IMI2
6th Call for proposals

Approved by the IMI2 Governing Board on 05.10.2015

IMI2-GB-DEC-2015-36 Annex

Document reference: IMI2/INT/2015-02065

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 maximize European added value in health research. Where appropriate, the involvement of regulators is also strongly encouraged.

Before submitting a proposal, applicant consortia should familiarise themselves with all Call documents such as the IMI2 Manual for evaluation, submission and grant award[5], and the IMI2 evaluation criteria. Applicants should refer to the specific templates and evaluation procedures associated with research and innovation actions (RIAs).

[1] The Council Regulation (EU) No 557/2014 of 6 May 2014 establishing the Innovative Medicines Initiative 2 Joint Undertaking (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_Call1/Manual_for_submission_evaluation_grant%20award_2014.06.26.pdf

Topic 1: Development of Quantitative System Toxicology (QST) approaches to improve the understanding of the safety of new medicines

Topic details

Topic code	IMI2-2015-06-01
Action type	Research and Innovation Action (RIA)
Submission & evaluation process	2 Stages

Specific challenges to be addressed

Modeling is fundamental to drug development. Methods range from simple models to predict a safe clinical starting dose based on the no-observed-adverse-effect-level (NOAEL) from preclinical species, to complex mechanistic physiologically based pharmacokinetic/ pharmacodynamic (PBPK/PD) models that predict patient outcomes in heterogeneous populations. Traditional pharmacokinetic/pharmacodynamic (PK/PD) modeling methods that involve the use of empirical mathematical relationships to link dose, exposure, and response have been the work horses in the context of drug discovery and development. These models, informed by *in vivo* data, have been used extensively to identify optimal doses and schedules. However, these 'black box' models are not well-suited to address species-specific differences or intra-individual differences in biological response to drug injury which limit their use as translational tools.

Recent developments in mechanistic and system modelling have been applied in toxicology. Broadly speaking, two distinct types of approaches have been applied in the field of quantitative or systems toxicology to date [1-5]. In the first approach, quantitative models are constructed in a hypothesis-driven and manually curated fashion by incorporating knowledge of toxicity mechanisms (e.g. DILI-Sym). The drawback here is that one risks omitting key mechanisms that may drive the biological outcome. In addition, these models may not account for novel mechanisms and interactions not captured by the hypothesis. In a second, data-driven approach, 'omics datasets are analyzed to generate signatures, or to characterize mechanisms of toxicity at a system-wide level. Signatures are useful but suffer from a number of limitations such as being highly dependent on the quality and prior definition of the training set compounds, or lacking ability to scale across systems (e.g. rat liver to rat hepatocyte), or dimensions (e.g. early stage of cell injury to late stage cell transformation). Another drawback with 'omics-based approaches is that it is not straightforward to reduce the dimensionality of these datasets in order to make them amenable to quantitative modeling.

These challenges highlight the need to develop innovative methodologies and practices to integrate the 'omics analysis and network analysis with quantitative mechanism-based models to form a new approach to drug safety assessment. The emerging field of Quantitative Systems Pharmacology (QSP) seeks to address this methodological gap via the development of mathematical models that account for the mechanisms underlying the response of integrated biological systems at the level of target cells and organs. In this approach, the system is comprised of the key molecular, cellular or organ level readouts (system variables), and their interactions (defined via system parameters) necessary to describe a given biological outcome. Compounds perturb the system by affecting particular variables, and the interactions in the system drive the eventual organism-level response. The advantage of this approach is that by quantifying the system properties for particular species or for particular subpopulations, we gain the ability to quantitatively translate the preclinical effects of a compound to patient populations.

Need and opportunity for public-private collaborative research

Despite more than a decade of work, 'omic and other high content approaches that have largely been used to identify signatures of toxicity, have not dramatically altered pharmaceutical safety assessment practices. Continued urgency to move away from traditional safety assessment methods is increasing pressure from both outside and within the industry to utilize new technologies more effectively. At the same time, the increasing availability of large comprehensive datasets, and the development of modeling and bioinformatics approaches presents us with an opportunity to develop quantitative approaches for predicting drug toxicity. The pharmaceutical industry must assume a leadership position on these strategies to ensure the applications are focused on the right problems, addressing the clinically relevant safety questions and using the most effective approaches. However, building Quantitative Systems Toxicology (QST) approaches requires a specific set of expertise from experimental sciences (toxicology, 'omics, drug metabolism and pharmacokinetics (DMPK), fundamental biology, mathematics), as well as computer science (Big data, computational biology, systems biology, modeling and simulation) that cannot be found in a single pharmaceutical company or academic institution.

Scope

The scope of this proposal is to 1) develop QST models for drug-induced toxicity with the focus on four different organ systems: heart, liver, kidney and the gastrointestinal (GI)-immune system, and 2) use this QST approach for the prediction of clinical toxicity using preclinical data. We require applicants to address the integration challenge in the context of models for all four organ systems proposed.

The models are expected to incorporate key events from one or more levels of biological organization (molecular/pathway level, cellular, organ level) that are involved in drug-induced pathogenesis and repair. Novel methods that merge classical compartment models or newer cell-based models of function with high content data to model biological networks important in pathogenesis and repair at the organ level are encouraged.

Objective 1: Develop an open (for the consortium members), focused and sustainable knowledge database to build system toxicology models.

The project is not designed around simple descriptive 'omic profiling of new studies to generate new signatures or building new databases. It is anticipated that applicants will already have data or access to data (e.g. leverage existing open public databases, non-proprietary data by EFPIA partner companies) and expertise in computation biology approaches to data analysis as well as expertise in modeling biological systems at different scales. The generation of new data that add to and support modeling efforts is anticipated based on a supportive gap analysis.

Objective 2: Provide a clearer understanding of the translational confidence from non-clinical species to human.

Approaches that do not address the translation issue are out of scope; the project is not designed to provide a detailed mechanistic model of responses in preclinical species only. Model toxicants and/or surgical models may be used where appropriate to capture dynamics of pathogenesis and repair, but the project should include relevant models of drug-induced injury and/or disease models relevant to human disease. Models that improve capabilities to extrapolate risk from non-clinical risk characterization to clinical outcomes are important.

Objective 3: Support key risk assessment decisions, such as safety margin, clinical monitoring and reversibility, using mechanistic and quantitative modelling.

Applicants are expected to provide/leverage existing PBPK models whenever possible to predict organ tissue concentrations, and provide methods to incorporate *in vitro* data to improve prediction (e.g. transporter assays). Applicants are expected to propose innovative methodologies to incorporate 'omics data and current state-of-the-art (bio) markers into the modeling effort with the emphasis on ability to identify cellular networks associated with functional changes and integrated stress responses to injury.

Proposals solely focused on black-box PK/PD modeling approaches to characterize exposure-response relationships are clearly out of scope.

Objective 4: Provide improved methods for visualizing and analyzing complex high content data to support drug safety assessment.

Proposals should include the design of usable interfaces for analysis of 'omic data, biological networks and their integration into PBPK models for use by industry, Regulators and health assessors. Improved methods for visualizing high content data in the context of biological networks and analysis of network perturbations as components of disease pathogenesis are needed. Methods that reduce the dimensionality and complexity of data to support modeling at the level of inter- and intra-cellular networks are an important component.

Objective 5: Help inform regulatory decisions by providing evidence supporting the usefulness of QST modelling to support safety risk assessments, analogous to how PBPK modeling is currently accepted in clinical plans and regulatory submissions in the context of drug-drug interactions.

Expected key deliverables

Deliverable 1: Knowledge bases to enable the development of QST models

The deliverables proposed under this section will help to address the needs of the toxicology community for more comprehensive coverage of mechanistic toxicity pathways from which to define a mechanism-based screening approach, as described in the report from the National Research Council 'Toxicity Testing in the 21st Century' vision.

- Develop a compendium database of biological interactions from public sources such as the Human Interactome Project (http://interactome.dfci.harvard.edu/H_sapiens/index.php) and Reactome (http://www.reactome.org/);
- compile a user-accessible library of calculated networks categorized and searchable by toxicant (e.g. drug), starting point (e.g. drug target), toxicity, or molecular component(s);
- validate or refine networks with experimental data coming from existing datasets or *de novo* data generated in experiments specifically designed to confirm particular steps of the pathway;
- use the small-scale networks as starting points for the development of quantitative models of pathway impact leading to the development of adverse events (AEs);
- reveal potential biomarkers of pathway perturbation leading to AEs and propose experiments to explore their use in a safety paradigm;
- develop new knowledge management tools to curate the datasets used to build the interactomes.

Deliverable 2: Identification of key biological networks

The deliverables proposed under this section should provide the proof-of-concept that an unsupervised network approach can be used to identify biological response networks associated with pathology, either concurrent or predicted, and describe differences in network responses across species (network preservation).

- Use unsupervised approaches to identify co-regulated networks (modules) that reflect important biological response pathways associated with mechanisms of toxicity;
- map the preservation of the identified networks/systems across species. It is anticipated that both rodent and human networks can be constructed, but other non-clinical species are not excluded;
- use these networks as starting points for the development of quantitative models of pathway impact leading to the development of adverse events.

Deliverable 3: Quantitative mechanistic models of toxicity supporting risk assessment

The deliverables proposed under this section will provide the mechanistic physiologically based pharmacokinetic/toxicodynamic (PBPK/TD) models for each organ/system in scope, to enable quantitative translation of preclinical data to the clinic, and the mechanistic understanding of drug-induced changes.

- Develop novel probabilistic models that merge systems level data with appropriate risk assessment approaches for human safety;
- prototype the models using nonclinical data;
- identify new sources of human systems level data;
- deliver parameterized species-specific PBPK/TD models for the chosen target organs;
- develop and validate specific translational workflows for each organ system using preclinical and clinical data for non-proprietary compounds;
- demonstrate the usability of the tool to address specific toxicity questions during drug development.

Deliverable 4: Open analytical tools and interfaces

- Develop innovative methodologies in data mining (big data), data aggregation and data curation to build reliable high quality dataset in support of deliverables;
- develop an accessible interface enabling analysis:
  - input into the platform (e.g. data/pathway upload/integration of existing open database from other consortia);
  - export from the platform;
  - analytical tools;
  - visualization of the knowledge;
- drive the use of a consistent, standard and open format for the data and the modelling platforms;
- develop an outline to ensure the sustainability of the database/tools developed within the consortium.

Expected impact

- A unique and curated data source feeding quantitative and system toxicology approaches;
- better predict interspecies similarity and expected/observed differences, and provide evidence the differences in biological networks across species contribute to differences in toxicity;
- refine drug safety assessments by incorporating new data into standard points of departure for risk assessment, such as NOAEL, margin of safety, etc., and identify novel translational safety biomarkers to improve clinical monitoring;
- improved ability to translate risk from nonclinical risk characterization to the probability of clinical adverse events;
- educational impact by providing simple output/visualisation to answer complex and specific safety queries;
- better guide the design of clinical trials by selecting patients less prone to toxicity;
- reduce animal usage in preclinical phases;
- provide white papers, guidance to support tox assessment with regulators.

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 on achievements, and incorporating, when possible, data and lessons learnt, while avoiding unnecessary overlapping and doubling of efforts.

The proposal should build on data, achievements and knowledge from relevant IMI projects such as e-TOX, SAFE-T, and MIP-DILI. It should look to incorporate data and knowledge from other open sources such as TG-GATES, DRUG MATRIX, and LINCS; these should be used as a source of valuable compound-target-adverse effect relationships.

The applicants are also invited to propose other potential collaborations as long as they are in line with the project's overall objectives.

Industry Consortium

- AbbVie (leader)
- Eli-Lilly (co-leader)
- Sanofi
- Astra-zeneca
- GSK
- Servier
- J&J
- Orion

Indicative duration of the project

The indicative duration of the project is 60 months.

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

Indicative budget

The indicative in kind contribution from the industry consortium is estimated at EUR 8 000 000. Due to the global nature of the participating industry partners part of these contribution may be provided from non-EU/H2020 associated countries.

The financial contribution from IMI2 JU will be a maximum of EUR 8 000 000.

Applicant consortium

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

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

The expertise required in this consortium covers three major areas:

- Toxicology sciences: comparative medicine (human and animal physiology), preclinical safety, *in vitro* /molecular&mechanistic toxicology including 'omics, computational toxicology;
- modelling and simulation: PBPK and Drug disposition modelling, quantitative and systems pharmacology;
- information systems: data management and curation, data integration, Big data mining, data visualisation, user-friendly interfaces.

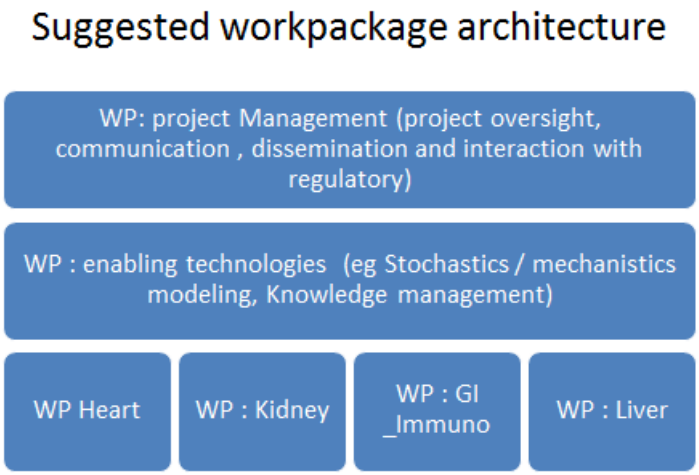
Applicants should show that they already have data or could access data (e.g., leverage existing open public databases, non-proprietary data by EFPIA partner companies) and expertise in computational biology approaches to data analysis and modeling. Nonetheless, it is anticipated that new experimental data would need to be generated for some organs/systems during the course of the project to test models and proof-of-concept. Applicants should have experience in generating high content data commensurate with the goals of the project, and finally applicants should demonstrate experience of previous interactions with regulators.

Suggested architecture of the full proposal

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

The Applicant Consortium is expected to address all the research objectives described in the Work Packages and make key contributions on the defined deliverables in synergy with the industry consortium. A suggested architecture is provided below, where the final organ-specific models are supported by transverse infrastructure and enabling tools which are needed.

The Work Packages below are quite broad in outline and different specific project proposals, along with proper justifications, within each Work Package are expected to be developed by the Applicant Consortium.



Work Package 1: Consortium Management and Oversight

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

- Industry contribution: alliance & project management including planning, budgeting, follow up and tracking, and consolidation of Work Package reports. Project risk management and comprehensive

communication and dissemination of its progress and its milestones are important additional elements of EFPIA contribution;

- expected applicant consortium contribution: providing detailed follow up and tracking, via regular Work Package reports, early report of any unexpected organisational or structural issues or delay with respect to the project deployment and intermediate objectives.

Work Package 2: Communication, Dissemination and regulatory interactions

The successful applicant consortium and the industry consortium will produce together a plan for regular interactions with regulatory authorities, the consortium will also contribute over the 5-year project duration to planned health literacy actions, project awareness, project milestones, presentations to stakeholders and media as appropriate.

- Industry contribution: logistics and organisational support, contribution of EFPIA experts as appropriate; this will include a dedicated website and organisation of milestone workshops for stakeholders (and the general public as appropriate);
- expected applicant consortium contribution: provide the scientific and medical content for building health literacy elements, consolidation and update over the project duration; provide personal and collegial contribution to the dissemination program implementation; authoring major papers in peer reviewed scientific journals.

Work Package 3: Database, Knowledge management and interface

This Work Package will address the structuration of the knowledge.

- Industry contribution: genomics and other ‘omics data, basic PBPK models of some organs;
- expected applicant consortium contribution: providing IT expertise on knowledge management, data curation according to the deliverables.

Work Package 4: Systems modelling technologies

This Work Package is designed to support building relevant biological networks from high content data.

- Industry and public partners will jointly contribute to mapping biological network systems level data from nonclinical and human organs of interest. Examples might include application of weighted-gene co-expression network analysis (WGCNA) to transcriptomic data;
- industry and public partners will determine which networks show higher association with concurrent pathology and predict development of pathology at later time points;
- for novel networks, EPFIA and academia will cooperate on understanding biological mechanisms reflected in the networks to support mechanism-based risk assessment;
- industry and public partners will develop methods to determine the preservation of biological networks from non-clinical species to humans for the individual organ systems (e.g. Heart, Kidney, GI..) or pathways (e.g. Nrf2, lipid metabolism);
- industry and public partners will cooperate to identify sources of human tissue for ‘omic analysis to support network construction. A key goal will be to associate networks with various phases of toxicity and organ pathogenesis, i.e. the initial damage phase followed by either an adaptive recovery response, or progression of pathogenesis to end-stage organ damage.
- Industry contribution: data, models and expertise in modeling1: real world experience in drug safety assessment.
- expected applicant consortium contribution: scientific expertise in systems modeling.

***Organ specific Work Packages*:**

Industry and public partners will jointly contribute to address the specifics described below. Industry will contribute modelling expertise, computational biology expertise, and a framework for managing high content data. EFPIA companies have experience with drug-induced injury and physiological perturbations associated with injury in all 4 organ systems and will contribute that expertise to the various **Work Package**s.

Work Package 5: Kidney

The kidney performs vital functions in electrolyte, acid-base and water balance as well as blood pressure, waste elimination, drug and drug metabolite clearance. There are a number of commonly used markers of renal function, e.g. blood urea nitrogen (BUN), creatinine clearance, urine protein, etc. In addition, novel markers of renal injury have been approved for nonclinical use, e.g. kidney injury molecule-1 (Kim-1), and are progressing toward clinical validation. Next generation systems biology approaches also afford an opportunity to merge 'omic data with known markers to better understand disease networks at the cellular and organ levels. Given the importance of kidney as a target for drug toxicity and the prevalence of chronic renal disease in certain patient populations, improved QST models could have real world applications in the near term.

Suggested deliverables:

1. Building a PBPK model (the baseline model) that incorporates the current state-of-the-art non-invasive markers (e.g. BUN, creatinine clearance, urine protein, Kim-1) to estimate renal function;
2. the functional unit of the kidney, the nephron, has segment-specific functions from the apical glomerulus to the distal collecting duct. Drug-induced kidney injury can target specific segments of the nephron. Models that incorporate parameters related to segment-specific compartments of physiological function are needed;
3. define sets of biochemical/cellular parameters, either invasive or non-invasive, that help map the trajectory of drug induced kidney injury and recovery from acute and chronic injury. Biochemical/cellular parameters might include measurements relevant to drug toxicity (oxidative stress, mitochondrial function, etc.), glomerular structure and function, tubule structure and function, progression of fibrosis and inflammation, etc.

Work Package 6: Heart

Cardiovascular toxicity is a major concern in drug development, and remains the leading cause of withdrawal of marketed drugs. Cardiovascular adverse events have a range of aetiologies including arrhythmias, myocardial infarction, congestive heart failure and coronary heart disease. There have been significant efforts at predicting QT interval prolongation, which is associated with Torsades de Pointes. Due to the understanding of the underlying mechanism, this has led to successful preclinical strategies to screen out this liability. There is a need to translate measurements of cardiac structural and functional changes observed in short term preclinical studies to effects that would be observed in particular patient populations upon long term dosing. This kind of question is best tackled using a QST approach that systematically integrates knowledge of toxicity mechanisms and of species-specific differences in response with the appropriate *in vitro*, *in vivo* and clinical datasets.

Suggested deliverables:

1. PBPK models to predict cardiac tissue concentrations; methods to incorporate *in vitro* data (e.g. transporter assays) for tissue concentration prediction;
2. (semi)-mechanistic models of hemodynamic changes that account for functional effects on heart rate, blood pressure, cardiac output [7] that can be used to quantitatively translate effects from preclinical species to humans;

3. approaches that link hemodynamic changes and cardiac pathology (e.g. cardiac arteritis);
4. models that can be used to link the dynamics of cardiac biomarkers such as troponin to changes in cardiac structure and function;
5. generation of focused *in vitro* and *in vivo* datasets to parameterize the QST model;
6. approaches that account for variability in physiological parameters and in cardiovascular responses in man that enable prediction of risk for particular patient populations;
7. informatics and Bioinformatics approaches to identify particular targets and pathways for inclusion in the QST model for cardiovascular toxicity. E.g. *in vitro* assays with known cardiotoxic compounds coupled with 'omics analysis to identify pathways and regulators of structural cardiotoxicity.

Approaches focused solely on QT prolongation and action potential are out of scope.

Work Package 7: Liver

The liver is arguably the most-studied target organ for drug-induced injury and along with heart, a major target organ for compounds terminated during development or after approval. There has been extensive work on PKPD models for drug metabolism and liver function in a variety of disease states. However, to date, 'omic data have not been incorporated into these models and methods are lacking to incorporate the wealth of transcriptomic data available from nonclinical models into deterministic models. In part, this can be attributed to our inability to reduce the dimensionality of 'omic data in ways that assist in modelling biological and biochemical processes and their impact on disease networks. The overarching goal of this work stream is to adapt existing models of liver function, injury and drug clearance into models that will accommodate more probabilistic 'omic inputs. It is envisioned that progress will lead to the identification of new models and biomarkers that will help predict and manage the occurrence of drug-induced liver injury.

Suggested deliverables:

1. Incorporate 'omics, e.g. transcriptomic, proteomic, and metabonomic datasets, into existing models for liver function with emphasis on:
    - ability to identify cellular networks associated with specific functional changes and integrated stress responses to injury;
    - ability to translate from nonclinical to clinical models and capture elements of species differences is desirable.
2. define sets of biochemical/cellular parameters, either invasive or non-invasive, that help map the trajectory of drug-induced liver injury and recovery from acute and chronic injury. Biochemical/cellular parameters might include measurements relevant to drug toxicity (oxidative stress, mitochondrial function, etc.), and the role of individual cell compartments, e.g. stellate cells, biliary epithelial, etc., along with biochemical measures of fibrosis and inflammation, etc;
3. models that can predict differences in hepatic injury between normal individuals and patients with co-morbidities such as diabetes by accounting for differences in metabolism;
4. it is desirable to link biochemical changes with measures of hepatic function such as drug clearance and biliary elimination in both nonclinical and clinical models.

Building physiological- or biochemical-based deterministic models from scratch is out-of-scope. Applicants are sought who have experience building liver models and computational biology expertise necessary to incorporate new types of data. It is understood that there are well developed PBPK modelling efforts already underway for liver, e.g. DILIsim and SymCyp. Proposals that can integrate existing commercial models into the project either through existing collaborations or new proposed collaborations are in scope.

Work Package 8: GI/immune System

Acute gastro-intestinal (GI) toxicity can be a key dose-limiting factor for oncology compounds, which can be severely toxic to the rapidly dividing cells of the intestinal epithelium. GI adverse events can also occur as a consequence of chronic inflammation upon drug treatment. The frequent on-target nature of GI toxicity, especially in the oncology domain, requires approaches that enable the quantitative prediction of the extent of toxicity and kinetics of recovery in humans. This will enable the selection of rational dosing strategies to mitigate GI toxicity. The intestinal epithelium, with its stem cell responses, rapid cell proliferation and differentiation, can also be thought of as a model system for studying drug effects on other such proliferative homeostatic systems (e.g. bone marrow) within the body. Hence mechanistic modelling approaches and quantitative translational approaches developed for this system may be adaptable to other toxicities as well. It is recognized that large datasets of responses for exemplar compounds may not readily be available for this target organ. Hence, this **Work Package** may involve a greater data generation component.

Suggested deliverables:

1. Mechanistic models that account for the proliferation and differentiation of cells in the intestinal epithelium that can be parameterized with species-specific values for cell numbers, cell division rates etc;
2. models that account for the interaction between immune cells and stem cells for predicting inflammation mediated chronic GI toxicity;
3. approaches that link the dynamics of biomarkers (e.g. citrulline) to GI damage and recovery;
4. approaches that incorporate *in vitro* toxicity data generated from *in vitro* 2D and 3D (e.g. gut organoids) for interspecies scaling.

Glossary

AE	Adverse Event
BUN	Blood Urea Nitrogen
DMPK	Drug Metabolism Pharmacokinetic
GI	Gastro-Intestinal
KIM-1	Kidney Injury Molecule-1
NOAEL	No-Observed-Adverse-Effect-Level
PBPK	Physiologically Based Pharmacokinetic
PBPK/PD	Physiologically Based Pharmacokinetic/ Pharmacodynamic
PBPK/TD	Physiologically Based Pharmacokinetic/ Toxicodynamic
PKPD	Pharmacokinetic/ Pharmacodynamic
QST	Quantitative System Toxicology
WGCNA	Weighted-Gene Co-Expression Network Analysis

References

[1]:Zhang B, Horvath S. A general framework for weighted gene co-expression network analysis. Stat Appl Genet Mol Biol. 2005;4 :17

[2]:Zhang JD, Berntenis N, Roth A, Ebeling M. Data mining reveals a network of early-response genes as a consensus signature of drug-induced in vitro and in vivo toxicity. Pharmacogenomics J. 2014 Jun;14(3):208-16

[3]:Workshop NIHSQuantitative and Systems Pharmacology in the Post-genomic Era: New Approaches to Discovering Drugs and Understanding Therapeutic Mechanism

[4]:WGCNA webpage UCLA

[5]:Adverse Outcome Pathways (AOP) approaches from the OECD

[6]:Catlett NL, Bargnesi AJ, Ungerer S, Seagaran T, Ladd W, Elliston KO, Pratt D. Reverse causal reasoning: applying qualitative causal knowledge to the interpretation of high-throughput data. BMC Bioinformatics. 2013; 14:340

[7]:Snelder et al, Br J Pharmacol, 2014

Topic 2: Establishing impact of RSV infection, resultant disease and public health approach to reducing the consequences

Topic details

Topic code	IMI2-2015-06-02
Action type	Research and Innovation Action (RIA)
Submission & evaluation process	2 Stages

Specific challenges to be addressed

Human respiratory syncytial virus (RSV) is a ubiquitous pathogen that impacts individuals at high risk of respiratory complications, mainly infants and the elderly.

RSV affects almost everyone worldwide early in life [1] and it is the most common source of severe respiratory illness in infants and children worldwide [2]. In the developed world, RSV is the most frequent reason that children are hospitalised during the winter months, but the problems and consequences of RSV infection are a global phenomenon.

In later life, RSV can represent a significant burden. Data relating to elderly and other at-risk populations is, however, limited, and this project will seek to address some of the challenges in terms of poor data in these important groups.

While exposure to RSV for otherwise healthy individuals normally yields largely mild symptoms and induces partial immunity, RSV is the attributable cause in 22% of all acute lower respiratory tract infections [3]. Infection can lead to acute episodes of bronchiolitis and pneumonia; causing unplanned physician visits, emergency room attendance, hospitalisation and, in a few cases, mortality. An estimated 3.4 million episodes of RSV require hospitalisation globally each season, with 66 000-199 000 deaths per year, largely in developing countries [3]. Furthermore, early infection and bronchiolitis caused by respiratory syncytial virus increases susceptibility to allergic asthma (38.4% vs 20.1% in a control group) [4,5] and is associated with wheezing.

The ability to identify RSV-infected individuals at increased risk of developing severe disease, or those with long-term chronic sequelae from early RSV infection, would greatly add to supportive care decisions or treatment options (especially as new antivirals become available). Other disease areas have identified biomarkers that can segment infected populations based on risk, and there is certainly a need in RSV to identify correlates of severe disease in order to recognise and treat those individuals at increased risk early on. Such correlates could also be used to support vaccine development as a means to objectively classify disease severity during clinical trials.

The short term consequences of RSV, together with putative longer term susceptibility to allergic asthma or wheezing, place a high resource and economic burden on healthcare systems and represent an area where vaccination may yield substantial system benefits in addition to individual level health benefits.

Despite the global impact and ubiquitous nature of RSV infection, estimates of the epidemiology and the burden associated with RSV are based on limited data and are often derived from reported cases rather than a full assessment of the disease and its consequences. Under-diagnosis, misreporting (coding) of disease and limited understanding of RSV limit the validity and utility of these estimates, preventing evidence based policy making and appropriate R&D investment in at risk populations.

Need and opportunity for public-private collaborative research

This project will address the need for a new way for public and private sectors to collaborate to ensure that valid and robust data relating to RSV is generated, analysed and communicated.

Incentives for the development of robust sources of data are today limited by the lack of funding for the prevention and treatment of RSV infection, classification of disease severity and prediction of long-term sequelae. Healthcare systems have little ability or incentive to identify RSV-induced events without the ability to act to prevent or offset the costs and healthcare consequences. Commercial agencies (the industry) are working to create new alternative preventative therapies, such as more widely available vaccines, but development is hampered by a poor understanding or ability to predict disease outcome, particularly in the very young or elderly and adult-high risk population, and insufficient investments in public health beyond the scope and budget for these programmes. **This project aims to align and understand the unmet needs in public health and** to develop a shared platform of knowledge with which to map out the disease and its sequelae and to identify the direct and long-term burden on healthcare systems.

A collaborative approach is required to establish a broad consensus on the impact of RSV and to rally both the industry and policy makers to change the treatment of this much-ignored disease. An IMI-based approach could ensure that different perspectives, and a wide range of different evidence sources, are gathered and synthesised. As described below, different stakeholders need to be involved in this public private partnership in order to secure its successful development and implementation:

Function	Contribution
Public Health	Establish priority and burden associated with RSV (including epidemiology and cost/disease burden) and initiatives to prevent and treat RSV
Industry – Big pharma and SMEs, including external investors such as venture capital funds	Establish at-risk populations, build evidence base to establish cost effectiveness of alternative treatment and prevention options. Develop specific data to support R&D decisions
Academia	Advance current research into RSV and establish unique data sources for further analysis
Clinical societies	Provides the clinical description of the need for prevention and treatment of RSV
Government, payers, & EU member states	Develop evidence base for the assessment of preventative approaches and treatment of RSV
Patients / Society	Develop and communicate the impact of RSV from the perspective of the patient and overall benefit to public health and society

Scope

This project will develop a detailed understanding of the clinical, economic and social impacts of RSV infection in infants, the elderly and other high risk populations. The collated data will drive new approaches to the prevention and treatment of RSV and its consequences and give a better understanding of the resource requirements and costs associated with RSV. Required outputs will address the following challenges:

- Lack of clear understanding of the public health need in RSV and the prioritisation of RSV;
- lack of a shared and robust understanding of the burden of disease and costs associated with current non-treatment and prophylactic approaches;

- lack of well-articulated incentives to conduct research into the prevention of RSV;
- lack of clear predictability or classification of disease severity and long-term consequences to aid in treatment and vaccine development.

Other pathogens that have similar disease burden and overlapping epidemiology where a public-private collaboration would help further understanding may be considered in scope and may include organisms such as rhinovirus, cytomegalovirus, hMPV or Group B *streptococci*.

Expected key deliverables

General:

- Create a multi-disciplinary, multi-stakeholder community with an in-depth comprehension of the burden of RSV on healthcare systems and societies. Assess synergies involved to study other pathogens depending on potential partner core capabilities and interest;
- inventory of available initiatives, knowledge and past and present efforts to increase our understanding of RSV;
- generate an analysis of the direct and indirect costs associated with RSV infections and avoidable costs including an analysis of important subgroups (infants, the elderly, other higher risk groups);
- provide for transparent reporting on data and analyses on RSV infection (burden, costs, etc) generated in the project, including transparency regarding the choice of respective data sets; the choice, structure and assumptions of the economic model and on any other assumptions to create consensus on the need for action to prevent RSV;
- improve linkage between public health perspectives on management of RSV and incentives for R&D investment;
- leverage existing cohorts and epidemiology networks, or establish new ones, to explore biomarkers associated with:
    - the severity of disease and long term sequelae;
    - protection from disease or re-infection;
    - outpatient and inpatient comparison;
    - the contribution of co-infections to disease severity;
    - the composition of the microbiome related to disease severity.

Data and future research platforms:

- Develop robust sources of evidence that can be used to create templates and sources of support for future research into RSV. These should include:
    - a validated and consolidated review of current literature and the evidence currently in the public domain;
    - a database of currently available data including data from surveillance studies, existing registries and other health system architecture;
    - a framework for analysing and aggregating the burden of RSV (including short, medium and long term consequences and costs);
    - a prospectively accrued registry capturing the true incidence of RSV induced events (such as GP attendance, hospitalisations, bronchiolitis, wheeze and asthma);
    - a clear publication and data availability plan to communicate outcomes of the various elements within the project.

Implementation

Provide clear and well documented plans for the communication of the burden of and priorities within RSV, ensuring the understanding of stakeholders. These plans should be tested with and then communicated to key leaders within Member States. Ensure disclosure and transparent reporting of data gained on RSV infection within the project.

Expected impact

Developing a robust dataset will give greater insight into RSV and its impact and costs and lead to better treatment and preventative options.

Action is, however, required to address the needs that will be identified and to create policy changes to improve outcomes and reduce the impact (financial and clinical) of RSV infection.

Potential synergies with existing Consortia

The project should develop synergies and explore collaboration with existing consortia and other relevant initiatives in order to avoid duplication of efforts. In particular, the project should attempt to build on previous initiatives both sponsored by National Governments (such as the Danish registry), industry sponsored initiatives (including existing registries relating to outcomes in previously vaccinated high risk individuals such as CARESS) and healthcare databases (claims and other databases).

Industry Consortium

- AstraZeneca (leader)
- Pfizer
- GSK
- Sanofi Pasteur
- Janssen

Indicative duration of the project

The indicative duration of the project is 60 months.

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

Such further work would be the natural progression of the project leveraging any success achieved. Building on these prior successes and positive results would maximise the long term impact of the larger project. Any proposed project extension would also take advantage of already established collaborations and networks forged in the overall project, thereby maximising efficiency on time and resources. A restricted Call would achieve this in the most efficient way. The detailed scope of the Call shall be described in the relevant Annual Work Plan.

Indicative budget

The contribution from the EFPIA participants is estimated at approximately EUR 14 500 000 and the IMI2 JU contribution will be up to EUR 14 500 000. However, the project's final budget may be lower depending on the

amount of data and resources that will be identified in the Full Proposal and that can be made available to the project (i.e. that will therefore not generate cost).

Applicant consortium

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

The applicant consortium is expected to address all the objectives as listed under the suggested Work Package and make key contributions to the defined deliverables in synergy with the industry consortium. Specifically the applicant consortium should offer at the minimum the following, originating in academic institutions, public health bodies and policy makers:

Work Package 1: Literature Review on RSV and the current perceptions on burden of disease

- ability to assemble and coordinate multi-stakeholder discussions;
- experience with systematic literature reviews and the consolidation of evidence from multiple data sources;
- experience with public health issue management and communication of key public health messages;
- experience of healthcare resource modelling and economic analyses.

Work Package 2: Consolidation of health care systems data

- ability to establish links with partner organisations to access diverse data sources;
- experience of handling and analysing complex and large data sets from multiple sources;
- understanding of the limitations of historical datasets and approaches to minimise these issues.

Work Package 3: Existing retrospective resource analysis

- ability to establish links with partner organisations to access diverse data sources;
- understanding of healthcare resource data sets and experience of developing financial frameworks;
- experience of developing economic models to address public health policy requirements;
- ability to communicate economic arguments to diverse stakeholder groups.

Work Package 4: Prospective data collection

- experience of the development of observational trials and registries;
- ability to assemble and coordinate multi-stakeholder, multi-country discussions;
- ability to overcome blocks to progress;
- infrastructure to conduct and experience in the analysis of large and complex/evolving datasets.

Work Package 5: Presumed risk factors and biomarkers for RSV-related severe disease and related sequelae

- ability to establish links with partner organisations to access diverse data sources;
- experience with biomarker discovery and assessment including establishing links with disease;

- ability to assemble and coordinate multi-stakeholder, multi-country discussions;
- understanding of epidemiology studies and networks in order to tap into existing cohorts or establish new studies;
- experience testing and analysing complex biomarker data sets.

Work Package 6: Management

- proven project management skills;
- ability to manage stakeholders and resolve blocks;
- proven ability to support and manage communications;
- ability to assemble and coordinate multi-stakeholder discussions.

Suggested architecture of the full proposal

The applicant consortium should include their suggestions for creating the Full Proposal architecture in their Short Proposal taking into consideration the industry contributions and expertise provided below.The below architecture for the full proposal is a suggestion; different innovative project designs are welcome, if properly justified.

Work Package 1: Literature Review on RSV and the Current Perceptions on Burden of Disease

In order to develop a full understanding of the global burden of RSV, the project should firstly capture in a systematic way the findings available within the existing literature worldwide.

The detailed literature survey should extract:

- epidemiology, patient subgroups and natural history of disease;
- clinical consequences of RSV overall and by patient type (in particular elderly and babies/infants and other high risk populations);
- directly observed costs and burden of disease;
- data on RSV transmission and contact studies to support the modeling of RSV transmission across dfferent age groups;
- differences between high, middle and low income countries;
- productivity and further impacts.

These data generated from the literature review, especially data relating to health economic research of RSV infection should be made publically available.

1. Epidemiology, patient subgroups and natural history of disease

The literature overview should give evidence to estimate the true prevalence range for RSV and its impact on health and social care. This review should take specific account of all at risk groups and subgroups including infants (particularly the premature and those born with heart and lung defects) and older adults.

The review should also take explicit account of the natural history of RSV globally and how this may be affected by climate, social economic setting, and of monitoring and prophylaxis.

2. Clinical consequences of RSV overall and by patient type (in particular elderly and babies/infants and other high risk populations)

The review should also explicitly address the challenge of understanding the direct short, medium and long term impacts of RSV infection by both severity of infection and the patient group infected. Within this evidence for the links between RSV and incidence of potentially associated outcomes should be explored, including:

- bronchiolitis and other acute respiratory disorders;
- hospitalisation, primary care and other healthcare resource usage;
- wheeze and asthma;
- comorbidities, bacterial or viral coinfections, frailty;
- secondary bacterial infections;
- other outcomes.

Putative links should be explored and a consolidated view of the impact of RSV established.

3. Directly observed costs and burden of disease

A literature review should be undertaken to understand the global and national costs and resource impact of RSV. This review should explore the costs of both short and long term effects of RSV as well as current protocols for the avoidance of RSV infection or of prophylaxis.

4. Productivity and further impacts

Finally, explicit research should be undertaken to establish the productivity and societal effects of RSV infection. These should review the estimated impact on days of work lost both directly (i.e. by the infected population) and in days lost caring for infected individuals.

Industry Contribution:

The industry has substantial experience in developing approaches to data and identifying epidemiological and resource usage trends. Pharmaceutical companies also have expertise to offer in analysing data relevant to infectious diseases, prophylactic approaches and healthcare resources.

Work Package 2: Consolidation of Health Care Systems Data

Work Package 1 develops a framework with which to understand the costs and consequences of RSV and a full understanding of the current published knowledge base. Work Package 2 builds on this by bringing together data from diverse sources (both surveillance records at the national and regional level and existing registry, observational and healthcare system data) to establish a detailed estimate of:

- real world incidence of RSV related healthcare consequences (as described by Work Package 1);
- treatment pathway for patients requiring intervention following RSV infection;
- current practices in terms of prophylaxis and the impact of these at the individual and population level.

This Work Package will build on the identified trends and causalities identified in Work Package 1 to strengthen evidence of the real life consequences of RSV infection.

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

It is likely that a stepwise approach will be required: firstly, identifying robust key data sources from critical regions and countries and aggregating elements of the data to establish a core data set; followed by the identification and addition of further data sources from other markets; finally, communication of the identified data to key stakeholders and policy makers, together with identified gaps and the need for future data, is needed.

Data collected from the above mentioned sources should be made publically available.

Industry Contribution:

The industry has related experience in the analysis and aggregation of large data sets from diverse settings. This knowledge would be applied to assist in the identification of potential data sources, establishment of links between sources of data (including overcoming barriers to the transfer of data) and creation of clear analytical plans.

Work Package 3: Existing retrospective resource analysis

Concurrently with Work Package 2, an establishment of the historically observed cost and resource consequences of RSV infection will deliver a clear picture of the need for action and prioritisation of RSV treatment or prophylaxis.

Specifically, alternative approaches should be taken to establish and populate mathematical models of healthcare resource use that may include:

- directly observed resource use and costs from existing registries and databases (for example, GPRD and claims datasets);
- imputed total resource requirements using reference costs and observed effects identified in Work Package 1 and Work Package 2;
- modelled outcomes and costs.

Outcomes should be presented to fully understand historical estimates of the healthcare resource impact of RSV across different at risk groups to assist in the development of clear policies towards RSV, the identification of populations at greatest risk and of highest cost, and for the identification of opportunities for R&D to establish new preventative treatments for RSV infection in areas of the highest unmet need. The choice of respective mathematical models of healthcare resource use and other economic models or potential alternatives generated in this WP should be explained and justified and made publically available.

Industry Contribution:

The industry has related experience in the analysis and aggregation of large data sets from diverse settings including economic modelling and healthcare resource utilisation. This knowledge, together with strong links across academic centres, would be applied to assist in the identification of potential data sources, establishment of links between sources of data (including overcoming barriers to the transfer of data) and creation of clear analytical plans models of the financial consequences of RSV infection.

Work Package 4: Prospective data collection

Having established the historical trends of RSV impact across both clinical outcomes and healthcare systems, it is anticipated that a large and multi-centre, multi-country observational or surveillance study will be required to fully understand the real world impact of RSV and to overcome the biases in historical data sources including:

- underreporting of incidence due to lack of healthcare attendance (particularly in some regions/countries);
- underreporting of effects due to lack of appropriate diagnosis or coding;
- overreporting of effects due to patient selection from very high risk;
- under- and over- reporting of healthcare resource uses due to the biases above.

A prospective approach should be developed to overcome these biases and to review subjects (in all risk categories and potential patient sub-groups) including:

- premature infants and those born with lung and heart conditions;

- the elderly;
- other patients at risk of developing severe RSV infections (others than babies and elderly);
- those vaccinated against RSV infection.

These prospective studies (surveillance) should cover appropriate time periods such that long term disease sequelae aspects can be also captured.

It is anticipated that, to drive changes in policy and to establish a clear imperative for further research and prevention of RSV, data will be collected, collated and analysed centrally and reported through a number of different channels including annual reports, manuscripts, communications to policymakers and key stakeholders in member states, data will be made available to all involved parties for further analysis.

Industry Contribution:

The industry has strong capability and experience in developing partnerships across academic centres to further research and establish multi-centre activities such as registries. The industry can also contribute to the development and dissemination of materials, particularly to stakeholders and policy makers within specific geographies.

Work Package 5: Presumed risk factors and biomarkers for RSV-related severe disease and related sequelae.

1. *Literature review*

In order to develop a full picture of the potential biomarkers known to date, the project should thoroughly collect and review the available data existing within published and un-published sources.

The detailed review should capture

- all published pre clinical and clinical biomarkers associated with severe disease and subsequent sequelae;
- immunogenicity and viral load data where available;
- all available unpublished data from epidemiology studies, vaccine trials, and other clinical settings, both inpatient and outpatient;
- a consideration of optimal animal models for pre clinical development.

A synopsis of the data should then be carried out in order to better understand the links between putative biomarkers and either protection against infection/disease or the development of severe disease and subsequent sequelae. From this work stream hypothesized biomarkers could be identified to support subsection 2) and the exploration of new biomarkers for RSV infection and disease.

Industry Contribution:

The industry has strong capability and experience in assessing literature and establishing hypothesis driven biomarker discovery. This knowledge would be applied to assist in the identification of potential biomarkers and establishment of links with severe disease. The inclusion of unpublished data from industry and academia would greatly assist in the development of strong links.

2. *Exploration of new biomarkers associated with protection and disease severity and long term consequences of RSV infection*

To support this work,existing samples and their associated clinical data will be shared and/or stored in a physical or virtual bio bank (data base) from past or ongoing epidemiological studies or through establishment of newly designed and initiated studies to investigate:

- the biomarkers associated with protection against or severity of the disease in i) infants, ii) children and iii) elderly populations;
- the risk of developing long term sequelae (wheezing, asthma) after RSV infection;
- samples of interest like serum (and plasma), nasal swabs/washings, sputum, peripheral blood mononuclear cells (PBMC), stool;
- the performance of these samples on assays such as, virus neutralisation assay (VNA), antibody binding (ELISA), antibody epitope mapping, viral and bacterial diagnostics, transcriptome analysis, intracellular cytokine staining (ICS) and microbiome analysis.

The identification of new biomarkers should include both a holistic approach and a more targeted one that will be designed according to observations and hypotheses generated in **Work Package** 6 subsection 1.

Industry Contribution:

The industry has related experience in establishing surveillance and epidemiological studies and the testing, analysis and aggregation of large data sets from diverse settings. This network, together with strong links across academic centres, would be applied to identify and/or validate biomarkers in samples obtained from existing or new epidemiology studies, establish testing approaches and perform data analysis.

Work Package 6: Management

Overall coordination of the project is key, given the inter-connectedness of all Work Packages. A multi-disciplinary, multi-stakeholder community with an in depth comprehension of the intricacies of complex data collection, analysis and communication together with the ability to coordinate across multiple geographies will be the key mechanism to achieve this coordination. This community should meet regularly throughout the project to ensure continued collaboration and progress against goals. Work Package 6 encompasses this element of the work, together with the administrative tasks involved with managing the project.

Industry Contribution:

Project/Alliance Management personnel, meeting facilities, communication expertise.

The consortium is expected to have a strategy on the translation of the relevant project outputs into regulatory, clinical and healthcare practice. A plan for interactions with Regulatory Agencies/health technology assessment bodies with relevant milestones and 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.

Glossary

ELISA	Enzyme-Linked Immunosorbent Assay
GPRD	General Practice Research Database
ICS	Intracellular Cytokine Staining
PBMC	Peripheral Blood Mononuclear Cells
RSV	Human Respiratory Syncytical Virus
VNA	Virus Neutralisation Assay

References

1. Virus Research 162, Issues 1–2, December 2011, Pages 80–99
2. The Lancet Volume 375, Issue 9725, 1–7 May 2010, Pages 1545–1555
3. *Nature Medicine* **18**, 1525–1530 (2012) doi:10.1038/nm.2896
4. Pediatric Allergy and Immunology Volume 16, Issue 5, pages 386–392, August 2005

Introduction to the IMI2 Big Data for Better Outcomes Programme (Topics 3 & 4)

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, and
- digital and other solutions that increase patient engagement.

Programme structure

The programme is expected to 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 Action (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 Alzheimer's Disease and Hematologic Malignancies topics are launched. A BD4BO Coordination and Support Action (CSA) is expected to be launched in the following weeks and align with the timelines of the current call. The European Distributied Data Network (DDN) and other disease-specific topics are expected to be launched in future Calls.

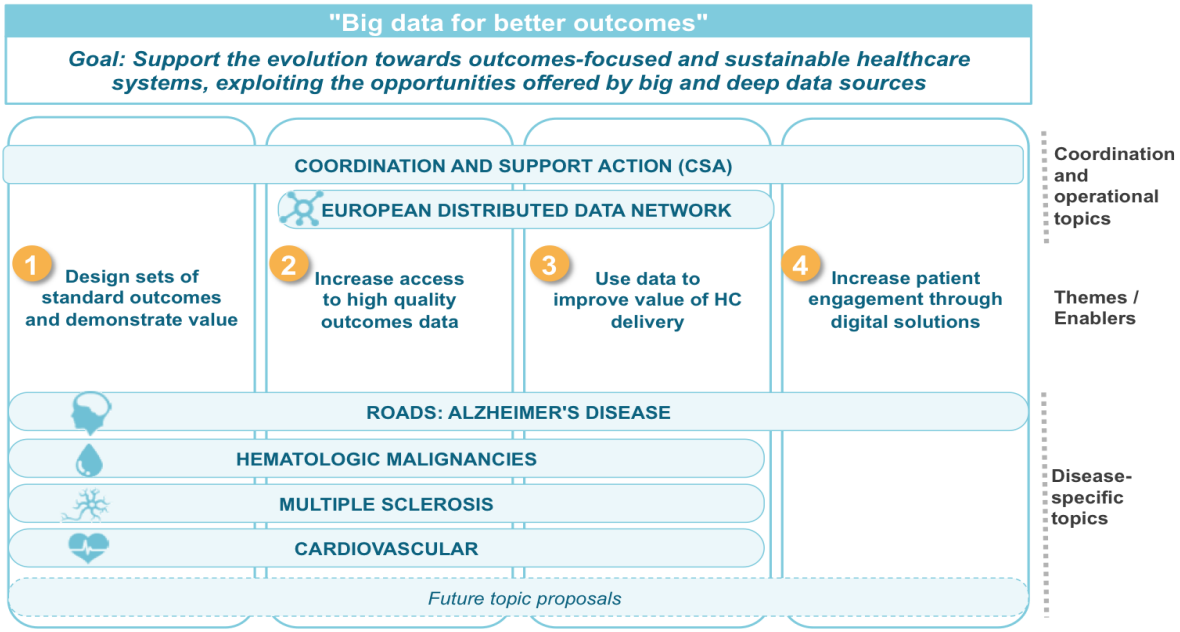


Figure 1: Programme structure, themes / enablers and CSA

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 (incl. 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 bring yield higher quality results, consistency and increased efficiency by avoiding duplication of work.

Two projects, the Coordination and Support Action (CSA), and European Distributed Data Network Project (DDN) will therefore offer service to and complement activities of diseases/therapeutic areas 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 disease/technology consortia will conclude collaboration agreements with the Coordination and Support Action consortium and the European Distributed Data Network consortium that will provide direct advice and support to Therapeutic Areas/Disease projects.

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 the evidence on the enablers of the value based healthcare systems focusing on health outcomes. This health care system transformation would encompass payments, consider value and support aligned incentives between primary and secondary care moving towards the same common goal of superior healthcare delivery and high quality data being made available. Therefore the engagement of patient organizations, 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 research methodologies in line with an outcomes focus.

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

Topic 3: Real World Outcomes Across the AD Spectrum (ROADS) to Better Care

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

Topic details

Topic code	IMI2-2015-06-03
Action type	Research and Innovation Action (RIA)
Submission & evaluation process	2 Stages

Specific challenges to be addressed

Of all age-related illnesses, perhaps none is of greater concern to the society than Alzheimer's disease (AD), the leading cause of dementia. The prevalence of dementia in Europe is expected to increase to 6.9 million in 2020 and nearly 10 million in 2040 in the absence of new, disease-modifying treatments [1] .

AD itself begins years or even decades before the onset of clinical symptoms. Symptoms are often undetected, diagnosis is delayed, and the disease is not managed optimally as access to care is fragmented. A lack of consensus on appropriate outcome measures perpetuates a passive attitude toward care. Ongoing debates regarding the cost-effectiveness of the few symptomatic pharmaceutical treatments indicated for AD highlight the challenges in acquiring and applying relevant, high-quality evidence for key stakeholders to make informed treatment and funding decisions.

Recent advances in biomarkers and genetics are beginning to allow the identification of at-risk individuals in very early stages of AD and should facilitate the development of novel treatments in the future. Technological advances in electronic data collection and management offer the opportunity to develop real world data to facilitate decisions that can be used to improve care.

Significant investments are ongoing to accelerate drug development from the perspective of biomarkers and randomized clinical trial (RCT) designs (e.g., validated endpoints). However, relatively little has been done to facilitate the collection and analysis of high quality real world evidence (RWE).

Many factors prevent the reliable prediction of the natural course of AD in real-world settings:

- lack of consensus on appropriate study designs and endpoints for non-RCTs;
- lack of measures that are transferable across various types of studies/systems (e.g. medical *vs*. social care systems);
- lack of AD-related cognitive and functional measures in medical/claims records that are relevant across the entire disease spectrum;
- lack of clarity on how to best model the natural history of the disease using real world data, particularly as disease stages are difficult to define outside of highly qualified assessment centres or research cohorts.

Innovative Medicines Initiatives (IMI) projects such as European Medical Information Framework (EMIF) and European Prevention of Alzheimer's Dementia (EPAD) address some of the gaps related to combining different types of data (e.g., biomarkers and electronic health records) and identifying patients prior to symptom development. However, none of these international large scale projects thus far have evaluated methods to map the biology/progression of the disease with longitudinal clinical outcomes and resource utilization which could inform cost-effectiveness evaluations and broader assessment of risk-benefit of new treatments and technologies.

The *R*eal World *O*utcomes Across the *AD S*pectrum (ROADS) topic proposes to develop and enhance public-private collaborative research programs to generate AD-relevant health and social care data to provide recommendations on methods and measures to optimize prospective data collection reflecting appropriate AD care and prevention. This first stage of a longitudinal project is aimed at informing a follow-up project to initiate prospective data collection and database improvement efforts.

Need and opportunity for public-private collaborative research

With much of the AD research community focusing on RCTs and operational efficiencies, relatively few efforts are focusing on how AD-related outcomes should be incorporated into a broader health and social care system to inform the natural history of the disease in real world settings. To ensure a successful outcome, these types of efforts are dependent on the collaboration between stakeholders, for example academic groups with expertise in chronic disease where there are no hard endpoints measurements. It also depends on input from data integration and Electronic Health Records (EHR) entities to help design and implement relevant data capture elements. Representatives from reimbursement/regulatory organizations are needed to recommend relevant effectiveness outcomes. Patient, caregiver, and advocacy organizations understand outcomes of relevance to them. The IMI design allows pharma companies to collaborate with academia, payer, regulatory and other important stakeholder partners to prepare health/social care and data systems for emerging new treatments that address the increasing societal burden of AD.

The timing of this topic is ideal given the positive model of other successful public-private collaborations relevant to the ROADS proposal, which may offer insights into study design elements and data capture as well as combining techniques that would be applicable to this work.

Scope

It is critical that current research methods and health-related data systems are evaluated for their ability to increase our understanding of AD across the spectrum of the disease. The ROADS project will therefore first evaluate appropriate outcome measures based on existing data which will later inform a second phase including prospective data generation. Through this process, trial and observational study design decisions can be properly informed, enhancing health care systems to evaluate new treatments as they become available.

The overall objectives of the ROADS to Better Care consortium (phase 1) are:

- Define a minimum set of measurable patient relevant real world outcomes. These outcomes should be aligned among key stakeholders on their relevance for different purposes (e.g. academic research, regulatory, HTA, funding and reimbursement, relative effectiveness assessment, clinical guidelines and optimization of healthcare systems);
- In collaboration with national health authorities, health technology assessment (HTA), and regulatory agencies, develop recommendations on appropriate AD-related cognitive, functional, and behavioural endpoints that can be used across various types of real-world research programs and data systems outside of clinical trials;
- Identify data sources and outline a data strategy (including data aggregation and gaps in data), to characterize the spectrum of AD across disease stages and multiple geographies and identify best practices in collecting real world clinical outcomes;
- In collaboration with patients and caregivers, identify new methods and technologies for incorporation into clinical and social care practice that would facilitate collection of patient/caregiver-centred outcomes;
- Provide recommendations of different approaches to model disease progression depending on data sources to enable better treatment selection and improved health care value for AD;

During the project, data analyses and the generation of hypotheses and modelling will be conducted with existing data from public and private consortia members.

The results of ROADS (first phase) will inform a second separate project (timing to be defined). This second phase will involve prospective data generation which may include, but not be limited to, (a) closing data gaps on AD in real world (b) further develop patient relevant outcomes in real world settings (c) deliver RWE with high quality standards that are recognized and accepted by industry, regulators and HTAs to support the evaluation of emerging AD interventions and (d) help optimize healthcare systems for better AD-related care.

Demonstrating the value of what can be achieved through dataset evaluations and analyses is expected to open the access to additional data sources. This will allow for efficient scoping of what can and should be done to prospectively collect relevant data in the second ROADS phase.

Expected key deliverables

Final deliverables will be determined by the consortium (i.e. including public partners) during the full proposal submission:

1. Define a set of real world outcomes for AD relevant to both patients and caregivers;
2. searchable web catalogue of available data sources (i.e. building on the EMIF platform and experience in data protection but expanding data sources beyond AD biomarkers);
3. evaluation of the suitability to combine data sources for use in natural history and effectiveness research (incl. white paper / publication) that reflects data needs of patients, payers, and providers beyond traditional randomized clinical trials endpoints;
4. integration strategy for multiple data sources and new electronic endpoint proposals (e.g. digital and mobile health solutions / options across clinical and pharmacoeconomic outcomes), aligned with payer/HTA guidelines and expectations;
5. articulation of how digital alternatives such as mobile health applications can play a role in improving the Patient Care Pathway (peer-reviewed publication), potentially including a demonstration project;
6. quantification of drivers of variation and heterogeneity for relevant outcomes / late stage endpoints to inform assumptions related to cost-effectiveness modeling across the spectrum of the disease;
7. transformation algorithm of existing cognitive and functional assessments across the disease spectrum to enable comparison of results;
8. set of statistical functions connecting intermediate instruments measures to predict late stage endpoints from variation in early stage measures;
9. publications on model archetypes that characterize the patient journey across the spectrum of disease using existing data sources to compare methodologies such as Time to event, Markov modeling, Linear Regression and Mixed-effect Model Repeated Measure (MMRM).

Alignment with HTA, regulators, payers and patient organizations is considered critical on all deliverables.

Expected impact

The first phase of ROADS provides an important initial step when building AD-relevant real world data sets that are suitable for answering questions about the natural history, cost-effectiveness, and clinical utility of new and innovative diagnostic and treatment interventions across the entire spectrum of the disease. The current supposed state is of disjointed and fragmented data sources and datasets which are probably sparse in relevant outcomes. We expect the proposed project to provide a road map of aligned outcomes and methods toward building data systems that will enable health and social care systems to efficiently enable initiation, maintenance, and evaluation of the right treatment to the right patient at the right time.

Engagement with HTA/national healthcare bodies, regulators, and patient advocacy groups will ensure that future prospective data collection efforts are relevant to access and reimbursement questions. The ROADS consortium is critical to ensure that the work proposed in its 2nd phase call is realistic in scope, relevant to stakeholder needs, and complementary to ongoing IMI2 and other EU collaborations for better patient outcomes from pre-clinical/early stages of the AD disease.

Collaboration Agreements

To ensure the interactions between the projects under the BD4BO programme, the ROADS consortium will conclude collaboration agreements with the forthcoming BD4BO Coordination and Support Action (CSA) consortium and European Distributed Data Network (DDN) consortium.

The collaboration agreements are expected to include details of the services provided by the CSA and DDN to the ROADS consortium 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.

Potential synergies with existing Consortia

- IMI-EMIF: Build upon databases (i.e. TransMart), informatics, phenotyping and biomarker tools developed as part of IMI-EMIF and incorporate into the ROADS project;
- IMI-EPAD: IMI-EPAD will likely feature risk stratification, clinical-trial ready cohorts and adaptive PoC clinical trials in prodromal and preclinical AD patient populations. This provides additional opportunity to develop and assess outcome measures;
- other organizations and programs that are not disease-specific but that will have relevant outputs include: RADAR (Remote Assessment of Disease and Relapse), MAPPs (Medicines Adaptive Pathways to Patients), Get Real, Green Park Collaborative (GPC), World Health Organization (WHO), OECD (Organisation for Economic Co-operation and Development), CAMD (Coalition Against Major Diseases).
- Furthermore synergies should be considered at the European level with relevant projects supported by the Joint Programming Initiative on Neurodegenerative Disease Research (JPND)[6] and other European research projects/programmes (e.g. RightTimePlaceCare[7], the Active Assisted Living programme[8] and the European Innovation Partnership on Active and Healthy Ageing[9]).

Industry Consortium

- Novartis (leader)
- Eli Lilly and Company (co-leader)
- Biogen (co-leader)
- Roche
- Janssen
- Pfizer
- MSD
- GE Health Care

Indicative duration of the project

While the estimated duration of this ROADS phase 1 project is 24 months, recommendations on alternative timings are welcomed as part of submitted proposals.

6 http://www.neurodegenerationresearch.eu/initiatives
7 http://rtpc.progressima.eu/index.php?id=14215#c83680
8 http://www.aal-europe.eu/
9 http://ec.europa.eu/research/innovation-union/index_en.cfm?section=active-healthy-ageing

Indicative budget

The indicative contribution from EFPIA companies is 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 financial contribution from IMI2 JU will be a maximum of EUR 4 000 000.

Applicant consortium

The applicant consortium will be selected on the basis of the submitted Short Proposal.
Applicants are expected to address all the above objectives in the Short Proposal (within the available duration and maximum IMI2 contribution) and demonstrate a relevant strategy for achieving them, through partnership with the industry consortium.

This may require mobilising as appropriate, expertise in regulatory policy, health technology assessment, payer/national health care system policy, observational/cohort study execution, economic modelling, informatics, statistics, data management and integration, healthcare privacy/ethics, health outcomes, age-related research, clinical research, and electronic medical records. The applicant consortium should include caregiver and patient advocacy organizations Given the short duration of the ROADS phase 1 project, and the necessity for the consortium to work together effectively from the start, applicants should clearly demonstrate that they possess the necessary resources and skills to comply with the proposed project timeline.

The applicant consortium should demonstrate to have already established contacts with some key organizations: such as Health Technology Assessment agencies, national payer organizations, providers, regulatory agencies and patient organisations in relevant Work Package and consultations. The role of these key organizations will be to provide guidance to develop recommendations on appropriate AD-related cognitive, functional, and behavioural endpoints that can be used across various types of real-world research programs and data systems outside of clinical trials.

The applicant consortium should also have the resources available to help manage a project-related website and information-sharing resources. Furthermore, access to real world datasets that include potential relevant outcomes and populations that have not yet been used in this context would be an additional expectation. The ability to engage across multiple geographies is also an expectation, with particular emphasis on countries with influential and highly technical health technology assessment requirements as well as countries that already have well-integrated data sources across different levels of health and social care services.

Suggested architecture of the full proposal

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

A suggested structure for the full proposal is given in this section, and modifications are welcomed as part of submitted Short Proposal. The ‘expected key deliverables’ from above are repeated below as suggestions of how to organise the **Work Package**s.

Applicants should include their proposed expertise and activities for **Work Package** 1, 5, 6, and 7 with the full understanding that these **Work Package** will be fully defined in collaboration with the industry partners at the Full Proposal stage to coordinate optimally with the forthcoming Big Data for Better Outcomes’ CSA.

The consortium is expected to have a strategy on the translation of the relevant project outputs into regulatory, clinical, healthcare and social care practice including informal care and dementia-friendly environments.

Work Package 1: Management and administration

- The overall objective for **Work Package** 1 is to establish a framework for collaboration and ensure minimization of duplicative work and maximization of sharing across the various Work Packages as well as ensure strategic alignment of efforts;
- this **Work Package** will also ensure coordination with the forthcoming Big Data for Better Outcomes CSA and Distributed Data Network (DDN) projects.

Proposed Deliverables:

1. Project planning program detailing bottom-up timeline calculations, resources and critical pathway across Work Packages;
2. Detailed budget estimates versus realised expenses;
3. Meetings planning and participation scheduling;
4. Logistics coordination, agendas and meeting materials support;
5. Writing of minutes and reports, communication of conclusions and documentation archiving.

Industry contribution

Project leadership expertize to ensure Work Packages maintain a clear understanding of objectives as well as providing necessary support to develop solutions when faced with stumbling blocks, maintain focus, momentum and motivation throughout the project duration.

Expected Applicant consortium contribution

1. Project Management Organization (PMO) to run the day to day operation aspects as per proposed deliverables.

Work Package 2: Outcome definition and mapping of RWE data sources

- Define AD-related real world outcomes of relevance to patients and caregivers (e.g. physical, emotional, financial, educational…);
- identify and assess data sources across the disease stages of AD (from pre-clinical to disability, institutionalization and death) that include clinical/health outcomes and economic outcomes (e.g., costs, utilities, QOL) of relevance to HTA / Payers. There should be a focus on outcomes and costs that accrue following the diagnosis of AD. This will enable decision makers to assess the value of a disease modifying therapy by addressing the prolongation of time to AD and its sequelae by a disease modifying therapy (DMT);
- establish guidelines for how to best combine RCT data with pragmatic and EMR-based research into a holistic data package for key decision-makers, building on work done through Get Real Consortium.

Proposed Deliverables:

1. defined a set of target real world outcomes for AD of relevance to patients and caregivers;
2. consensus on what constitutes a meaningful delay in disease progression from both a clinical and economic perspective aligned with relevant stakeholders for different uses (e.g. health economic evaluation, reimbursement, funding etc.);

3. catalogue of available data sources and framework around addressing patient confidentiality concerns as well as data ownership concerns;
4. evaluation of suitability for combining clinical data, claims data, social care data, and other sources (white paper / publication);
5. evaluation of suitability for use in natural history and effectiveness research (white paper / publication).

Industry contribution:

Work package co-leaders, relevant literature reviews, data reviews already completed, technical writing support, relevant information on patient journey, treatment options and outcomes to be measured, analysis on clinical endpoints and their link to outcomes, HEOR analysis to align on relevance of outcomes, workshop facilities and costs, tools to assess quality of data sources, dissemination cost of publications. Consider contributing existing retrospective data or trial data that may not be exploited (e.g. due to trial termination but may include proxy end-points for RWE such as patient reported outcomes, caregiver burden, resource utilization as exploratory end-points).

Expected Applicant consortium contribution:

1. perform literature/database review;
2. expertise on bringing together different stakeholders (eg. patients organizations, clinical practice, regulatory, HTA, Payers) and aligning on relevant outcomes;
3. expertise in chronic disease outcomes;
4. analysis of suitability of outcomes;
5. technical writing support;
6. development of on-line search tool.

Work Package 3: Integration of RWE data

- Integration strategy for multiple data sources and new electronic endpoint proposals (e.g., mapping digital solutions/options across outcomes);
- articulate how digital alternatives can play a role in improving the patient care pathway;
- application of recommendations in specified geographies.

Proposed Deliverables:

1. map of data solution options applicable to different real-world outcome measures supporting pharmacoeconomic evaluations (not already addressed by EPAD/EMIF and other IMI or existing consortia efforts);
2. peer reviewed publications on role and good practice of digital applications supporting improvement of the patient care pathway;
3. demonstration project of mobile health solutions based on recommendations in specified geographies.

Industry contribution

Work Package co-leaders providing experts on RWE design and database integration and in-house digital solutions for demonstration projects. Contributing existing retrospective real world data or trial data that may

not be exploited (e.g. due to trial termination but may include proxy end-points for RWE such as patient reported outcomes, caregiver burden, resource utilization as exploratory end-points).

Expected Applicant consortium contribution

1. Mapping of current digital solutions;
2. expertise in data integration;
3. expertise in RWE-related research methods;
4. creation of electronic data modules;
5. technical writing support;
6. analyses of existing data-sets accessed by applicants (e.g. from hospitals, practices, care in the community, financial information, imaging, portable devices, social networks and crowdsourcing).

Work Package 4: Modelling and Simulation

- Develop a disease model for the natural history of AD from preclinical to later stage, using existing data and focusing on real-world outcomes;
- establish guidelines and best practices on combining existing and future data sources to increase the strength of evidence for proposed models of the natural history of AD.

Proposed Deliverables:

1. Analysis Plan;
2. drivers of outcome variation that are relevant to cost-effectiveness and disease modelling assumptions;
3. set of statistical functions connecting intermediate instruments measures to predict late stage endpoints from variation in early stage measures (i.e. defining transformation algorithm);
4. publications on model archetypes that characterize the patient journey across the spectrum of the disease using existing data sources to compare methodologies (i.e. Compare AD models based on different analytical methods);
5. set of hypothesis for the RWE prospective study supporting the second phase.

Industry contribution

Work package co-leaders, modelling expertise, available models, clinical trial expertise on intermediate instruments measures, analytical tools, available transformation algorithms, available statistical functions or work on quantifying drivers of outcome variation, if required prospective data to quantify drivers of outcome variation, dissemination costs of publications.

Expected Applicant consortium contribution

1. Creation of data warehouse/data integration tool;
2. execution of observational research, experience in combining clinical and real world data sources;
3. develop a model of disease progression;
4. expertise in health economic modelling;
5. data analyses of existing data-sets accessed by applicants.

Work Package 5: HTA & regulatory agency integration

- Position current regulatory / HTA sources of advice on AD study design / outcome measures and current limitations;
- regulatory / HTA position on relevant key AD outcomes measures and (in partnership with Work Package 2)
- regulatory / HTA position on relevant evidence requirements to support regulatory / HTA (re)assessments (in partnership with Work Package 2/3);
- position on the role of diagnostics / biomarkers on patient outcomes, diagnostic accuracy and cost of resource utilisation in future regulatory / HTA agency interactions;
- incorporate impact of diagnostics/biomarkers on patient outcomes, diagnostic accuracy, cost of resource utilization.

Proposed Deliverables:

1. regulatory / HTA expert panel to inform and evaluate Work Package plans and output;
2. face-to-face meeting with relevant stakeholders;
3. white paper/publications to guide second stage of ROADS.

Industry contribution

Provide expertise in developing proposals and recommendations to gain HTA & regulatory acceptance including writing of briefing-books as well as presentations of positions and supporting arguments on behalf of the consortium.

Expected Applicant consortium contribution

1. Recruitment of relevant HTA/regulatory experts;
2. experience with appropriate venues/consultancy options with payer/regulatory groups;
3. technical writing support.

Work Package 6: Communication and Patient/Healthcare Provider Engagement

- Develop communication strategy for information flow across Work Packages, with other related IMI projects and with external consortia and initiatives;
- identify appropriate and novel means of disseminating findings from Work Packages to relevant stakeholders, especially patient groups and relevant professional organizations;
- connect data sources and provide data access for different users (in collaboration with BD4BO Distributed Data Network and other IMI efforts);
- coordinate and facilitate in-person meetings for ROADS consortium.

Proposed Deliverables

1. Input into evaluations of different work packages;
2. provide data access for different users;
3. communication plan.

Industry contribution

Work package co-leaders, travel support, writing/social media support, facilitation of contacts with advocacy/professional organizations. Coordination of interactions and integration of data sources with the BD4BO Distributed Data Network systems, coordination of data access across different users.

Expected Applicant consortium contribution

1. Dissemination of key findings;
2. resources to create communications in various formats (i.e. Configure data sources and access to connect to the BD4BO Distributed Data Network);
3. forum for gathering patient and healthcare provider input.

Work Package 7: Ethics and Legal

- Advise Work Package on ethical and legal implications of proposed recommendations;
- partner with Work Package to make sure ethical issues and patient/caregiver-focus are central to discussions;
- ensure coordination with the Big Data for Better Outcomes' programme;
- ensure awareness and responsiveness to EU legislation that impacts data usage (e.g., privacy laws, data portability laws).

Proposed Deliverables

1. Input into evaluations of different work packages;
2. white paper/publications;
3. guidance on addressing patient confidentiality concerns as well as data ownership concerns.

Industry contribution

Work package co-leaders providing technical-writing support, dissemination, cost of publications and coordination with the BD4BO programme.

Expected Applicant consortium contribution

1. Expertise in applicable laws and ethical principles of human subjects research and data sharing, technical writing support.

Glossary:

AD	Alzheimer 's Disease
BD4BO	Big Data for Better Outcomes
CAMD	Coalition Against Major Diseases
CSA	Coordination and Support Action

DDN	Distributed Data Network
DMT	Disease Modifying Therapy
EFPIA	European Federation of Pharmaceutical Industries and Associations
HER	Electronic Health Records
EMIF	European Medical Information Framework
EMR	Electronic Medical Records
EPAD	European Prevention of Alzheimer's Dementia
GPC	Green Park Collaborative
HTA	Health Technology Assessment
IMI	Innovation Medicines Initiative
MAPPs	Medicines Adaptive Pathways to Patients
MMRM	Mixed-effect Model Repeated Measure
OECD	Organisation for Economic Co-operation and Development
PMO	Project Management Organization
QOL	Quality of LifeRADAR – Remote Assessment of Disease
RCT	Randomized Clinical Trial
ROADS	Real World Outcomes Across the AD Spectrum
RWE	Real World Evidence
WHO	World Health Organization

Reference

[1] Liara Rizzi et al, BioMed Research International, Volume 2014, Article ID 908915, 8 pages.

Topic 4: Development of an outcomes-focused data platform to empower policy makers and clinicians to optimize care for patients with hematologic malignancies

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

Topic details

Topic code	IMI2-2015-06-04
Action type	Research and Innovation Action (RIA)
Submission & evaluation process	2 Stages

Specific challenges to be addressed

Hematologic malignancies (HMs) account for about one-third of cancer cases in children and about one-third of cancer deaths. They include a number of different pathologic conditions affecting all ages, although several diseases are more common in the elderly. For the purpose of this project, in order to maximize the focus of resources, the consortium will focus on disease areas with high unmet need: non-Hodgkins lymphoma (NHL), acute lymphoblastic leukemia (ALL), acute myeloid leukemia (AML), chronic lymphocytic leukemia (CLL), multiple myeloma (MM) and myelodysplastic syndrome (MDS). Despite recent improvements in treatments and in survival rates, a significant proportion of patients will relapse and require further lines of treatment. In addition, as recent advances have improved duration of survival, the quality of life during and after treatment is an increasing key focus of treatment development.

The biopharmaceutical industry in partnership with academia is on the cusp of delivering breakthrough solutions in HMs through innovations such as immune-modulatory approaches, with early trials demonstrating unprecedented response rates in patients with great unmet needs. The urgency of bringing these life-saving technologies with speed and efficiency to patients, who otherwise have no options, is clearly recognized and validated through special designations from the regulatory bodies.

Due to the rarity of the conditions and the diverse healthcare practice across EU, current healthcare systems are challenged with (1) lack of definition and alignment on outcomes that are relevant to all stakeholders and patients with HMs in particular, (2) policy makers having limited benchmark data to evaluate the risk/benefit ratio and value, (3) personalised medicine allowing for more focused treatment options thus increasing the difficulty of demonstrating the risk/benefit in the real world in rare diseases, (4) clinicians having to make treatment choices based on short-term, surrogate and often not comparable data, (5) patients not having access to the right treatment at the right time, and (6) payers having the need to make reimbursement decisions on life prolonging options with limited data and finite budgets. For example, a search of the latest studies of patients with HM who underwent stem cell transplantation reveals several studies with rather small sample sizes and disparate outcomes measures that make it challenging to arrive at conclusive outcomes and benefits.

Need and opportunity for public-private collaborative research

Most healthcare (HC) stakeholders are aware of the need to define and measure standard outcome measures especially for rare and orphan medical conditions. Collaboration across different stakeholders is needed to define standard sets of outcome indicators that should always be measured and ensure these are used for decision-making by key healthcare systems stakeholders (e.g. clinicians to select most appropriate therapies, policy makers for risk-benefit assessments, understanding of the short and long term risk/benefit profile, etc.).

First, outcomes identification and definition requires participation not only of patients who suffer from HMs, but also of relevant experts to ensure that all treatment options, including advanced therapies, are considered and relevant risk factors are understood. That includes physicians from different specialties and countries, academics, researchers and database experts. Furthermore, longer term outcome indicators, such as mortality, are often too inefficient to use for decision making and intermediate clinical surrogate markers correlated to those outcomes are required for efficiency (e.g. to identify the need to change treatment early, predict drug impact on outcomes in the real world). Pharma companies are key stakeholders who rely on these defined clinical endpoints to develop and deliver on pre-defined outcomes.

Next, collaboration among HC systems stakeholders is also necessary to capture and aggregate data, analyze it and extract relevant insights. Bioinformatics is maturing in responding to the needs of large-scale data analysis and interpretation, by implementing a common ontology, preserving data linkage and combining relational and non-relational data sets. These can allow researchers, clinicians and policy makers to make real-time, evidence-based decisions on a much larger data set to optimize outcomes for patients, institutions and governments.

In addition, the European Commission, academia and industry have already invested significantly in the field of HM and progress has been made in creating a network of European registries (European Leukemia Net), the standardisation of European and International diagnosis, data sets and tissue banks, and various disease specific registries across the EU or within an individual country. The project will benefit from the public-private partnership to continue this approach for future research in HM.

Finally, engagement of payers, providers and regulators will ensure these outcomes and clinical endpoints are really measured and leveraged by clinicians and policy makers to optimise decisions on care, value based assesments, reimbursement and patient access.

Scope

Key objectives include:

- define standard sets of outcomes for HMs that are relevant and meaningful to patients and clinicians in order to be used in real world and to provide an understanding of how to measure, more consistently, data on HMs:
    - this will be completed in collaboration with National Health Authorities; Health Technology Assessment Bodies (HTAs); regulatory agencies; payers; providers; local and international guidelines; professional bodies within this specialty; and patients;
    - this will allow for alignment on relevance of different outcomes for different uses (e.g. clinical decisions, reimbursement, value assessment, etc.);
    - may include patient reported outcomes and long term risk/benefit profile;
- communicate and support the use of the defined standard outcomes data sets on selected HMs, including ALL, NHL, AML, CLL, MM, and MDS, to support future data collection so that data is available, comparable and interoperable across European countries. This will be complemented with identification of best practices in linking the data sources including data on inpatient and outpatient care as well as considering the collection of information directly from patients on their quality of life and life style factors;
- develop a data sharing platform that empowers clinicians and policy stakeholders to improve decision making and provide appropriate treatments to patients with HMs;
    - allow for rapid and continuous access to implement a common data model across the different data sources;
    - identify and provide a data governance framework addressing concerns such as data privacy, data quality, ownership and access rights to support research;
- propel key medical and policy initiatives through fact based decisions from much larger and diverse data sets that have been harmonized and queried by medical and non-medical experts. Proactively design data platform standards that allow a streamlined path to real-world health data including molecular level profiling - for both the provider and patient;

- outline a plan to ensure sustainability of the platform beyond the lifetime of the proposed project;
- ensure the partnership collaborates with and builds on other IMI projects such as the Electronic Health Records Systems for Clinical Research (EHR4CR) and the European Medical Information Framework (EMIF), and projects under the IMI2 Big Data for Better Outcomes (BD4BO) programme such as the Coordination and Support Action (CSA) and the Distributed Data Network (DDN).

Expected key deliverables

Deliverables are expected to cover the 3 objectives for selected HMs: (1) definition and alignment on outcomes to be measured (2) harmonization of data capture and (3) development of a platform for data aggregation and analysis. The final deliverables will be agreed jointly by the Industry consortium and the successful applicant during the preparation of the Full Proposal and are likely to include the following:

- set of standard outcomes, clinical endpoints and patient centred quality of life that should be measured for selected HMs, including ALL (pediatric and adult), NHL, MM , AML, CLL, and MDS;
- set of standard and exploratory molecular tests that should be performed for selected HMs (as detailed above);
- alignment of key HC stakeholders (patients / professional bodies and associations / payers / regulators / HTAs / providers / experienced database experts) on the relevance of different outcome indicators for specific usages (e.g. approvals, benefit/risk and clinical value assessments, reimbursement, etc.);
- mapping of potential data sources across EU that could be useful for the scope and purpose defined;
- description of methods and tools for data capture for required outcomes measures identifying current overlaps and gaps for each data source (including patient centric outcomes);
- strategy on the assessment of data quality, and data curation for integration of data sources;
- harmonized quality, technical and governance standards for data capture;
- creation of large, harmonized data sets that form a repository of HM data for exponential types of queries over and above what each original data set was designed to deliver individually, queries include but are not limited to;
    - understanding of the current unmet need in HMs;
    - prediction of patient outcomes based on treatment practice;
    - complications associated with treatment and comorbid conditions;
    - standardized metrics of what will be measured as the outcomes' endpoints for evaluation in the future;
    - health economic outcomes research (HEOR; including patient reported outcomes, PRO) considerations and associated costs;
- establishment and development of a pan-EU framework to value and evaluate health outcomes achieved with innovative therapies for HM.

Harmonization with HTA, regulators and payers will be considered to gain advice and alignment on all recommendations. Frequent engagement and in-person symposia with representatives of agencies responsible for granting patient access and reimbursement decisions will be needed.

Expected impact

Anticipated benefits for patients, healthcare providers and manufacturers:

- improved clinical development based on clear definition of endpoints, outcome measures and aligned Industry, HTA and EMA requirements leading to consistent assessments across EU;

- better understanding of the natural history of the disease and data to enable giving the right treatment to the right patient at the right time;
- ability to prove the value, safety and effectiveness of innovative therapies for HMs;
- faster patient access to innovative therapies as soon as these are registered;
- results of proposed IMI project with regard to definition and measurement of outcomes should serve as base for similar projects in other regions and for future evolving advanced therapies.

Collaboration Agreements

To ensure the interactions between the projects under the BD4BO programme, the Hematologic Malignancies consortium will conclude collaboration agreements with the forthcoming BD4BO Coordination and Support Action (CSA) consortium and European Distributed Data Network (DDN) consortium.

The collaboration agreements are expected to include details of the services provided by the forthcoming CSA and DDN to the Hematologic Malignancies consortium 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.

Potential synergies with existing Consortia

The consortium will ensure to leverage all expertise, knowledge and evolving evidence from past and current consortia such as IMI GetReal (Inclusion of real world data into development programmes), EMIF and EHR4CR (data aggregation). Expertise within the PARENT initiative could also be leveraged during the project to support the definition of outcomes and how to measure them.

Industry Consortium

- Novartis (lead)
- Celgene (co-lead)
- Bayer
- Janssen
- BMS
- Menarini
- Amgen

Industry consortium will:

- manage large-scale collaborations and partnerships across geographies and specialties;
- provide relevant data sets (existing & future) on treatments and outcomes in HM;
- bring expertise in the performance of clinical trials in HM with or without involvement of advanced therapies;
- bring expertise in the capture and analysis of outcomes research including Real World Data, biomolecular samples, etc.;
- bring expertise in statistics, in data mining and in merging large data sets from various sources;
- bring expertise in project and result communications, and legal and regulatory requirements relevant to the project.

Indicative duration of the project

The indicative duration of the project is 60 months.

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

Indicative budget

The indicative in kind contribution from the Industry Consortium EFPIA companies is estimated at EUR 20 000 000. Approximately a third of this contribution will be in the form of data that would include but not be limited to prospective data from clinical trials and registries collecting real world outcomes. Due to the global nature of the participating industry partners part of these contribution may be provided from non EU/H2020 Associated Countries.

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

Applicant consortium

The applicant consortium will be selected on the basis of the submitted Short Proposal. Applicants are expected to address all the above objectives in the Short Proposal (within the available duration and maximum IMI2 contribution) and demonstrate a relevant strategy for achieving them, through partnership with the industry consortium.

The applicant consortium is expected to be multidisciplinary and to contribute with patient groups, high level academic scientists, representatives of regulatory agencies, HTA bodies, reimbursement agencies, technology companies and cooperative groups.

The applicant consortium is expected to own, or have the ability to access, patient-level data in each of the diseases of interest. This data should represent a clinical setting such as registries, claims, EHRs, *et cetera*, ideally, from multiple sources to enable the pooling of data for outcomes assessment from a pan-EU perspective.

Genomic data may also be included but is not a pre-requisite for a registry to be considered for this project.

In addition, a long term aim of the project is to ensure the future of the platform beyond the project lifetime and ensure the sustainability of the analyses, guidance, and tools within the platform. The applicant consortium shoud ensure that this aim is a key element in all the Work Package.

In addition, specific expertise in the following areas is required:

- experience and expertise in the regulatory, public health environment and policy development, and/or capacity to engage with Regulatory affairs, Healthcare/data privacy ethics, Health Outcomes;
- knowledge of the regulatory, legislation, and HTA requirements across Europe;
- clinical expertise in the key diseases areas of the Call topic;
- expertise in HEOR, PROs, data analytics, epidemiology, modelling, and translational science;
- patient and carer experience and interactions with healthcare systems;
- analytical expertise, expertise in data management, data meta-analysis, test systems;
- data collection, linkage, analytical methods, and collaborative aspects;
- to enable effective communication between key stakeholder groups.

Suggested architecture of the full proposal

The applicant consortium should include their suggestions for creating the Full Proposal architecture in their Short Proposal taking into consideration the industry contributions and expertise below:The below architecture for the full proposal is a suggestion; different innovative project designs are welcome, if properly justified.

The consortium is expected to have a strategy on the translation of the relevant project outputs into regulatory, clinical and healthcare decision making practice including health technology evaluations. A plan for interactions with regulatory agencies/HTA bodies with relevant milestones and resources allocated should be proposed to ensure this e.g. use of methods to value and evaluate innovative therapies for selected hematologic malignancies.

Applicants should include their proposed expertise and activities for Work Package 1, 6, 7 and 8 with the full understanding that these Work Package will be fully defined in collaboration with the industry partners at the Full Proposal stage to coordinate optimally with the forthcoming Big Data for Better Outcomes' CSA.

A plan for aspects related to sustainability, including a mechanism for access to aggregrated results and specific analyses on the data beyond the duration of the project, should also be proposed.

Work Package 1: Project management

Responsible for acting as a coordinating body during the life of the project to manage consistency, timelines, budget and communication across the project. The project is expected to have a high level of complexity with many stakeholders (academic and industry), parallel activities across work packages, and involving multiple individuals with varying roles and time allocation on the project, or within a work package. in addition, the various parties involved will have different objectives and focuses depending on their particular expertise, role or affiliation.

Proposed Deliverables

1. Project design and charters with clear accountabilities;
2. project governance structure;
3. provide coordination and support to project teams;
4. ensure key cross-functional partners are engaged;
5. provide a consistent, project-wide view of progress, issues, and interdependencies;
6. project level communication of key information throughout change effort (e.g. timelines, updates, directives, etc.);
7. project timelines and budget tracking and communication to Governance to ensure budget/timelines keep in to plan.

Industry contribution

Work Package co-leaders to drive the coordination with other projects within the programme and support with project design and day to day operation including project tracking and reporting, meetings, internal communication, etc.

Expected Applicant consortium contribution

1. Work Package co-leaders to drive the coordination with other projects within the programme and support with project design and day to day operation including project tracking and reporting, meetings, internal communication, budget management, etc.

Work Package 2: Outcomes definition

Proposed Deliverables:

1. define a set of outcomes for HM that should include both clinical outcome measures and patient factors for patients and caregivers. These outcomes should be defined for as a standard outcome set applicable to all HMs as well as specific outcome set for selected HMs, including ALL, NHL, MM , AML, CLL, and MDS; However, these outcome measures may also be of use to other HM diseases currently not in scope of this project but which may be considered in the plans for sustainability of the project;
2. production of a guidance document;
3. publications.

Activities:

- literature review on outcomes and definition of relevant outcomes in collaboration with key opinion leaders (KOLs), patients, providers, registry experts, etc.;
- establish value to patients beyond clinical outcomes (e.g. PRO, QoL);
- alignment of a core standard outcome set with KOLs, patients, providers, registry experts;
- alignment with payers, providers, regulatory agencies, HTA agencies, etc. on relevance of the core standard outcome set for different uses (e.g. reimbursement, value assessment, etc.), through organization of workshops.

Industry contribution:

- clinical/medical and safety expertise;
- expertise from HEOR, Epidemiology, translational science (in key disease areas);
- patient advocacy expertise;
- medical writing and medical communication expertise;
- Work package co-chairs.

Expected applicant consortium contribution:

1. expertise on defining sets of relevant outcomes in collaboration with multiple stakeholders also conducting literature reviews;
2. potential data management/programming expertise if academia consortium data to be shared within project;
3. the consortium is expected to bring expertise from the following disciplines: medical, academia, regulators, HTAs, payers, clinical research organisations, patient organisations, and cooperative groups.

Work Package 3: Data access

Proposed Deliverables:

1. data governance framework to address data privacy, ownership and access rights in combination with Work Package 8;
2. platforms for data capture and recommendations on best tools and methods to capture the desired outcomes;

3. mapping of potential data sources across EU that could be useful for the scope and purpose defined.

Activities:

- governance framework;
- define common data model;
- mapping of existing data sources (i.e. clinical, biological, genetic, observational data, PRO and HEOR, and others as applicable);
- liaise with potential partners in future data collection;
- data Due Diligence;
- develop (with Work Package 4) infrastructure for data entry and aggregation for de novo collection (or augmentation) of data (e.g. clinical, biological, genetic, observational data, PRO and HEOR, and others as applicable);
- augmentation;
- recurring augmentation costs.

Industry contribution:

- governance (HTA, Governmental affairs, legal, etc.);
- knowledge of current environment and data availability;
- deep expertise in application of common data models and execution;
- data due diligence.

Expected applicant consortium contribution:

1. patient-level data or ability to access patient-level data such as registries, claims, EHR, (epi)genetic profile, etc. for research use. At least one European registry per disease of interest is expected;
2. assessment of data quality;
3. experience on common data models;
4. mapping of existing data sources.

Work Package 4: Data platform

Proposed deliverables:

1. large, harmonized data sets of data (e.g. including clinical, genetic profile, treatment outcomes as applicable) that can be used to generate evidence from the whole and/or defined subsets of the patient population of interest;
2. sustainability plan for the platform.

Industry contribution:

- product development and diagnostics, specifically on regulatory relevant endpoints;
- clinical/medical, HEOR, and market access input and guidance as needed into queries arising from data set creation, curation, and integration;
- data management, relevant pre-defined data analysis, identify opportunities and challenges with datasets from Work Package 3, manage external partners (if applicable) for data curation and utilization;

- IT, implementation of data platform strategy, manage external partners for platform and portal for providers to access data to compare treatment options;
- datasets may be contributed to the project, types of datasets include, but are not limited to: registries and other kinds of observational research, clinical trial datasets;

Expected Applicant consortium contribution:

1. medical/scientific community: data ownership, clinical endpoints definition, healthcare delivery;
2. datasets that could be contributed to project include, but are not limited to: registries, multi- or single centre treatment databases, investigator sponsored studies;
3. healthcare administration bodies: logistics aspects of classical and new diagnostics and therapeutic interventions, availability and distribution of technologies and expertise within healthcare systems, social impact of diseases and treatments; such bodies could also contribute data, e.g. from EHRs, healthcare services databases or other;
4. external partners: data management, i.e. curation, hosting platform, access portal, security.

Work Package 5: Data analytics for therapies valuation

Proposed deliverables:

1. guidance document on how to undertake statistical analysis including modeling using the platform;
2. definition of questions to answer through aggregated data in the platform and identification of required data sources, based on mapping;
3. standard code for core algorithms and analyses to run routinely against datasets via the common data model and standard code to address core research questions;
4. prospective evaluation of core algorithms and analyses (exploitation of standard outcomes, clinical endpoints, patient factors in future studies, molecular data.);
5. data modeling repository customized for different outcomes and research questions;
6. define a Pan-European framework to value and evaluate health outcomes achieved with any therapeutic intervention through natural history data specifically in HMs;
7. scientific publications and communications.

Activities:

- develop, validate, and deploy algorithms and code for standard analyses on the platform;
- prepare methodological guidelines on using data platform for descriptive and comparative research and for disease modelling, including;
- for selected HMs, develop a disease-progression model adapted to HEOR needs, incorporating;
- establish guidelines for how to combine different types of data (such as RCT data with observational data) to achieve a holistic data package which can then be used for modelling and to derive treatment guidelines for communication with key decision-makers and health care providers;
- coordination with existing IMI projects (EMIF, EHR4CR), the DDN, and other relevant projects within the Big Data for Better Outcomes programme to identify synergies.

Industry contribution

Clinical/Medical reviewer (physician or safety physician) to give input into relevant questions for clinical, safety risk/benefit outcomes questions, data analysis plans and to provide Subject Matter Expert guidance to other functions.

- HEOR, data needs to assess and establish value of therapeutic interventions, including appropriate measures to establish value to patients beyond clinical outcomes (e.g. QoL, impact on caregivers etc.);
- market access, to establish relevant questions for reimbursement bodies, at national, regional and local level ;
- statistical analysis including experience in analysis of observational data;
- data synthesis and pooling methods (including Bayesian approaches);
- medical writing and communication expertise.

Expected Applicant consortium contribution:

1. Medical/Scientific community expertise in
   - clinical/medical, healthcare assessment and HEOR expertise in creation of relevant questions as outlined in industry contribution;
   - statistical expertise in descriptive, comparative, and predictive methods (frequentist and Bayesian) including expertise in use of observational data;
   - disease modelling expertise (including use of large data sets; clinical, epidemiological and/or HRQOL based data; bio-informatic analysis);
   - engagement and communication of clinical and research community.

Work Package 6: HTA, EMA, payers integration

1. Proposed deliverables:
2. face-to-face meetings with relevant stakeholders to achieve understanding of mutual opportunities, challenges and needs, define common goals and roles and responsibilities to maximize data utilization;
3. provide advice and support to other Work Packages for HTA, regulators, payers, and patients advocacy groups to use findings from those and write papers / publications relevant for those stakeholders.

Industry contribution:

- regulatory, reimbursement and HTA expertise; establishing partnerships with relevant stakeholders based on common goals;
- editorial support;
- medical expertise.

Expected Applicant consortium contribution:

1. medical/scientific community: establish link between clinical outcomes and value creation (for individuals and society); insight in future developments in diagnostics and therapeutics;
2. regulatory, reimbursement, HTA bodies and patient organisations**:** healthcare delivery needs, gaps and opportunities; insight into policy evolution and potential changes;
3. patients advocacy and representative groups: provide point of view of patients in terms of relevant outcomes and current challenges within healthcare delivery.

Work Package 7: Dissemination and communication

Proposed deliverables

1. overall communication strategy for the project including a communication plan by stakeholder type;
2. external publications on outputs of project through white papers, conferences;
3. develop and manage communication via web portal;
4. repository of key documents;
5. quality assessment documents.

Activities

- compiling and disseminating communication material to all relevant partners;
- message development and guidance to all work-packages;
- production of high-quality public relations materials;
- communicate with other relevant IMI projects, including other projects within the Big Data for Better Outcomes programme.

Work Package 8: Legal, ethics and governance

Develop an ethical and legal framework to provide guidance on addressing patient confidentiality concerns and data ownership concerns to other Work Packages.

Proposed deliverables:

1. guidance on ensuring patient confidentiality is maintained according to relevant regulations and data ownership aspects are taken into proper considerations;
2. input into evaluations of different Work Package including legal and ethical guidance on issues as needed;
3. oversight of white papers and pubications.

Actions:

- advise Work Package on ethical and legal implications of proposed recommendations;
- ensure awareness and responsiveness to European and national legislation that impacts data usage (e.g. privacy laws, data portability laws);
- coordinate with other relevant IMI projects, including projects within the Big Data for Better Outcomes.

Industry contribution

- legal expertise;
- compliance;
- patient advocacy;
- communication (linked to Work Package 7 activities).

Expected Applicant consortium contribution:

1. legal and ethical expertise;
2. compliance expertise.

Glossary:

ALL	Acute Lymphoblastic Leukaemia
AML	Acute Myeloid Leukaemia
CLL	Chronic Lymphocytic Leukaemia
CSA	Coordination and Support Action
DDN	Distributed Data Network
EFPIA	European Federation of Pharmaceutical Industries and Associations
EHR	Electronic Health Records
EHR4CR	Electronic Health Records for Clinical Research
EMIF	European Medical Information Framework
FTE	Full Time Equivalent
HC	Healthcare
HEOR	Health Economics and Outcomes Research
HM	Haematological Malignancies
HTA	Health Technology Assessment
IMI	Innovative Medicines Initiative
KOL	Key Opinion Leader
MDS	Myelodysplastic Syndrome
MM	Multiple Myeloma
NHL	Non-Hodgkin Lymphoma
PARENT	PAtients REgistries iNiTiative
PRO	Patient Reported Outcomes
QOL	Quality of Life
RCT	Randomised Clinical Trial
RIA	Research and Innovation Action

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 6 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-IMI2-2015-06
Type of action	RIA - research and innovation action
Publication Date	**06 October 2015**
Stage 1 Submission start date	**06 October 2015**
Stage 1 Submission deadline	**12 January 2016 (17:00:00 Brussels time)**
Stage 2 Submission deadline	**14 June 2016 (17:00:00 Brussels time)**
Indicative Budget	
From Industry consortia (EFPIA companies)	EUR 46 500 000
From the IMI2 JU	EUR 46 500 000

Call Topics

IMI2-2015-06-01	The indicative contribution from EFPIA companies is EUR 8 000 000 The financial contribution from IMI2 is a maximum of EUR 8 000 000	Research and Innovation action. Two-stage submission and evaluation process. Only the applicant consortium whose proposal is ranked first at the first stage is invited for the second stage.
IMI2-2015-06-02	The indicative contribution from EFPIA companies is EUR 14 500 000 The financial contribution from IMI2 is a maximum of EUR 14 500 000	Research and Innovation action. Two-stage submission and evaluation process. Only the applicant consortium whose proposal is ranked first at the first stage is invited for the second stage.

IMI2-2015-06-03	The indicative contribution from EFPIA companies is EUR 4 000 000 The financial contribution from IMI2 is a maximum of EUR 4 000 000	Research and Innovation action. Two-stage submission and evaluation process. Only the applicant consortium whose proposal is ranked first at the first stage is invited for the second stage.
IMI2-2015-06-04	The indicative contribution from EFPIA companies is EUR 20 000 000 The financial contribution from IMI2 is a maximum of EUR 20 000 000	Research and Innovation action. Two-stage submission and evaluation process. Only the applicant consortium whose proposal is ranked first at the first stage is invited for the second stage.

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

List of countries and applicable rules for funding

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

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

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

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

(ii) secondary and higher education establishments;

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

(c) the Joint Research Centre;

(d) international European interest organisations.

Admissibility conditions for grant proposals, and related requirements

Part B of the General Annexes[11] to the H2020 Work Programme shall apply mutatis mutandis for the actions covered by this Call for proposals.

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

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

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 IMI 2 evaluation criteria (Excellence, Impact and Quality and efficiency of the implementation)[12] according to the submission stage

Type of action	Excellence	Impact	Quality and efficiency of the implementation*
RIA and IA	The following aspects will be taken into account, to the extent that the proposed work corresponds to the topic description in the IMI2 annual work plan: **clarity and pertinence of the objectives;** **credibility of the proposed approach;** **soundness of the concept, including trans-disciplinary considerations, where relevant;** **extent that proposed work is ambitious, has innovation potential, and is beyond the state of the art;** **mobilisation of the**	The following aspects will be taken into account, to the extent to which the outputs of the project should contribute at the European and/or International level: **the expected impacts of the proposed approach listed in the IMI2 annual work plan under the relevant topic;** **enhancing innovation capacity and integration of new knowledge;** **strengthening the competitiveness and industrial leadership and/or addressing specific societal challenges;** **improving European citizens' health and wellbeing and**	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**

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

	necessary expertise to achieve the objectives of the topic and to ensure engagement of all relevant key stakeholders.	**contribute to the IMI2 objectives;**[13] **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.	**management and sustainability plan.**

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

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

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

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.[14].

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.

[13] 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)

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

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.

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 to 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 two-stage evaluation procedure involving clinical studies, the use of this template is mandatory in order to provide experts with the necessary information to evaluate the proposals. The template may be submitted as a separate document.

Ethical issues should be duly addressed in each submitted proposals to ensure that the proposed activities comply with ethical principles and relevant national, Union and international legislation. Any proposal that contravenes ethical principles or which does not fulfil the conditions set out in the H2020 Rules for Participation, or in the IMI2 Call for proposals shall not be selected. [15]

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

[15] Article 19 of *Horizon 2020 Framework Programme*, and Articles 13 and 14 of the *Horizon 2020* Rules for Participation

1. disseminate scientific publications on the basis of open access[16].(see “Guidelines on Open Access to Scientific Publications and Research Data in Horizon 2020”);

1. 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.

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

3. Disseminate a description of resources[17] according to well-established metadata standards such as the Dublin Core (ISO15836) in order to make the resources included and generated by the IMI Actions discoverable for metrics and re-use.

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

Consortium agreements

In line with the Rules for Participation and Dissemination applicable to IMI2 actions[18] and the IMI2 model grant agreement:

participants in research and innovation actions are required to conclude a consortium agreement prior to grant agreement;

[16] 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

[17] Examples of resources are (a collection of) biosamples, datasets, images, publications etc.

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