas, and also in literature search, review and assessment
- data management: data access and data cleaning expertise
- biostatistics/programming: data analysis and programming expertise
- medical writing: protocol and report
- medical communication: protocol and report.

Work package 4 : Data collection

The key goal of WP4 will be to collect information on risk factors of poor outcomes in AF, HF and ACS in a subpopulation identified as per WPs 2, 3 and 4. This includes identification of subgroups of patients with a particularly high risk of poor outcomes, and validation of tools to stratify these subgroups, allowing clinicians and pharmaceutical developers to develop cost-effective treatment strategies that direct the right drugs to the patients who need them most.

- the information of interest represents various 'omic measurements, including genotype, proteomic phenotype, other relevant biomarkers as well as patient reported outcomes and quality of life aspects;
- it is planned to evaluate biomarkers at multiple time points to enable analysis of disease dynamics;
- studies will be designed and prioritised to evaluate the utility of specific biomarkers as well as to optimise and identify new biomarker information for the purposes listed above. Similarly, measurement instruments will be developed to target relevant information on patient reported outcomes and quality of life components;
- conduct targeted protein-omic assessment to stratify patients according to their likelihood of HF, ACS and stroke on a two to five year time horizon. Serial protein measurements will create a longitudinal proteomic data profile for each patient that can be queried against a variety of cardiovascular outcomes. This dataset, combined with others generated as part of WP3 and WP4, will enable researchers to subtype cardiovascular disease in novel ways, improve predictions of event risk, create profiles for response/non-response to various classes of therapeutic treatment, and ultimately match individual patients with specific treatments for optimal effectiveness. Functional enrichment analysis will be considered if appropriate;
- another 'omic assessment will be genotyping. There are a number of genes associated with each of the disorders (AF, HF and ACS). Further genome-wide sequencing methods will be important in understanding the genetic contribution more comprehensively for them. In addition to genomic information, other studies, such as methylation analysis and transcriptomics (particularly to study regulatory RNAs including microRNAs and long non-coding RNAs) have already identified some key mechanisms of genetic control that impact these disorders and further studies are likely to add value to the identification of causative mechanisms. The ability to test multiple variants and genes simultaneously at ever lower cost and an increasing evidence base that variants can provide risk prediction information.[78] Identifying further associated variants and working towards understanding effects on drug response that allow the stratification of therapies will be significantly enhanced by this approach;
- access to data: Applications will be submitted to an approval committee to gain access to 'restricted access' datasets identified as relevant by partners from the compiled list. To access datasets from academic and private institutes, collaborations /partnership/ licensing of datasets will be established as required;
- standardisation of diverse datasets: the created datasets will be standardised consistently with the efforts in WP3.

Industry contribution

- design and implement studies that can achieve subtyping and applying tools to stratify patients at risk for poor outcomes in ACS, AF and HF, thereby enabling improved treatment strategies;
- evaluate available patient cohorts for suitability in patient consents, biological sample and clinical information;
- provide CVD9 score for a subcohort of patients using the SOMAscan assay during the project;
- provide genotyping for a subcohort of patients;
- integrate and analyse 'omic characterisation data together with relevant outcomes for optimisation of algorithms providing predictive analytics;
- required expertise:

[78] EHJ, doi:10.1093, 2013

- biostatistics/clinical trial design;
- bioinformatic analysis;
- database integration;
- actionable information delivery (e.g. patient stratification);
- medical management;
- patient advocacy;
- health economic analysis;
- clinical/translational research expertise.

Expected applicant consortium contribution

- Identification of potentially relevant cohorts will be achieved by the applicant consortium, which will detail availability of biobanked plasma/serum and other suitable samples with proper patient consents, together with disease outcomes (e.g. ACS, stroke, HF, kidney failure, etc.) as defined by WP2 and other measurements relevant to the designated analyses. Cohorts may also be developed and managed by the applicants prospectively;
- cohort access: identify or establish patient cohort with suitable patient consent, biological samples and clinical information availability;
- study design: design and implement studies that can achieve the key goal of this project and thereby enable improved treatment strategies;
- medical: clinical management in the key diseases areas;
- care innovation: collaborate with participating EFPIA members to explore alternative approaches to managing patients at high risk of cardiovascular disease events as defined by data from WP3 and WP4;
- bioinformatics: integrate and analyse 'omic characterisation data together with relevant outcomes information.

Work package 5: Data analysis

- understand how patients with diseases of interest are treated, geographical differences in treatment, and the levels of treatment adherence;
- provide output in terms of results such as point estimates of parameters of interest (i.e. prevalence and incidence rates, relative risks, mortality, case fatality, survival rates, re-hospitalisation rates, etc.) accompanied with confidence intervals to serve all stakeholder needs with relevant data to be applied for improvement of patients as the ultimate goal;
- quantification of drivers of outcome variation;
- tables, figures and other visualisation types for study reports, publications, guideline documents etc;
- ensure preparedness for ad hoc analysis for specific applications, for example relative survival estimation, standardised morbidity/mortality ratios and other analyses;
- identify and/or develop best clinical practices and coordinate with industry leaders representing future technology;
- evaluate novel tools and strategies for predictive analytics, patient stratification and surrogate markers for specific outcomes;
- provide training on how to use and interpret the information.

Industry contribution

- informatics;
- hard ware expertise;
- information optimisation expertise;
- programming;
- biostatistics;
- imaging expertise;
- data handling/visualisation expertise;
- data analysis;
- clinical and safety expertise;
- quality of life, patient reported outcomes and other HEOR expertise;
- study design and epidemiologic data analysis expertise;
- patient advocacy expertise;
- medical writing;
- e-health experts (e.g. remote monitoring, imaging, etc.);
- collaboration with additional health systems to test and refine stratification strategies.

Expected applicant consortium contribution

- medical: data access, clinical expertise and scientific input;
- informatics: choice of data model, information optimisation and hardware expertise;
- biostatistics/programming: data access, data analysis and programming expertise;
- HTA/regulatory: drug approval and reimbursement procedure input, comparative analyses of relevance, etc.;
- government: data ownership controlling access;
- other: data collection techniques, hardware and software development and optimisation.

Work package 6: Dissemination and communication

- overall communication strategy for the project including a communication plan by stakeholder type;
- coordination with CSA and communicate with other relevant IMI projects, including other projects within the Big Data for Better Outcomes Programme;
- message development and guidance to all work packages;
- production of high-quality public relations materials;
- external publications on outputs of project through white papers, conferences;
- compiling and disseminating communication material to all relevant partners;
- develop and manage communication via web portal and other social media tools;
- repository of key documents;
- quality assessment documents.

Industry contribution

- medical communication;
- media interactions;
- medical writing;
- contact with HCP professional organisations and their communication group, i.e. ESC;
- contact with patient organisations.

Expected applicant consortium contribution

- pharma communication and/or media expertise;
- HCP professional organisations, i.e. ESC;
- clinical expertise in the key diseases areas;
- guideline commissions;
- expertise on payers / healthcare provider financing;
- market research organisation;
- public relations organisation;
- communication contacts with relevant public health services, governmental bodies, health authorities, and patient organisations.

Work package 7: Ethics, legal and data privacy

Develop an ethical and legal framework to provide guidance on addressing patient confidentiality and data ownership concerns to other work packages in close coordination with the CSA for the Big Data for Better Outcomes programme.

Deliverables

- guidance on ensuring patient confidentiality is maintained according to relevant legislation and data ownerships aspects are taken into proper consideration (in coordination with the CSA and the DDN);
- input into evaluations of different WPs including legal and ethical guidance on issues as needed;
- oversight of white papers and publications.

Industry contribution, expertise required

- legal expertise;
- compliance expertise;
- communication (linked to WP6 activities).

Expected applicant consortium contribution

- legal and ethical expertise;
- compliance expertise;
- patient advocacy expertise.

Glossary

AF	Atrial Fibrillation
ACS	Acute Coronary Syndrome
CSA	Coordination and Support Actions (within the Big Data for Better Outcomes programme)
DDN	Distributed Data Network
EHR4CR	Electronic Health Records for Clinical Research
EMIF	European Medical Information Framework
ESC	European Society of Cardiology
HEOR	Health Economics Outcomes Research
HF	Heart Failure
HCP	Health Care Provider
HTA	Health Technology Assessment
ICPE	International Society for Pharmacoepidemiology
ISPOR	International Society for Pharmacoeconomics and Outcomes Research
OHDSI	Observational Health Data Sciences and Informatics
PRO	Patient Reported Outcomes

Conditions for this Call for proposals

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

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

Applicants intending to submit a short proposal in response to the IMI2 Call 7 should read this topic text, the IMI2 Manual for submission, evaluation and grant award and other relevant documents (e.g. IMI2 model Grant Agreement).

Call identifier	H2020-JTI-IMI2-2015-07- two-stages
Type of action	RIA – Research and Innovation Actions
	CSA – Coordination Support Actions
Publication date	**18 December 2015**
Stage 1 submission start date	**18 December 2015**
Stage 1 submission deadline	**17 March 2016 (17:00:00 Brussels time)**
Stage 2 submission deadline	**6 September 2016 (17:00:00 Brussels time)**

Indicative budget	
From industry consortia (EFPIA companies)	EUR 46 802 000
From the IMI2 JU	EUR 46 802 000

Call topics

IMI2-2015-07-01	The indicative contribution from EFPIA companies is EUR 12 000 000 The financial contribution from IMI2 is a maximum of EUR 12 000 000	Research and Innovation Actions. Two-stage submission and evaluation process. Only the applicant consortium whose proposal is ranked first at the first stage is invited for the second stage.
IMI2-2015-07-02	The indicative contribution from EFPIA companies is EUR 4 685 000 The financial contribution from IMI2 is a maximum of EUR 4 685 000	Research and Innovation Actions. Two-stage submission and evaluation process. Only the applicant consortium whose proposal is ranked first at the first stage is invited for the second stage.
IMI2-2015-07-03	The indicative contribution from EFPIA companies is EUR 1 500 000 The financial contribution from IMI2 is a maximum of EUR 1 500 000	Research and Innovation Actions. Two-stage submission and evaluation process. Only the applicant consortium whose proposal is ranked first at the first stage is invited for the second stage.

IMI2-2015-07-04	The indicative contribution from EFPIA companies is EUR 8 025 000 The financial contribution from IMI2 is a maximum of EUR 8 025 000	Research and Innovation Actions. Two-stage submission and evaluation process. Only the applicant consortium whose proposal is ranked first at the first stage is invited for the second stage.
IMI2-2015-07-05	The indicative contibution from EFPIA companies is EUR 7 370 000 The financial contribution from IMI2 is a maximum of EUR 7 370 000	Research and Innovation Actions. Two-stage submission and evaluation process. Only the applicant consortium whose proposal is ranked first at the first stage is invited for the second stage.
IMI2-2015-07-06	The indicative contribution from EFPIA companies is EUR 3 550 000 The financial contribution from IMI2 is a maximum of EUR 3 550 000	Coordination and Support Actions. Two-stage submission and evaluation process. Only the applicant consortium whose proposal is ranked first at the first stage is invited for the second stage.
IMI2-2015-07-07	The indicative contribution from EFPIA companies is EUR 9 672 000 The financial contribution from IMI2 is a maximum of EUR 9 672 000	Research and Innovation Actions. Two-stage submission and evaluation process. Only the applicant consortium whose proposal is ranked first at the first stage is invited for the second stage.

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

List of countries and applicable rules for funding

By way of derogation[79] from Article 10(1) of Regulation (EU) No 1290/2013, only the following participants shall be eligible for funding from the Innovative Medicines Initiative 2 Joint Undertaking:

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

b) which fall within one of the following categories:

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

ii. secondary and higher education establishments;

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

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

c) the Joint Research Centre;

d) international European interest organisations;

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

Admissibility conditions for grant proposals, and related requirements

Part B of the General Annexes[80] to the H2020 Work Programme shall apply *mutatis mutandis* for the actions covered by this Call for proposals.

Eligibility criteria

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

Types of action: specific provisions and funding rates

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

Technology Readiness Levels (TRL)

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

Evaluation

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

The proposals are evaluated against the specific IMI2 evaluation criteria (excellence, impact and quality and efficiency of the implementation)[81] according to the submission stage

Type of action	Excellence	Impact	Quality and efficiency of the implementation*
RIA and IA	The following aspects will be taken into account, to the extent that the proposed work corresponds to the topic description in the IMI2 Annual Work Plan/Call for proposals: **clarity and pertinence of the objectives;** **credibility of the proposed approach;**	The following aspects will be taken into account, to the extent to which the outputs of the project should contribute at the European and/or International level: **the expected impacts of the proposed approach listed in the IMI2 annual work plan under the relevant topic;** **enhancing innovation**	The following aspects will be taken into account: **coherence and effectiveness of the project work plan, including appropriateness of the allocation of tasks and resources;** **complementarity of the participants within the consortium (where**

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

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

	soundness of the concept, including trans-disciplinary considerations, where relevant; **extent that proposed work is ambitious, has innovation potential, and is beyond the state of the art;** **mobilisation of the necessary expertise to achieve the objectives of the topic and to ensure engagement of all relevant key stakeholders.**	**capacity and integration of new knowledge;** **strengthening the competitiveness and industrial leadership and/or addressing specific societal challenges;** **improving European citizens' health and wellbeing and contribute to the IMI2 objectives;**[82] **any other environmental and socially important impacts;** effectiveness of the proposed measures to exploit and disseminate the project results (including management of IPR), to communicate the project, and to manage research data where relevant.	**relevant);** **clearly defined contribution to the project plan of the industrial partners (where relevant);** **appropriateness of the management structures and procedures, including risk and innovation management and sustainability plan.**
CSA	The following aspects will be taken into account, to the extent that the proposed work corresponds to the topic description in the IMI2 Annual Work Plan/Call for proposals: **clarity and pertinence of the objectives;** **credibility of the proposed approach;** **soundness of the concept, including trans-disciplinary considerations, where relevant;** **quality of the proposed coordination and/or support measures.** **mobilisation of the necessary expertise to achieve the objectives of the topic and to ensure engagement of all relevant key stakeholders.**	The following aspects will be taken into account, to the extent to which the outputs of the project should contribute at the European and/or International level: **the expected impacts of the proposed approach listed in the IMI2 annual work plan under the relevant topic;** **contribute to the IMI2 objectives;**[83] **effectiveness of the proposed measures to exploit and disseminate the project results (including management of IPR), to communicate the project, and to manage research data where relevant.**	The following aspects will be taken into account: **coherence and effectiveness of the project work plan, including appropriateness of the allocation of tasks and resources;** **complementarity of the participants within the consortium (where relevant);** **clearly defined contribution to the project plan of the industrial partners (where relevant);** **appropriateness of the management structures and procedures, including risk and innovation management (and sustainability plan where relevant).**

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

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

Scores must be in the range 0-5. Half marks may be given. For the evaluation of first-stage proposals under a two-stage submission procedure, the threshold for individual criteria is 3. There is no overall threshold.

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

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

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

The full evaluation procedure is described in the IMI2 Manual for submission, evaluation and grant award in line with the H2020 Rules for Participation[84].

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

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

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

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

Indicative timetable for evaluation and grant agreement

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

Budget flexibility

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

[84] http://www.imi.europa.eu/sites/default/files/uploads/documents/IMI2_CallDocs/IMI2_SubmissionManual_Dec2015.pdf

Financial support to third parties

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

Submission tool

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

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

Others

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

http://ec.europa.eu/research/participants/portal/doc/call/h2020/h2020-phc-2014-single-stage/1600139-essential_information_for_clinical_studies_en.pdf. (*link to IMI website will be available after Call publication*)

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

Ethical issues should be duly addressed in each submitted proposal to ensure that the proposed activities comply with ethical principles and relevant national, Union and international legislation. Any proposal that contravenes ethical principles or which does not fulfil the conditions set out in the H2020 Rules for Participation, or in the IMI2 Call for proposals shall not be selected. [85]

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

1) Disseminate scientific publications on the basis of open access[86].(see 'Guidelines on Open Access to Scientific Publications and Research Data in Horizon 2020').
2) Include a data management plan outlining how research data will be handled during a research project, and after it is completed, as part of the Full Proposal. (see Guidelines on Data Management in Horizon 2020 providing guidance for the collection, processing and generation of research data). In order to ensure adherence to the legislation concerning protection of personal data, controlled access digital repositories and data governance will need to be considered.
3) Use well-established data format and content standards in order to ensure interoperability to quality standards. Preferably existing standards should be adopted. Should no such standards exist, consideration should be given to adapt or develop novel standards in collaboration with a data standards organisation (e.g. CDISC).
4) Disseminate a description of resources[87] according to well-established metadata standards such as the Dublin Core (ISO15836) in order to make the resources included and generated by the IMI actions discoverable for metrics and re-use.

[85] Article 19 of *Horizon 2020 Framework Programme*, and Articles 13 and 14 of the *Horizon 2020* Rules for Participation
[86] Article 43.2 of Regulation (EU) No 1290/2013 of the European Parliament and of the Council laying down the rules for participation and dissemination in *Horizon 2020 - the Framework Programme for Research and Innovation (2014-2020)* and repealing Regulation (EC) No 1906/2006

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

Consortium agreements

In line with the Rules for Participation and Dissemination applicable to IMI2 actions[88] and the IMI2 model grant agreement, participants in IMI2 actions are required to conclude a consortium agreement prior to grant agreement.

[87] Examples of resources are (a collection of) biosamples, datasets, images, publications etc.
[88] Regulation (EU) No 1290/2013 of 11 December 2013 and Commission Delegated Regulation (EU) No 622/2014 of 14 February 2014.