IMI2

23rd Call for proposals

Annex IV to the 3rd Amended IMI2 JU Annual Work Plan and Budget for 2020 approved by the IMI2 JU Governing Board on 19 June 2020 per Decision n° IMI2-GB-DEC-2020-20

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Introduction

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

The Innovative Medicines Initiative 2 Joint Undertaking (IMI2 JU) has been created[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 IMI2 JU objectives are usually implemented through Research and Innovation Actions (RIAs), and Coordination and Support Actions (CSAs) where public and private partners collaborate, joining their expertise, knowledge and resources.

The initiative should therefore seek to involve a broader range of partners, including mid-sized companies[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 JU. The scientific priorities for 2020 for IMI2 JU have been prepared based on the SRA.

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

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

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

[1] Council Regulation (EU) No 557/2014 of 6 May 2014 establishing the Innovative Medicines Initiative 2 Joint Undertaking (IMI2 JU), OJ L 169, 7.6.2014, p. 54–76.
[2] http://www.who.int/medicines/areas/priority_medicines/en/
[3] Under IMI2 JU, mid-sized companies having an annual turnover of EUR 500 million or less not being affiliated entities of companies with an annual turnover of more than 500 million; the definition of 'affiliated entities' within the meaning of Article 2(1)(2) of Regulation (EU) No 1290/2013 applies mutatis mutandis. Where established in an EU Member State or an associated country, are eligible for funding.
[4] http://www.imi.europa.eu/sites/default/files/uploads/documents/About-IMI/research-agenda/IMI2_SRA_March2014.pdf

Applicant consortia shall ensure that where relevant their proposals are in compliance with the General Data Protection Regulation (EU) 2016/679[5] and Clinical Trial Regulation (EU) 536/2014[6] (and/or Directive 2001/20/EC[7)] and any relevant legislation[8].

Before submitting a proposal, applicant consortia should familiarise themselves with all Call documents such as the IMI2 JU Manual for submission, evaluation and grant award[9], and the IMI2 evaluation criteria. Applicants should refer to the specific templates and evaluation procedures associated with the topic type Research and Innovation Actions (RIA).

[5] Regulation (EU) 2016/679 of the European Parliament and of the Council of 27 April 2016 on the protection of natural persons with regard to the processing of personal data and on the free movement of such data, and repealing Directive 95/46/EC (General Data Protection Regulation), OJ L 119, 4.5.2016, p. 1–88.
[6] Regulation (EU) No 536/2014 of the European Parliament and of the Council of 16 April 2014 on clinical trials on medicinal products for human use, and repealing Directive 2001/20/EC, OJ L 158, 27.5.2014, p. 1-76.
[7] Directive 2001/20/EC of the European Parliament and of the Council of 4 April 2001 on the approximation of the laws, regulations and administrative provisions of the Member States relating to the implementation of good clinical practice in the conduct of clinical trials on medicinal products for human use (the "Clinical Trials Directive), OJ L 121, 1.5.2001, p. 34.
8 Directive 95/46/EC on the protection of individuals with regard to the processing of personal data and the free movement of such data and implementing national laws, OJ L 281, 23.11.1995, p. 31–50.
[9] https://www.imi.europa.eu/sites/default/files/uploads/documents/apply-for-funding/call-documents/imi2/IMI2_ManualForSubmission_v1.7_November2018.pdf

Topic 1: Returning Clinical Trial Data to study participants within a GDPR compliant and approved ethical framework

Topic details

Topic code	IMI2-2020-23-01
Action type	Research and Innovation Action (RIA)
Submission and evaluation process	2 stages
IMI2 Strategic Research Agenda - Axis of Research	Adoption of innovative clinical trial paradigms
IMI2 Strategic Research Agenda - Health Priority	Other

Specific challenges to be addressed by public-private collaborative research

A large amount of high-quality health data is collected during clinical studies (interventional and non-interventional), but, beyond the immediate objectives of the study, these valuable data are not used to the extent they merit. Subject to appropriate legal grounds, these data could be used to enrich patients' healthcare records to improve clinical decision-making and reduce duplication in procedures/investigations. In addition, returning clinical trial data to patients could allow them to contribute their data for additional scientific research (e.g. patient-powered research), in particular for rare diseases where treatments and data are scarce or unavailable. Finally, the lack of transparency and sharing of clinical trial data could contribute to the lack of patient willingness to be involved in studies, delays in clinical study set up and conduct, and delays in conducting health research in Europe to the detriment of vulnerable patients and public interest in general.

Some of the main barriers to returning clinical trial data to study participants include:

- Complexities of determining acceptable common data format, processes or infrastructure;
- Complexities of the International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (ICH), Good Clinical Practice (GCP) and EU Clinical Trial Regulation (CTR) (e.g. including study integrity, privacy and confidentiality); and
- Lack of harmonisation of the national legal framework related to processing of health-related data across Member States and need for additional guidance on some practical aspects of the implementation of the General Data Protection Regulation (GDPR), whether for primary and/or secondary use of individual clinical trial data (personal data).

At the same time, there is an increasing awareness that greater transparency and engagement with study participants are needed in clinical research, and that the return of study participants' clinical trial data can address those needs.

In order to tackle these challenges, a multi-national public-private partnership including many of the actors involved in clinical trials processes is necessary:

- Collaboration of **industrial and academic clinical trial sponsors** to develop EU-wide standards for (i) data return to individual study participant and (ii) secondary use of clinical data, as well as to propose and agree on those common standards with ethics committees and personal data protection authorities;
- Collaboration with both **healthcare providers and relevant Electronic Health Record (EHR)/clinical trial technology vendors** to develop the process for returning these data electronically to the patient (directly through an EHR system where possible, or through other means (either electronic or non-electronic) where such a system is not possible), taking into account ongoing and previous activities on

European interoperable EHR exchange in alignment with the European Electronic Health Record exchange format (EEHRxF) as set out in Commission Recommendation C(2019) 800[10];

- Inputs from various **EU regulators** will be essential to the success of this project and required to develop common, validated usability and privacy standards. Involvement of **legal counsels and ethics, and data protection experts** will be crucial as data return will have to be compliant with GDPR as well as with local legal and ethical requirements.
- Substantial, focused input from **study participants, patient organisations and healthcare professionals** to fully understand what data would be the most important to return to them, what data would be acceptable for being shared with researchers, and how such data may best be returned and/or shared.

Scope

This project has two main objectives, which are equally important:

- The first one is to align local and pan-European implementations and best practice for handling personal data protection regulations in order to foster the harmonisation of the legal framework applicable to medical research in the Member States;
- The second one is to deliver a pan-European prototype process to return clinical trial data to study participants, building on previous and ongoing EU-level activities on citizen-centric access to health records. This prototype process will be delivered as part of the project alongside a robust business plan to ensure its sustainability.

To support these objectives, the project will:

- Define harmonised rules for complying simultaneously with data protection regulations, regulatory requirements and ethical standards in Europe. These rules are to be endorsed by appropriate regulatory bodies and patients;
- Define which, when and how clinical trial data should be returned to study participants, including for integration in, or interconnection with, patients' individual health records management files or applications and, where they exist, national and/or hospital EHR systems (for clarity, no 'lay summaries' or other expert analyses are within the scope of this project) and EHR standards such as EEHRxF;
- Define data governance models for cases where individual clinical trial data is (or can be) utilised for both healthcare decision making and future research, taking into account previous and ongoing EU-level activities on data governance in these fields;
- Ensure that the whole process, from collection of data to its destruction or anonymisation, including sharing of individual personal data, is aligned with the study participants' expectations and the authorities and ethics committees' standards and procedures, and documented in binding and/or approved standards or guidance documents.

Expected key deliverables

The overarching project deliverable is a working prototype demonstrating how study participants can visualise (directly or indirectly with a healthcare professional), query and share the clinical trial data returned to them. It should cover the following:

- A test version of the prototype process, agile enough to be interoperable in most countries, should be delivered by mid-term, with the final version delivered by month 42 to allow for implementation of the business plan in the final six months.

[10] https://ec.europa.eu/digital-single-market/en/news/recommendation-european-electronic-health-record-exchange-format

- For at least one "real" study (type and medical area to be proposed by participating EFPIA companies) the prototype process should demonstrate within a proof of concept mechanism how relevant clinical trial data can be:
    - Either integrated or interconnected with at least two existing repositories (e.g. data in national or hospital patients' EHRs or in other
    - System/application directly accessible to patients); and
    - Can be re-used in further medical health research or clinical studies.
- The working prototype process must be delivered alongside a robust business plan to ensure it is mature enough to pave the way for the development of a sustainable and effective platform after the end of the project.

In addition, the project will have to produce the following key deliverables:

- At least three different decision committees established:
    - One in charge of defining reasonable expectations of researchers, and involving technical experts (including for the anonymisation of health data), healthcare professionals (HCPs)/principal investigators (PIs), and experts in genetics counselling (made up of members of the consortium and external/invited members);
    - One in charge of defining legal and ethical acceptance of proposals, and involving data protection authorities (DPAs) and ethics committees (ECs/International Review Boards (IRBs)) from at least five of the top 10 European countries conducting the most significant number of clinical trials (made of external/invited members); and
    - One in charge of representing patient expectations and involving patient associations (made up of members of the consortium and, if needed, external/invited patient association members).
- Published aligned position papers from the above decision committees, including the proposed regulatory standards and guidance documents. They should include an official opinion of the regulators (e.g. of the European Data Protection Board (EDPB)), where possible;
- Workshops organised with the aim to foster harmonisation of the health data processing provisions across Member States. Decision positions should, where possible, include an official opinion of the regulators (e.g. EDPB) at the end of the project;
- Proposed harmonised standards to be applied to personal data by operational stakeholders, such as sponsors' and investigators' study teams. These documents will have to be discussed with and agreed upon, as much as possible, by decision committees. The proposed standards and documents must at least specify:
    - Which exact data elements and which categories of studies would be suitable and useful for both for being returned to study participants and for further research;
    - How to make individual clinical study data available for return to study participants;
    - How to allow the processing of individual clinical trial data for re-use in further clinical research projects, including guidelines (a) for consent, either initial (whether for interventional or for non-interventional studies) or for returning data; (b) for selecting the most appropriate legal basis; (c) for clarifying their consequences on patients' rights as granted by the GDPR, in particular their right to be informed and to object; and (d) for establishing contractual agreements among parties conducting trials (in particular between sponsors and investigators/investigational sites using decision trees or other tools to assign appropriate role to each party – i.e. controller, processor, joint-controllers or co-controllers).
- Proposed harmonised standards on how to transform personal clinical data into fully anonymised health data (which are no longer subject to GDPR and other local data protection regulations);
- Proposed harmonised technical standards necessary to handle the data, and including:
    - The analysis of existing standards for securely hosting and exchanging health data;

- The selection of preferred standards for such activities including definition of
- type/timing;
- The assessment of interoperability of clinical trial data with patients' individual health records management files or applications and/or, where existing, national or hospital EHR systems.

- Public release of final harmonised, acceptable technical requirements derived from the above deliverables and position papers, including at least those that allow:
  - Data retrieval and upload;
  - Study participants' access to data, and ability to know what their personal data is being used for and solutions to object/opt-out for any or all further uses of their personal data (preferably in a centralised, multilingual cross-country and cross-sponsor platform);
  - Delivering the data or enabling the patient to handle the data, with the option for the patient to donate the data once for all for scientific research.
- Public release of final harmonised and approved (by data protection authorities and ECs) standards and guidance documents as implemented in industry-wide approach such as a GDPR code of conduct, defining:
  - How to return individual clinical trial data to study participants in Europe (including for study participants to make such data available in EHR or other systems and for further research); and
  - When and how (considering data quality) to deliver which data or annotations of data, specific to the stakeholder (e.g. patient, healthcare professional, sponsors, etc.).

Expected impact

In their proposals, applicants should describe how the outputs of the project will contribute to the following impacts and include, wherever possible baseline, targets and metrics to measure impact:

- **For patients:** the project results should **empower patients** by returning their clinical trial data to them and to their medical records. Data acquired during clinical trials will aid better shared medical decision-making and reduce duplication in procedures/investigations;
- **For healthcare professionals:** enriched healthcare data obtained during clinical care should **aid better clinical decision** making and reduce duplication in patient procedures/investigations;
- **For EU research:** giving patients control of their clinical trial data will **open possibilities for ethical data re-use** e.g. if the patients opt in to donate their data to a common data sharing platform;
- **For pharma:** returning clinical trial data to study participants during study conduct has the potential to **improve adherence** to study procedures and **improve overall patient retention**. **Facilitate conduct and setup** of clinical studies as well as access to health data for research. Doing this in a meaningful way will further help to educate patients and in doing so empower them to be equal partners in the management of their disease;
- **For regulators:** it is an opportunity to exchange opinions with counterparts from other countries and researchers to propose informed workable aligned positions;
- **From a societal perspective:** the project will **increase the transparency** of clinical study and therefore increase the **trust** of patients in clinical research. At a time where clinical trials are increasingly complex, this may help with recruitment for studies and **improve oversight by patients and regulators** on clinical data re-use.

In their proposals, applicants should outline how the project plans to leverage the public-private partnership model to maximise impact on innovation, research & development; regulatory, clinical and healthcare practices, where relevant. This could include a strategy for engagement with patients, healthcare professional associations, healthcare professionals, regulators, ethics committees, HTA agencies, payers etc., where relevant.

In addition, applicants should describe how the project will impact the competitiveness and growth of companies, including SMEs.

Moreover, in their proposals, applicants should outline how the project will:

- Manage research data and adhere to ethics requirements[11] ;
- Disseminate, exploit, and sustain the project results. This may involve engaging with suitable biological and medical sciences research infrastructures[12];
- Support the improvement of the interoperability of EHRs by aligning with the EEHRxF;
- Communicate the project activities to relevant target audiences.

Potential synergies with existing consortia

Synergies and complementarities should be considered with relevant national, European and non-European initiatives (including suitable biological and medical sciences research infrastructures) in order to incorporate past achievements, available data and lessons learnt where possible, thus avoiding unnecessary overlap, and duplication of efforts and funding.

To tackle challenges and ambitious objectives, the project should leverage outcomes of past IMI JU and EU or other programmes. The selected consortium is expected to acknowledge and integrate the following resources:

- Harmonised consent forms and guidance documents for clinical trials and secondary use of data and biological samples[1] as outcomes of the IMI DO-IT decision committees;
- BBMRI Code of Conduct for health research, when available;
- ECRIN European Clinical Research Infrastructures Network;
- EUCROF Code of Conduct for clinical trials, when available;
- Relevant insights and work from the complementary Patient Data Return Initiative (PDAI) founded in 2017 by a group of Pharmaceutical companies. Though that ongoing initiative does not focus on legal or regulatory requirements of EU Member States, its progress on the data sharing process (e.g., technical insights), insights from stakeholders (such as patient groups and sponsors) on the value of returned data, and insights from completed data sharing pilots (best practices) are expected by PDAI to be available for this project by its commencement;
- Particular attention should also be paid to the initiatives piloting decentralised clinical trials, aligning clinical study data with EHRs, implementing blockchain and federated technology for secure infrastructures, aligning on data sharing with patients and/or HCPs.

Industry consortium

The industry consortium is composed of the following EFPIA partners:

- Sanofi (Lead)
- Medidata (Co-Lead)
- Abbvie
- Astra Zeneca

[11] Guidance on data management is available at http://ec.europa.eu/research/participants/docs/h2020-funding-guide/cross-cutting-issues/open-access-data-management/data-management_en.htm
[12] http://www.corbel-project.eu/about-corbel/research-infrastructures.html

- Bayer
- Janssen
- Pfizer
- Servier
- Takeda

The industry consortium will contribute the following expertise and assets:

- Expertise in conducting studies (data management, study/trial operational management, biostatistics);
- Expertise in the relevant legal framework (GDPR and CTR);
- Experience in networking with EU and local healthcare and data protection regulators;
- Expertise in sensitive data exchange and in building digital infrastructure;
- Expertise in data security and data anonymisation;
- Expertise in data protection and transparency;
- In addition, the industry consortium will act as a liaison with the patient data return initiative (PDAI).

Indicative duration of the action

The indicative duration of the action is 48 months.

This duration is indicative only. At stage 2, the consortium selected at stage 1 and the predefined industry consortium may jointly agree on a different duration when submitting the stage 2 proposal.

Indicative budget

The financial contribution from IMI2 JU is a maximum of EUR 3 260 000.

The indicative in-kind and financial contribution from EFPIA partners is EUR 4 930 000.

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

Expertise and resources expected from applicants at stage 1

The stage 1 applicant consortium is expected, in the submitted short proposal, to address all the objectives and key deliverables of the topic, considering the expected contribution from the industry consortium which will join at stage 2 to form the full consortium.

The stage 1 submitted short proposals should include suggestions for creating a full proposal architecture which could be in line with the suggested architecture described below, though this architecture is only a suggestion.

This may require mobilising, as appropriate the following expertise:

- Academic clinical trials sponsors from at least five different European Member States (including at least one central/eastern European Member State);
- Robust legal, ethics and data protection expertise (including for clinical studies);

- Proven expertise in working/collaborating with ethics committees and personal data protection authorities, as advice from various EU regulators will be essential to the success of this project and required to develop common, validated usability and privacy standards;
- Healthcare professionals;
- Participants with robust expertise in health and clinical data interoperability and secured exchanges, in EHR and in clinical trial databases, and including those operating in a commercial environment;
- Study participants and patient organisations.

It would also be crucial to include relevant SMEs. SMEs could, for example, be beneficial in the legal and data protection areas as well as interoperability of data and framework for their secured exchanges.

The size of the consortium should be proportionate to the objectives of the topic while ensuring its manageability. Ethics committees and regulators will have to be invited afterwards. They are not expected to be part of the applicant consortia.

Considerations for the outline of project work plan

In their stage 1 proposal applicants should:

- Give due visibility on project management, data management and ethics; dissemination, exploitation and sustainability; and communication activities. This should include the allocation of sufficient resources for these tasks, which will be further developed in stage 2 proposal;
- Consider including a strategy for ensuring the translation of the project results into drug development, regulatory, clinical and healthcare practices and/or decision-making processes.

Suggested architecture

Work Package 1 – Legal and Regulatory Framework

The goals of this work package are to:

- Align IMI DO-IT harmonised consent form (http://bd4bo.eu/wp-content/uploads/2019/03/DO-IT_WP4_D4.10_Level3_Clinical-ICF.docx) and supporting guidance documents (https://bit.ly/3a7yARK) with recent updates in EU laws and in line with EDPB standards, as well as local regulatory body opinions;
- Work locally with selected countries in order to get those documents officially approved by the appropriate authorities;
- Develop additional template and guidance documents necessary for primary and secondary use of clinical data in compliance with GDPR, referencing variations between and/or within Member States (including for managing privacy notices and rights/choices for secondary use through a patient portal) as well as for contracting with individual investigators/institutional investigation sites;
- Manage adequate experts' committees of patients, authorities and experts in personal data protection to review, discuss and take position on proposed guidance documents.

Work Package 2 – Standards

The goals of this work package are to:

- Review and elaborate upon standards and guidance documents;
- Provide recommendations;
- Develop new standards when necessary;

- Submit standards (in particular regulatory ones) for approval to appropriate governing authorities/regulators.

Work Package 3 – Technology Framework

The goals of this work package are to:

- Develop a technology framework that can be based on existing technologies or on new potential tech development;
- Isolate and handle potential technical issues;
- Set-up the process that will be deployed in WP4.

Work Package 4 – Working Prototype process

The goals of this work package are to:

- Deploy a working prototype process to establish viability, and to suggest overall direction, as well as provide feedback. It should at least provide study participants (or their chosen physician) with direct access to the individual clinical data or documents, and where possible, in an interoperable electronic format to comply with the GDPR portability right;
- Integrate with EHR/other system;
- Facilitate future research.

Work Package 5 – Communication, Dissemination & Stakeholder engagement

The goals of this work package are to:

- Establish a website and all appropriate tools for communications purposes;
- Establish a communication structure and implement it on project basis (training webinars, stakeholder engagement meetings);
- Conduct surveys with patients, HCPs, etc;
- Establish and organise dissemination of project results;
- Build adherence of relevant stakeholders.

Work Package 6 – Business Plan and Sustainability

The goals of this work package are to:

- Establish, early in the project, a robust business plan to sustain the projects results
- Implement the business plan, including marketing of the solutions to relevant end-users.

Work Package 7 – Project management and overall coordination

Additional considerations to be taken into account at the stage 2 full proposal

At stage 2, the consortium selected at stage 1 and the predefined industry consortium jointly submit the full proposal developed in partnership. The full proposal is based upon the selected short proposal at stage 1.

In the spirit of the partnership, and to reflect how IMI2 JU call topics are built on identified scientific priorities agreed together with EFPIA beneficiaries/large industrial beneficiaries, these beneficiaries intend to significantly contribute to the programme and project leadership as well as project financial management. The final architecture of the full proposal will be defined by the participants in compliance with the IMI2 JU rules and with a view to the achievement of the project objectives. The allocation of a leading role within the consortium will be discussed in the course of the drafting of the full proposal to be submitted at stage 2. To facilitate the formation of the final consortium, until the roles are formally appointed through the consortium agreement, the proposed project leader from among EFPIA beneficiaries/large industrial beneficiaries shall facilitate an efficient negotiation of project content and required agreements. All beneficiaries are encouraged to discuss the project architecture and governance and the weighting of responsibilities and priorities therein.

Data Management

In their stage 2 proposal, applicants should give due visibility to data management including use of data standards. A full 'data management plan' (DMP) as a distinct deliverable must be delivered within the first 6 months of the project. The DMP needs to be kept up to date with the needs of the project and as such be updated as necessary during its lifetime.[13] The DMP has to reflect on the legal, regulatory and ethical guidance from work packages 1 and 2.

Dissemination, exploitation and sustainability of results

In their stage 2 proposal, applicants must provide a draft plan for dissemination and the exploitation, including sustainability of results. A full plan as a distinct deliverable must be delivered within the first 6 months of the project.[14], and updated during the project lifetime and could include identification of:

- Different types of exploitable results;
- Potential end-users of the results;
- Results that may need sustainability and proposed sustainability roadmap solutions.

Sufficient resources should be foreseen for activities related to dissemination and exploitation, including the plan for the sustainability of the project results. This may involve engaging with suitable biological and medical sciences Research Infrastructures (RIs).[15]

Communication

The proposed communication measures for promoting the project and its findings during the period of the grant should also be described and could include a possible public event to showcase the results of the project.

[13] Guidance on data management is available at http://ec.europa.eu/research/participants/docs/h2020-funding-guide/cross-cutting-issues/open-access-data-management/data-management_en.htm
[14] As an additional dissemination obligation under Article 29.1 of the IMI2 Grant Agreement will apply.
[15] http://www.corbel-project.eu/about-corbel/research-infrastructures.html

Introduction to IMI2 Antimicrobial Resistance (AMR) Accelerator programme (topic 2)

Background and problem statement

The discovery and development of new prevention and treatments to address antimicrobial resistance (AMR) is an undisputed European and global challenge that is compounded by a low return on investment (RoI) for the pharmaceutical sector. This low RoI is driven largely by the lack of established reimbursement models and standard methods to express the true societal value for new technologies addressing AMR. This has subsequently led to a reduction in resources across the pharmaceutical industry and a decline in scientific discoveries. Overall this situation has compromised the delivery of new options to treat and prevent resistant infections. This was highlighted in the European One Health Action Plan against Antimicrobial Resistance (for more info please visit the following link: https://ec.europa.eu/health/amr/sites/health/files/antimicrobial_resistance/docs/amr_2017_action-plan.pdf. Beyond Europe, it is of note that AMR is one of four public health concerns that has been raised to the level of discussion at the UN General Assembly (September 2016), putting it on a par with HIV and Ebola. Additionally, drug resistant tuberculosis (TB), which is the largest single contributor to AMR health, mortality, and economic impact.

There are significant scientific challenges to the discovery and development of new agents to treat and prevent AMR infections, including those caused by Gram-positive and Gram-negative bacteria, *Mycobacterium tuberculosis*, and non-tubercular mycobacteria (NTM). As an example, despite there being an extensive number of essential bacterial targets, no novel mechanism antibiotics for Gram-negative infections have been approved in 40 years.

Furthermore, despite some recent progress, we have a poor understanding of how to rationally design potent small molecules that are optimised to treat life-threatening multi-drug resistant (MDR) Gram-negative pathogens. Models, approaches, and tools developed by large pharma or public entities to support antibiotic drug development need to be validated and shared more widely to serve the AMR community at large. At the same time, alternative approaches to treating infections require robust validation. The same is true for platforms that enhance the success of vaccines and monoclonal antibodies, or new imaging platforms to measure pharmacodynamic responses at the site of action.

In TB, the world's leading infectious disease killer with 1.7 million deaths in 2016, (from WHO TB report 2017, Executive Summary at the following link, http://www.who.int/tb/publications/global_report/Exec_Summary_13Nov2017.pdf) there is an acute need for the development of a novel combination regimen with an indication for the treatment of any form of TB ('pan-TB regimen') that will be more effective, shorter, and safer than current existing options. This applies to all types of TB (drug-sensitive (DS), multi-drug resistant (MDR) and extensively-drug resistant (XDR-TB)). A pan-TB regimen would encompass at least three new chemical entities, with properties better suited to protect against emerging resistance both individually as well as in combination. Many scientific hurdles must be overcome to understand how multiple chemical entities can be combined most successfully, keeping synergistic drug activity, drug-drug interactions, and translational aspects in mind. Regimen development in TB has provided and will continue to lead to learnings that will help to develop new treatments, including combination regimens, for other infections that have relied on mono-therapy thus far.

Overall objectives of the AMR Accelerator

The aim of the AMR Accelerator is to progress a pipeline of potential medicines, including but not limited to new antibiotics, to treat patients with resistant bacterial infections in Europe and across the globe or to prevent them. Specifically, if successful, projects in the AMR Accelerator are expected to deliver up to >10 new preclinical candidates and >5 'phase 2-ready' assets over a roughly seven-year period.

The AMR Accelerator provides, under one operational structure, a wide-ranging series of projects that addresses many of the scientific challenges in AMR. The scientific scope is broad, including prevention (vaccines, monoclonal antibodies (mAbs), immunoprophylaxis, other means) and treatment (new antibiotics, non-antibiotic alternatives, and combinations). For clarity, the term 'AMR' should be interpreted to include Gram-positive and Gram-negative bacteria, tuberculosis (TB) and non-tubercular mycobacteria (NTM). Within this broad scope, projects in the AMR Accelerator develop new pre-clinical tools and methods, validate alternative or 'non-traditional' approaches, progress potential new treatments through phase 1-3 clinical trials, and analyse data from EFPIA-funded clinical trials to assist in the translation of preclinical data to clinical results of novel anti-infective agents and vaccines. The AMR Accelerator will also potentially generate new clinical/regulatory phase 2-3 pathways. Over the past years, IMI's New Drugs for Bad Bugs (ND4BB) programme has created a vibrant drug discovery and development network in AMR, and met important milestones. The AMR Accelerator complements and augments the capabilities of the IMI ND4BB programme[16].

Progression of successful assets beyond the scope of the AMR Accelerator (pillar-dependent, see below) may occur, as appropriate, by other mechanisms such as EU funding programmes within Horizon 2020 (including SME instruments) or future framework programmes, InnovFin instruments, Structural Funds, venture capitals, other internal R&D funding mechanisms, etc. In addition, the applicable principles from the Davos Declaration on Antimicrobial Resistance– January 2016 or the Industry Roadmap for Progress on Combatting Antimicrobial Resistance – September 2016 (https://www.ifpma.org/wp-content/uploads/2016/09/Roadmap-for-Progress-on-AMR-FINAL.pdf[17]) should be taken into account.

The AMR Accelerator programme will contribute to one of the three pillars of the European One Health Action Plan against Antimicrobial Resistance 'Boosting research and development and innovation in AMR' (June 2017: https://ec.europa.eu/health/amr/sites/health/files/antimicrobial_resistance/docs/amr_2017_action-plan.pdf). The AMR Accelerator programme will also directly address the IMI2 JU objective to 'develop new therapies for diseases for which there is a high unmet need, such as Alzheimer's disease and limited market incentives, such as antimicrobial resistance' (Article 2(b)(iii) of the Council Regulation establishing IMI2 JU: http://eur-lex.europa.eu/legal-content/EN/TXT/?uri=celex%3A32014R0557)

The AMR Accelerator programme structure

The AMR Accelerator programme consists of three pillars under which multiple actions are expected:

- **Pillar A:** Capability Building Network (CBN)
- **Pillar B:** Tuberculosis Drug Development Network (TBDDN)
- **Pillar C:** Company-specific Portfolio Building Networks (PBNs)

The two-stage IMI2 JU Call 23 includes one topic (topic 2) under Pillar A to complement the actions funded under IMI2 JU Call 15, IMI2 JU Call 16 and IMI2 JU Call 20.

For the new topic for Pillar A, launched as part of IMI2 JU Call 23:

- the indicative EFPIA in-kind contribution will be EUR 2 760 000

The EFPIA in-kind contribution will be matched by IMI2 JU funding across the whole of the AMR Accelerator and not necessarily 1:1 on an individual project or pillar basis.

[16] https://www.imi.europa.eu/projects-results/project-factsheets/nd4bb
[17] For example, points 3 and 4 from the 'Roadmap for Progress'.

The overall IMI2 JU financial contribution to the AMR Accelerator topics under Pillars A, B and C will be a maximum of EUR 251 230 000.

Pillar A: Capability Building Network (CBN) to accelerate and validate scientific discoveries.

The CBN : 1) creates a coordination and support group to assist in the effective management of projects across the AMR Accelerator and; 2) delivers pre-competitive science to accelerate scientific discoveries in AMR, the results of which will be disseminated widely. The CBN includes projects to further basic science and discoveries to enable future drug discovery and development in the prevention (vaccines, mAbs, immunoprophylaxis, and others) and treatment of MDR bacterial infections including tuberculosis (TB), and non-tubercular mycobacteria (NTM). Although most research in the AMR Accelerator related to TB is conducted in the TBDDN (below), TB projects could occur in the CBN if the scientific concepts are of broader applicability (e.g. immunoprophylaxis).

The initial action in the CBN, COMBINE – 853967 selected under Pillar A from IMI2 JU Call 15 topic 7[18], and containing the coordination and support group[19], implements a coordination and support group that supports the operations of all projects in the AMR Accelerator with effective management, communication, and data capture capabilities. The initial CBN action also focuses on the collection, sharing, and analysis of vaccine and/or antibacterial clinical trial data and the optimisation of animal infection models for bacterial infections.

The action in the CBN resulting from IMI2 JU Call 23 topic 2, will implement a research and innovation action to develop a framework for setting up antimicrobial resistance (AMR)-focused economic evaluations of vaccines and monoclonal antibodies (mAbs). A mathematical model will be developed and made publicly available to assess the impact of vaccines or mAbs strategies in the reduction of AMR.

Pillar B: Tuberculosis Drug Development Network (TBDDN) to accelerate and validate scientific discoveries and advance the R&D pipeline of new and innovative agents to address the global TB epidemic.

The TBDDN works to address the innovation gap in the discovery and development of a pan-TB regimen by combining access to novel drug candidates with innovative tools and incorporation of clinical trial data to accelerate the discovery of new combination regimens for the treatment of TB.

The platform is self-sustained and independent from other similar activities (Integrated Research Platform (IRP), TB Drug Accelerator (TBDA)). It is anticipated that there will be linkages with the TBDA (for more info on TBDA please visit: http://partnerships.ifpma.org/partnership/tb-drug-accelerator-program). It provides ready-to-use services for rapid progression of available (first line) new and innovative candidates. The platform is partly supported by the coordination and support group from Pillar A but includes management resources to self-sustain its scientific and financial reporting as well as innovation management procedures.

ERA4TB – 853989, selected under Pillar B from topic 8 of IMI2 JU Call 15 results in an action that creates a group to profile and progress anti-TB compounds from advanced lead through phase 1 and to collect, share, and analyse TB clinical trial data. Additionally, it addresses the development of new alternative anti-tubercular drugs (for example, host-defence or virulence approaches).

Topic 3 of IMI2 JU Call 20 will result in an action that will develop and implement innovative, state-of-the-art adaptive clinical trial designs for the field of TB regimen development able to define the therapeutic dose for existing experimental New Chemical Entities (NCE's) within treatment combinations. Additionally, it will exploit innovative technologies (including biomarkers and diagnostics) to facilitate and monitor adherence in resource-poor settings, while generating evidence that shorter regimens improve adherence.

[18] https://www.imi.europa.eu/sites/default/files/uploads/documents/apply-for-funding/open-calls/IMI2_Call15_CallText.pdf
[19] For additional details see the topic 7 "Capability Building Network" of IMI2 JU Call 15

Pillar C: Portfolio Building Networks (PBN) to advance the R&D pipeline of new and innovative agents to address AMR.

As in the CBN, the overall scientific scope in the PBN is broad, including prevention (vaccines, mAbs, immunoprophylaxis, and others) and treatment (new antibiotics, non-antibiotic alternatives, formulation strategies, and combinations). Within this broad scope, the PBN provides a mechanism for dedicated partnerships between EFPIA companies and SMEs and/or academic teams for the discovery and development of new antibacterial assets, including in select cases TB and NTM. Assets and projects originate from SMEs, academia, or EFPIA companies, and are jointly progressed or studied, including both pre-clinical work and potentially phase 1-3 clinical development. The PBN is also potentially useful to generate new clinical/regulatory phase 3 pathways for pathogens such as NTM and to conduct phase 2 trials in TB.

Collaboration agreements

To ensure smooth operation of the projects in the AMR Accelerator, the grant agreement of the first CBN action (COMBINE – 853967 selected under Pillar A from IMI2 JU Call 15 topic 7, and containing the coordination and support group[20]) is complementary to all the grant agreements of actions selected under Pillars B and C (via IMI2 JU Call 15 topic 8, IMI2 JU Call 16 topics, IMI2 JU Call 20 topic 3 and potential future additional calls for proposals), as well as probable future grant agreements from actions selected under Pillar A. In addition, all grant agreements of actions under pillar B will be complementary between them. The respective options of Article 2, Article 31.6 and Article 41.4 of the IMI2 JU Model Grant Agreement[21] will be applied. Accordingly, the consortia selected under Pillars A, B, and C will conclude collaboration agreements with the COMBINE – 853967 consortium selected from IMI2 JU Call 15 topic 7. These collaboration agreements will provide the framework for COMBINE – 853967 to provide day-to-day support of projects in the AMR Accelerator programme, and will ensure the exchange of relevant information, exploration of synergies, collaboration where appropriate, and avoid duplication of efforts.

Furthermore, a memorandum of understanding (MoU) will be pursued between the Pillar B TBDDN actions (ERA4TB – 853989 and Call 20 topic 3) and the Integrated Research Platforms (IRP) action of IMI2 JU Call 15 topic 1 (EU-PEARL – 853966) to cover collaboration and sharing of information on TB-related activities. The MoU should constitute one deliverable in each action resulting from ERA4TB-853989 and topic 3 of IMI2 JU Call 20. Similarly, when reasonable, a MoU should be pursued between potential TB-focused actions under Pillar C of the AMR Accelerator (resulting from IMI2 JU Call 16) and TBDDN actions, as well as the IRP action of IMI2 JU Call 15 topic 1 (EU-PEARL – 853966), with appropriate provisions to protect confidentiality of the interactions between the consortia and their intellectual property rights.

Need and opportunity for public-private collaborative research

The discovery and development of new antibiotics and alternative treatment and prevention options for multi-drug resistant infections is a high medical and societal need. The AMR Accelerator will address multiple challenges in a coordinated programme, which offers excellent opportunities for collaborative work between different sectors and disciplines. Moreover, operating with the support of the coordination and support group in the CBN will allow for greater efficiency, by reducing the need for duplicative management structures or processes.

Due to the current low return on investment that developers can expect for agents to address AMR, this scientific area has not received the investment that was seen in the ‘call to action’ to address HIV/AIDS and on par with the public health threat. Consequently, public-private partnerships (PPPs) such as the framework provided by the IMI2 JU continue to be critical to that effort.

[20] For additional details see the topic 7 “Capability Building Network” of IMI2 JU Call 15.
[21] See: https://www.imi.europa.eu/sites/default/files/uploads/documents/reference-documents/h2020-mga-imi_en_v5.pdf

Excellent examples have been the previous and current investments by the European Union and IMI (ND4BB, Model-based preclinical development of anti-tuberculosis drug combinations (PreDiCT-TB), More Medicines for Tuberculosis (MM4TB), Open Collaborative Model for Tuberculosis Lead Optimisation (ORCHID), anTBiotic), the NIH (Tuberculosis Research Units Network, TBRU-N) and the Bill & Melinda Gates Foundation (TB Drug Development Accelerator and TB Alliance discovery portfolio). Multiple new drug candidates are in the pipeline for the treatment of TB for the first time in decades, and are reaching or about to reach the clinic. Existing drugs are being repurposed or optimised for TB with the potential of shortened treatment duration for drug-sensitive TB and safer, shorter treatments for MDR-TB. In ND4BB, immense progress has been made from basic science to discovery of novel lead molecules through to running interventional clinical trials.

However, more work is critical to continue to address the constantly emerging global challenge of AMR. For example, there is a challenge of maturing the TB pipeline from the selection of candidates to progression through phase 1 studies, in addition to parallel studies to determine the optimal combinations to create new pan-TB regimens. Also, the ever-evolving resistance landscape requires additional investment to validate new tools and approaches, in addition to progressing potential new therapies to prevent and treat bacterial infections.

Acting to address these challenges in a single, coordinated Accelerator offers excellent opportunities for collaborative work between different sectors and disciplines in an area of critical scientific need.

The development of the AMR Accelerator will contribute to a vibrant AMR community in Europe and will offer potential opportunities for individual partners, such as:

- Capability Building Network:
    - Play key role in a EU AMR programme with connectivity to the broader global agenda on AMR;
    - Enable SME, and/or academic groups to progress pre-competitive basic science project in the AMR field;
    - Provide an opportunity to work within a broad network of researchers focused on AMR science and gain additional experience in AMR science and drug discovery.
- Tuberculosis Drug Development Network:
    - Enable SME and/or academic groups to progress pre-competitive basic science project in the TB field;
    - Enable SME and/or academic groups to progress potential drugs from pre-candidate status through to ‘ready for phase 2’ status, including, but not limited to GLP and GMP scale up, formulation, toxicology studies, and phase 1 clinical studies, including preclinical combinations of drugs;
    - Provide the opportunity to work within a broad network on researchers focused on TB drug discovery.
- Portfolio Building Network:
    - Provide the opportunity for SMEs and/or academic groups to partner with EFPIA companies to enable progression of promising assets or technologies to key milestones, creating value and sharing risk. There will be potential to further extend such partnerships with EFPIA companies beyond the scope of the AMR Accelerator following project completion;
    - Allow a vibrant partnering ecosystem that will benefit SMEs or academics with early stage assets based on pre-agreed conditions and milestone decision points.

Applicants to Calls launched as part of the AMR Accelerator programme should consult the IMI2 JU Model Grant Agreement and IMI2 JU Annotated Model Grant Agreement, as well as a short questions and answers document available at https://www.imi.europa.eu/sites/default/files/uploads/documents/apply-for-funding/open-calls/Questions_and_answers_on_the_AMR_accelerator_programme.pdf.

Topic 2: Modelling the impact of monoclonal antibodies and vaccines on the reduction of antimicrobial resistance

Topic details

Topic code	IMI2-2020-23-02
Action type	Research and Innovation Action (RIA)
Submission and evaluation process	2 stages
IMI2 Strategic Research Agenda - Axis of Research	Innovative medicines
IMI2 Strategic Research Agenda - Health Priority	Vaccines

Specific challenges to be addressed by public-private collaborative research

Unmet medical needs

Antibiotics have greatly improved the health and life expectancy of human beings, but antimicrobial resistance (AMR) is rising, and deaths due to infections have been predicted to exceed the ones caused by cancer by 2050[22]. The World Health Organization (WHO)[23] and the Centers for Disease Control and Prevention (CDC) of the United States[24] have recently listed the priority human pathogens with threatening drug-resistance patterns. New generation antibiotics, vaccines and antibody-based biologics can all contribute to the response to the global challenge of antimicrobial resistant pathogens.

Challenges

Vaccines and monoclonal Antibodies (mAb) may reduce antimicrobial resistance (AMR). However, individual vaccine developers and manufacturers, as well as organisations developing mAbs and health authorities, acting alone, do not have the resources and the full expertise required to make a realistic and comparable assessment of the use of the different products on the reduction of AMR. This could instead be possible through the development of a mathematical model. For such a model to be representative of the concerns and interests of the various actors (i.e. industry and the public health sector), it should take into account the perspectives of these different actors in order to capture all relevant impacts both in terms of costs and health outcomes.

Therefore, quantifying the impact of vaccines and mAbs requires a broad collaboration involving partners from academia and industry to tackle the following specific challenges:

- **Measurement of the burden of disease (BOD) and costs of AMR:** there is a need for a disaggregation of the BOD by subpopulation to compare the cost-effectiveness of targeting strategies to go beyond the work performed by Cassini et al[25] **Error! Reference source not found.**. This would require a much more granular estimation of the burden to capture which subpopulation (e.g. migrants, elders, patients with certain comorbidities, surgery procedures, long-term care residents, etc.) are contributing most to the health burden, through which types of infection and which type of AMR. This granularity is critical to inform strategies that are most likely to reduce the AMR burden. The future burden estimations will also try to include potential

[22] https://amr-review.org/Publications.html
[23] https://www.who.int/en/news-room/detail/27-02-2017-who-publishes-list-of-bacteria-for-which-new-antibiotics-are-urgently-needed
[24] https://www.cdc.gov/drugresistance/biggest-threats.html?CDC_AA_refVal=https%3A%2F%2Fwww.cdc.gov%2Fdrugresistance%2Fbiggest_threats.html
[25] Cassini et al have estimated the BOD in the EU but they did not forecast the BOD in specific target groups and they did not adjust the models "for age-specific risks, co-infections, appropriateness of antibiotic therapy, or for type of care, assuming common transition probabilities for all subgroups".

incremental side effects such as increased disability, due to the fact that certain key surgery procedures will be less accessible thanks to the increased risk AMR will pose to the safety of surgeries. Once a more granular burden of disease is built, it could be possible to test which vaccine and monoclonal antibodies need to be prioritised and through which targeting strategy. As such, it requires access to multiple data sources to quantify the burden of disease and cost of AMR.

- **Limitation of models in capturing the complexity of AMR:** no model structure has yet fully captured (a) the direct effect of vaccines and mAbs in preventing bacterial infections and how this reduces morbidity and mortality, the spread of the pathogens (including antibiotic resistant strains) and the limit in the use of antibiotics to treat them; (b) the indirect effect of creating herd immunity (including the reduction of infection in immunocompromised, elderly and cancer patients); and (c) the variation in strain prevalence across countries and subpopulations. Modellers from academia should team up with modellers from industry to develop, test and make publicly available a more complex and complete model, taking into consideration academic, public health and industry perspectives.
- **Real data are not easily available to set parameters for the models**. This gap is frequently filled by running mathematical models with differential equations, which are based on assumptions that are not validated against real data. There is a need to generate new data and to use existing data from studies to improve the predictions.
- **There is insufficient information on the cost-effectiveness of vaccination and mAb strategies against AMR pathogens**. With so many pathogens and resistance profiles, there is a need to determine which vaccines and mAbs should be prioritised first and what population groups should be targeted. Scarce resources and opportunity costs require a more qualified approach than just generic statements on the usefulness of vaccines or mAbs to tackle AMR. Academic partners and industry need to agree on how cost-effectiveness should be estimated or what type of target population should be covered.
- **Model forecasts need to be validated**. The CDC and the ECDC rely upon surveillance systems that are far from perfect in terms of AMR standardised case definition and representativeness from states and countries. There is a need to calibrate the models by filling information gaps and verifying assumptions, on the basis of real data coming from the health care systems in a few pilot countries sourced from national information systems.

Scientific opportunity

Tackling the above-mentioned challenges will clarify which are the most cost-effective vaccines and mAb strategies to reduce infections and antibiotic consumption, increasing our ability to create a sustainable solution to AMR. It requires gathering the best European scientists, data analysts and data scientists, and modellers from academia and industry, to work together to make use of existing and future data, to develop specific models and to test, run and improve these models on publicly available platforms. This will allow regulators, policymakers, industry and HTA bodies to benefit from science-based evidence on the real impact of specific vaccines or mAbs on AMR. The success of the project depends strongly on complementarity between the academic partners specialised in model development, AMR assessment, epidemiology and health economics, and the industry partners with expertise on technical and clinical development, as well as on model development. Models are simplified versions of a complex reality and can be influenced by the approach taken by modellers who bring their own backgrounds, perspectives and training. Allowing an exchange of views and information between the various actors (in particular industry, academics, regulators, HTA bodies, and policymakers) will allow the improvement of the structure of the model and better inform its parameters, reducing thus both structural and parametric uncertainties in the outcomes. In addition, limiting industry-driven biases in model development will create a better chance that the policy options supported by the model outcomes will be acceptable to the decision makers who are frequently in the public sector.

Reasons for a public-private partnership

AMR has gradually depleted the antibiotic armoury and disaster will strike when the last class of antibiotics becomes ineffective. A model will have the benefit of predicting the reduction of AMR associated with novel mAb and vaccination strategies against AMR pathogens. This information should allow public health institutes and/or companies to select the right direction among several priorities. The results of the model shall then be used to better inform policy decisions which are more likely to be accepted and implemented if both the private and public sector perspectives are taken into account. Joining forces increases the chance that all points of view of the major actors

feed into the analysis and produce final results that are *are more likely to be agreed upon* because they have been built through a consensus process[26]. Whatever interventions and target groups will be prioritised, subsequent health interventions need to be financed through private and public resources and therefore it is important that both perspectives are taken into account during the modelling exercise.

Combining different perspectives, scientific interests, domains and expertise will create synergies that are not possible if academia or industry operate in isolation. The only way to address the challenges ahead is therefore through a public-private partnership that brings academia and industry together in a common effort.

Scope

The goal of the project is to **develop a framework for setting up antimicrobial resistance (AMR)-focused economic evaluations of vaccines and mAbs. The challenges include a measurement of the present rate of growth of AMR, its main drivers, its health and economic consequences, and which vaccines and mAbs might have the best chance of reducing the rate of AMR growth and the related health and economic consequences.** The model will build upon the work done by previous models in depicting the infection dynamics of key pathogens in specific populations that lead to antibiotic consumption and AMR, and will simulate the impact of mAb and vaccination strategies on the chain of events.

In a systematic review on AMR mathematical models, Birkegård et al [2] found that few selected studies fulfilled the TRACE modelling practice guidelines[27]. The recommendations of the authors for future mathematical models on AMR included: "a) model the biological processes mechanistically, b) incorporate uncertainty and variability in the system using stochastic modelling, c) include a sensitivity analysis and model external and internal validation".

The project has the following objectives:

- **Evaluate the burden of disease of AMR** by estimating inpatients' (acute care hospitals and long-term care facilities) and outpatients' infection rates in at least 8 EU countries for which suitable data is collected and available, as well as in the US[28], and the relative attributable risk for morbidity, mortality and costs.
- **Build a comprehensive AMR model** (i.e. model structure, parameters, assumptions) based on an analysis of the strengths and weaknesses of existing models, and a gap analysis.
- **Collecting, gathering, and analysing data** from existing databases to feed the model.
- **Develop and test a cost-effectiveness analysis (CEA)** to estimate the cost and benefits of covering defined target groups (e.g. 18+, 60+, surgeries) with mAbs and vaccines.
- **Set up a study** to test, monitor, evaluate and improve the model.
- Ensure a **public and broad access to the model**.

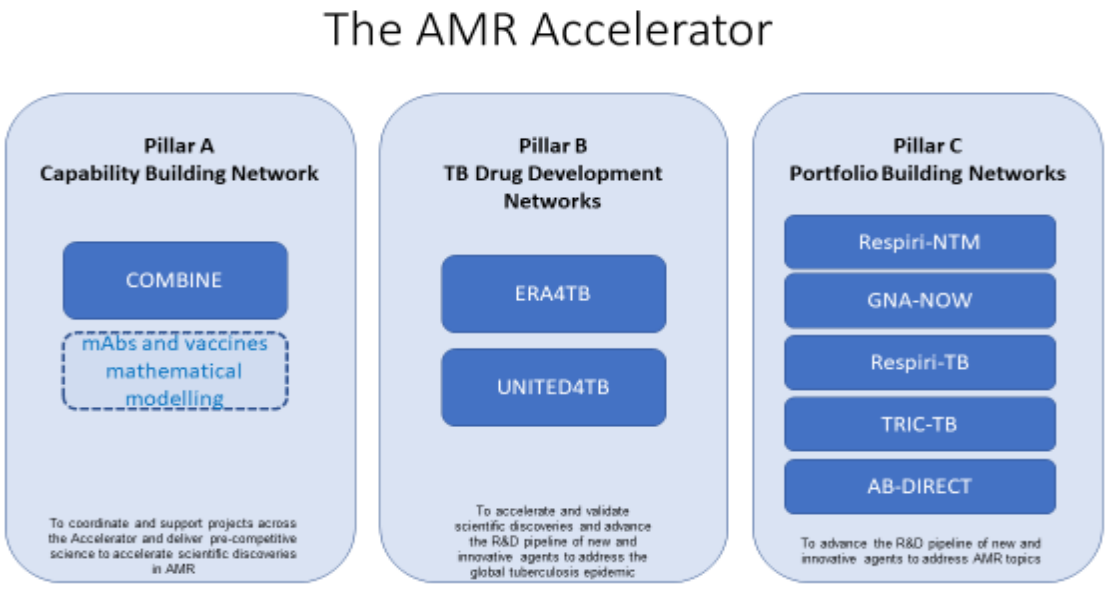
The model and studies should not target specific bacteria, but should apply as a general tool adaptable to various bacteria.

[26] As an example, when building Disability Adjusted Life Years lost because of AMR, the industry might be more inclined to give more weight to the productive age groups while the public-health perspective might give equal weight to all age groups.
[27] TRACE is a general framework for documenting a model's rationale, design, and testing. The TRACE guidelines include the following 8 elements: "1) Problem formulation (clear formulation of the objective and a description of the context of the model); 2) Model description (written description of model elements to allow readers to understand and replicate the model); 3) Data evaluation (an assessment of the quality of data used to parameterise the model); 4) Conceptual model evaluation (a list and explanation of the most important conceptual design decisions); 5) Implementation verification (internal validation of the model, testing for programming errors and assessing model performance); 6) Model output verification (external validation, testing whether the model output matches the observations); 7) Model analysis (mainly sensitivity analysis); 8) Model output corroboration (a comparison of model output with data that were not used to create the model)
[28] Access to data from the US will be provided by the EFPIA Partners who have licenses to databases.

Collaboration agreement(s)

To ensure smooth operation of the projects in the AMR Accelerator, the grant agreement of the first CBN action (COMBINE – 853967 selected under Pillar A from IMI2 JU Call 15 topic 7, and containing the coordination and support group[29]) is complementary to all the grant agreements of other actions selected under Pillars A, B and C (via IMI2 JU Call 15 topic 8, IMI2 JU Call 16 topics[30], IMI2 JU Call 20 topic 3[31], IMI2 JU Call 23 topic 2 and related grant agreements).

The respective options of Article 2 (complementary grant option), Article 31.6 (complementary grant option) and Article 41.4 of the IMI2 JU Model Grant Agreement will be applied. Accordingly, the consortia selected under this topic from the AMR Accelerator Pillar A will conclude a collaboration agreement with the COMBINE – 853967 consortium selected from IMI2 JU Call 15 topic 7. This collaboration agreement will provide the framework for COMBINE – 853967 to provide day-to-day support of projects in the Accelerator, and will ensure the exchange of relevant information, exploration of synergies, collaboration where appropriate, and avoid duplication of efforts.



The action in the CBN resulting from this topic 2 in IMI2 JU Call 23, will implement a research and innovation action to develop a framework for setting up antimicrobial resistance (AMR)-focused economic evaluations of vaccines and monoclonal antibodies (mAbs). A mathematical model will be developed and made publicly available to assess the impact of vaccine or mAb strategies in the reduction of AMR.

Expected key deliverables

- Burden of Disease caused (BOD) by AMR. The systematic review of the literature on the BOD of AMR will lead to an **epidemiological repository** of incidence, prevalence, disability (e.g. disability-adjusted life years – DALYs,

[29] For additional details see the topic 7 "Capability Building Network" of IMI2 JU Call 15.
[30] https://www.imi.europa.eu/sites/default/files/uploads/documents/apply-for-funding/open-calls/IMI2_Call16_CallText.pdf
[31] https://www.imi.europa.eu/sites/default/files/uploads/documents/apply-for-funding/open-calls/IMI2_Call20_CallText.pdf

quality-adjusted life year – QALYs), mortality, short- and long-term disability, consumption of antimicrobials, costs and other parameters associated with main pathogens and population groups. The repository will provide the basis for the estimation of the BOD caused by infectious disease and the contribution due to AMR. This repository will be complementary to the following existing databases:

- In comparison with to the current ECDC database and any relevant valuable national database on AMR that is based on laboratory reporting, this repository will provide all the estimates available in the literature, with more information, for example, on incremental costs associated with AMR from case control studies.
- Similarly, the notifications of infectious diseases of the ECDC database are very useful for surveillance, but cannot be used to estimate or infer population incidence. The project repository will provide a rich data source of the incidence of pathogens by target group derived from the literature.

Reliability should be ensured by a thorough quality control policy to be implemented before placing any information on incidence of infections in the repository, with a description of the method used to estimate the incidence.

For this deliverable, the consortium should particularly, where appropriate, build on existing work, avoiding duplication of efforts.

- A **systematic review of mathematical models** on the effect of vaccines and mAbs on AMR. The review should include the analysis done on the impact of vaccines against main bacteria such as, for instance, pneumococcus or *Haemophilus influenzae*. This will help to identify the strengths and weaknesses of existing models, and suggest new data gathering and analytical strategies to tackle limitations and fill gaps.
- Construction of a **mathematical model**. The mathematical model should be developed on an open-source basis and be made available to the research and scientific community at the end of the project. The structure will build upon what has already been done and will consider potential entry points in which real data could anchor the model to real operational settings as examples of AMR control. Examples include the screening at admission for methicillin and carbapenem resistance in a sample of hospitals, not only in the EU but also possibly in the US where additional data are available. In mathematical modelling, the main problem is to parametrise the model. It is unlikely that all the parameters could be available just using data from EU countries and for this reason, some extrapolations would be needed from the literature. Some parameters for which there is insufficient information from published studies carried out in the EU may require some inference to be deduced from the US studies, as most of the published research currently comes from there. For example, it is frequently difficult to have the attributable costs or the attributable mortality due to AMR per se (taking into account comorbidities).
- **Economic evaluation of alternative mAbs and vaccines** strategies. Several scenarios will be tested, comparing mAb vs vaccines, and different mAb strategies separate from different vaccine strategies. The comparator will be existing AMR control strategies. Different approaches leading to different scenarios would have to be presented and tested in sensitivity analyses in order to assess their impact on model outcomes. The potential biases and validity of each scenario should be discussed, without excluding the possibility of using an alternative scenario as the base case.
- The results will suggest the strategic directions on where to invest and the relative target product profiles of mAb and vaccines.
- Monitoring and evaluation plan. A detailed multi-year plan on how to monitor AMR will be tested in a few countries to verify the assumptions and predictions of the model.

Expected impact

The **epidemiological repository** that will be obtained in Work package 1, besides providing a transparent basis for the BOD estimation, will be made accessible through an internet database to be designed within the project. Any researcher will benefit from using the most comprehensive database on the epidemiology of infectious diseases and resource consumption associated with sensitive and resistant pathogens. Producing a reliable repository with clear description of the methods used to derive the estimates of the BOD and AMR will benefit the credibility of the results of the mathematical model. During the project, the access will be free of charge. After the end of the project, the conditions for access will depend on the operational model to ensure the maintenance and sustainability of the

databases, and compliant with the IMI2 JU intellectual property policy. The ambition is to favour open access as much as possible.

The results of the mathematical model (publicly available and free of charge) will allow policymakers and healthcare managers to make informed decisions on vaccines and mAb strategies. The impact will include clear direction for EFPIA partners and health care authorities on which research and development strategies should be prioritised to reduce AMR through vaccine and monoclonal antibodies.

Better chance of preserving the efficacy of last-resort antimicrobials. As an example, the European Centre for Disease Prevention and Control has published guidelines for the screening of patients at high risk for Carbapenem Resistant Enerobacteraceae (CRE) and Carbapenemase Producing Enterobacteriaceae (CPE) at the time of admission [3]. The retrospective record review will provide an assessment on their status of implementation and will allow estimatation of the resources required to put in place a functional screening and surveillance system for CRE and CPE, as well as other types of resistance.

Testing the sustainability of the study approach by financing a multi-year monitoring and evaluation system in key health units of a few pilot countries. The impact will be a strengthening of the existing AMR surveillance systems, and a verification of the assumptions and parameters underlying the model. For example, an initial model focused on a specific vaccine or mAb might provide an initial base which will be fine-tuned according to real data, and which will be further expanded to other promising mAbs and vaccinations, with further fine-tuning.

In their proposals, applicants should outline how the project plans to leverage the public-private partnership model to maximise impact on innovation, research & development; regulatory, clinical and healthcare practices, as relevant. This could include a strategy for engagement with patients, healthcare professional associations, healthcare providers, regulators, HTA agencies, payers etc., where relevant.

In addition, applicants should describe how the project will impact the competitiveness and growth of companies including SMEs.

In their proposals, applicants should outline how the project will:

- Manage research data including use of data standards[32];
- Disseminate, exploit, and sustain the project results. This may involve engaging with suitable biological and medical sciences research infrastructures[33];
- Communicate the project activities to relevant target audiences.

In addition, the following additional exploitation[34]/dissemination[35] obligations must be considered to maximise impact:

- Ensure that the models that will be developed remain available online and updated after the end of the project and for a period up to 5 years.

Potential synergies with existing consortia

Synergies and complementarities should be considered with relevant national, European and non-European initiatives (including suitable biological and medical sciences research infrastructures in order to incorporate past achievements, available data and lessons learnt where possible, thus avoiding unnecessary overlap, and duplication of efforts and funding.

[32] Guidance on data management is available at http://ec.europa.eu/research/participants/docs/h2020-funding-guide/cross-cutting-issues/open-access-data-management/data-management_en.htm
[33] http://www.corbel-project.eu/about-corbel/research-infrastructures.html
[34] Article 28.1 (Additional exploitation obligations) of the IMI2 Grant Agreement will apply.
[35] Article 29.1 (Additional dissemination obligations) of the IMI2 Grant Agreement will apply.

Industry consortium

The industry consortium is composed of the following EFPIA partners:

- GlaxoSmithKline Biologicals
- Janssen Vaccines & Prevention
- Pfizer

The industry consortium plans to contribute the following expertise and assets:

- GlaxoSmithKline Biologicals

Expertise: epidemiology, biostatistics, infectious disease modelling, health economics, database management, web design, vaccine pre-clinical and clinical science, mAb pre-clinical and clinical science, translational research, immunology, phenotypic and genetic characterisation of microbial strains.

Model development: allocation of a dedicated modeller to co-develop the model with other partners.

Databases access: access to CPRD (Clinical Practice Data Linkage) and IBM Truven Marketscan (including US data).

- Janssen Vaccines & Prevention

Expertise*:* clinical development, market access and modelling.

Model development: allocation of a dedicated modeller to co-develop the model with other partners.

- Pfizer

Expertise*:* clinical development, market access and modelling.

Indicative duration of the action

The indicative duration of the action is 60 months.

This duration is indicative only. At stage 2, the consortium selected at stage 1 and the predefined industry consortium may jointly agree on a different duration when submitting the stage 2 proposal.

Indicative budget

The financial contribution from IMI2 JU is a maximum of EUR 6 500 000.

The indicative in-kind and financial contribution from EFPIA partners is EUR 2 760 000.

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

Expertise and resources expected from applicants at stage 1

The stage 1 applicant consortium is expected, in the submitted short proposal, to address all the objectives and key deliverables of the topic, considering the expected contribution from the industry consortium which will join at stage 2 to form the full consortium.

The stage 1 submitted short proposals should include suggestions for creating a full proposal architecture, which could be in line with the suggested architecture described below, though this architecture is only a suggestion.

This may require mobilising, as appropriate the following expertise:

- Epidemiology;
- Statistics;
- Health Economics;
- Microbiology;
- Laboratory techniques associated with AMR;
- Database management, data scientists;
- Database web programming;
- Computational and mathematical modelling in infectious diseases;
- Management Information Systems;
- GDPR compliance.

The consortium should involve and associate key actors from academia that have conducted/are planning to conduct mAb clinical trials or are involved in mAb research.

- It is important to involve public health agencies/authorities because their expertise can substantially contribute to the scientific soundness of the study and because it is important to add their perspective[36]. This will ensure that the project will fully consider public health needs and is not mainly driven by pharma industry. Regulatory authorities could also have an interest to be involved in the consortia to ensure the design of the model will meet their expectations.

The size of the consortium should be proportionate to the objectives of the topic while ensuring its manageability.

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

- Access to CDC and ECDC databases;
- Expertise in dealing with data (retrieve, curate and analyse data), including data coming from US databases;
- Access to hospital information systems and general practitioner databases for the retrospective data collection;
- Access to the health information systems in the countries selected by the applicants.

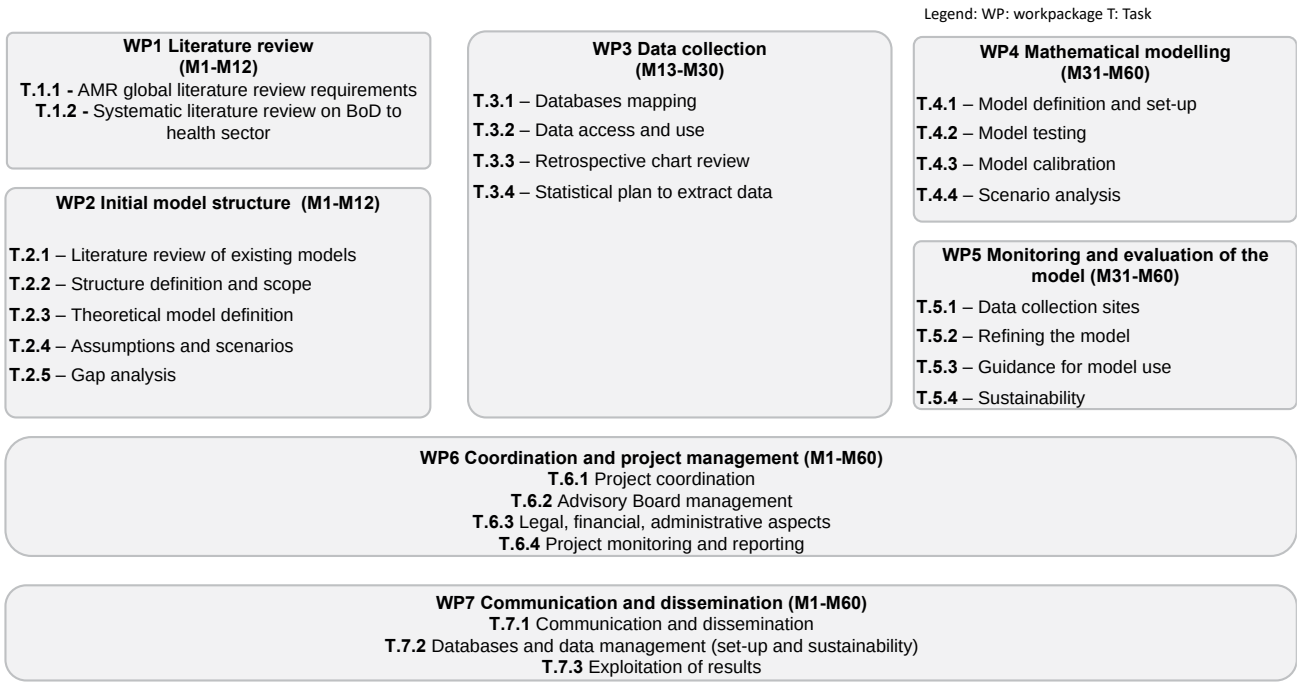
Considerations for the outline of project work plan

In their stage 1 proposals applicants should:

- Give due visibility on data management; dissemination, exploitation and sustainability; and communication activities. This should include the allocation of enough resources for these tasks which will be further developed in stage 2 proposal;
- Consider including a strategy for ensuring the translation of the projects results to drug development, regulatory/ health technology assessment (HTA) settings (e.g. through scientific advice/ qualification advice /opinion, etc.), clinical and healthcare practices and/or decision-making processes.

[36] To avoid potential conflicts of interest or issues from PHA to participate in a consortium with EFPIA partners, the applicants should propose the best and most realistic way to include these organisations.

Suggested architecture



Work Package 1 – Burden of disease due to AMR

The goals of this work package are:

The estimations of the inpatients' and outpatients' infection rates should at least be sorted by sensitive and resistant pathogens by population group (e.g. age, presence/absence of comorbidities), by type of disease, by type of surgery and other specific categorisation of patients.

Work Package 2 – Model structure development

These developments could include different activities such as:

- Conducting a systematic review of the models used to predict the influence of mAbs and vaccines for treatment or prevention. The review will help to clarify model structure, parameters, assumptions, strength and limitations, and gaps to be filled.
- Clarifying the scope: AMR is a universal and a complex phenomenon. Bacteria develop resistance by natural selection even without the use of antibiotics and this fraction of natural AMR is rarely taken into account. Such natural selection is speeded up when antibiotics are used for animal and human health and then antibiotics are released in the environment, ending up in the food chain. Covering all the variables influencing the complexity of AMR development in the different sectors (natural development, food production, veterinary health and health care) would be impossible, and a narrower focus is needed to make the study manageable. The model is likely to cover the health sector, leaving out the contribution of the veterinary and agricultural sectors and the natural selection of resistant strains.
- Identifying assumptions and information gaps in parameters will involve a review of the disease ecological dynamics, notably:
    - Natural history of disease for sensitive and resistant pathogens in the general population or in health care settings including asymptomatic incubation, latency, infective stage, differential probability of transmission between a susceptible and a resistant strain, fitness costs, probability of acquiring resistance if exposed;

- AMR Diagnostics sensitivity, specificity and positive/negative predictive values;
- Attributable outcomes by sensitive and resistance pathogen considering comorbidity, age and other confounders;
- Type of antibiotic consumption, with a special focus on carbapenems, extended spectrum beta-lactamase, fluroquinolones and 3rd generation cephalosporines and the probability of acquiring specific resistance if exposed to these antibiotics.

Work Package 3 – Data gathering

The goals of this work package are:

Databases already identified by industry include the Marketskan[37] and other claims (e.g. Kaiser Permanente) databases in the US, the NHS[38] and GP databases[39] in the UK, the Epidemiologie – France Portal Health Database[40], the health care database of the German Institute of Medical Documentation and Information[41], Health for All Italia[42]. Examples of data to be collected from databases include MRSA and CRE screening and isolation carried out in US and UK hospitals, as well as similar national surveillance data from the EU Member States. This care-focused approach has the main objective of operationalising the issue of AMR by modelling different impact pathways for vaccines and mAbs while narrowing the scope of both to nosocomial transmission. This approach will also geographically focus on the EU as priority settings because data are available and screening processes are in place for priority pathogens. Besides providing a specific operational context, this focus on MRSA and CRE screening also has the advantage of being of high priority in EU countries' policy agendas.

Work Package 4 – Cost-effectiveness analysis (CEA)

The cost-effectiveness will be estimated for alternative target product profiles. The WP4 will for instance have to decide:

- Which vaccines and mAbs should be included in the model. The first skeleton of the model will be based on previous assessments of the impact of existing vaccines, for example the impact of Pneumococcal Conjugate Vaccine on penicillin non-susceptible strains and the impact of influenza immunisation programmes on antibiotic prescription. This initial assessment will provide a better idea of how experience has tried to depict the patient pathways through which prevention of infection on specific bacteria and viruses can impact antibiotic consumption, AMR, health outcomes, resource consumption and costs. This initial model construction could be expanded to other vaccines and mAbs, generating several potential models and identifying common elements which could produce a core structure which could be adapted to model the impact of other vaccines and mAbs.
- Whether or not to limit the perspective to health care costs or to add social costs, too. Examples of health care costs include lengthier hospitalisation of AMR hospital infections vs the same type of infection due to sensitive bacteria. Costs will take into account the different health care systems of the EU and other countries. Cost comparability will have to consider inflation adjustment for estimates taken in different time periods, and the exchange rates of different currencies vs the reference currency (e.g. USD). An example of social costs might include lost income due to incremental length of hospitalisation and other social consequences.
- What to include in the existing standard of care (comparator). The incremental benefits of mAbs and vaccines will be compared with existing preventive strategies (e.g. Methicillin Resistant *Staphylococcus aureus*

[37] https://www.ibm.com/products/marketscan-research-databases
[38] https://www.nhs-database.co.uk/
[39] https://www.cprd.com/home/
[40] https://epidemiologie-france.aviesan.fr/en
[41] https://www.dimdi.de/dynamic/en/further-services/health-care-data/
[42] https://www.istat.it/it/archivio/14562

(MRSA) screening and isolation), stewardship for the correct antibiotic prescription, and similar existing activities.

- The patients' pathways by type of health care setting. This includes the various steps patients go through between admission and discharge (e.g. carbapenem resistant screening and isolation) to capture all the costs due to resource consumption and the transmission dynamics (e.g. in the case of not complying with screening and isolation).
- The strategic options will be evidence-based, through the selection of interventions on the basis of their demonstrated efficacy in clinical trials, their feasibility and operational effectiveness in clinical settings, and their targeting strategies to provide the most health gains and economic savings.
- Predict potential impact of novel vaccines and mAbs against AMR in reducing the emergence of resistance.

The model should also inform future research agendas by exploring the impact of uncertainty around (expected) data gaps. Notably, to explore uncertainty around 1) attributable incidence of resistance acquisition due to antibiotic exposure, and 2) differential probability of transmission between susceptible and resistant strains (fitness cost). This exploration will help to dentify drivers of both structural and parameter uncertainty on costs, impact and cost effectiveness, therefore setting future research agenda items.

Work Package 5 – Evaluation

The goals of this work package are:

The objective is to set up a long-term monitoring and evaluation strategy to calibrate the model. This will be done by building a monitoring and evaluation system in a few pilot countries to verify certain assumptions of the model and the reliability of parameters. The type of data, the structure of the data gathering and reporting will depend on the knowledge acquired from WP1–WP4. Attempts will be made to find out whether or not the COMBACTE network (e.g. COMBACTE –MAGNET) or other consortia have carried out similar types of management information systems to evaluate the results of AMR models.

Work Package 6 – Coordination and Management

The goals of this work package are:

The project will require strong coordination between the partners and regular follow-up of progress. A steering committee will be formed by representatives of EFPIA and BRF (Beneficiaries Receiving Funding) to steer the direction towards achieving the objectives. The coordinator will set up a project management office to ensure strong coordination and management.

In addition, the model should be tested under a collaborative study that should be developed as a horizontal activity within WPs 2, 3 and 5, in which an academic partner will be the sponsor, responsible for recruiting other academic institutions and hospitals that will participate in the implementation of the study. The sponsor institution will appoint core staff in charge of managing the study.

Work Package 7 – Communication and Dissemination.

The goals of this work package are:

The progress of activities will be summarised on a website or in newsletters that will be distributed at regular intervals to all partners. Scientific publications will also be prioritised to inform about the model and draw attention of the vaccine and modeller communities. General annual meetings will be convened to summarise annual achievements in project WPs and a final Workshop will provide the overall results. Dissemination of results will be carried out also by participating in scientific conferences and annual meetings from public health agencies (e.g. PHE annual meetings).

Additional considerations to be taken into account at the stage 2 full proposal

At stage 2, the consortium selected at stage 1 and the predefined industry consortium jointly submit the full proposal developed in partnership. The full proposal is based upon the selected short proposal at stage 1.

In the spirit of the partnership, and to reflect how IMI2 JU call topics are built on identified scientific priorities agreed together with EFPIA beneficiaries/large industrial beneficiaries, these beneficiaries intend to significantly contribute to the programme and project leadership as well as project financial management. The final architecture of the full proposal will be defined by the participants in compliance with the IMI2 JU rules and with a view to the achievement of the project objectives. The allocation of a leading role within the consortium will be discussed in the course of the drafting of the full proposal to be submitted at stage 2. To facilitate the formation of the final consortium, until the roles are formally appointed through the consortium agreement, the proposed project leader from among EFPIA beneficiaries/large industrial beneficiaries shall facilitate an efficient negotiation of project content and required agreements. All beneficiaries are encouraged to discuss the project architecture and governance and the weighting of responsibilities and priorities therein.

Data Management

In their stage 2 proposal, applicants should give due visibility to data management including use of data standards. A full 'data management plan' (DMP) as a distinct deliverable must be delivered within the first 6 months of the project. The DMP needs to be kept up to date with the needs of the project and as such be updated as necessary during its lifetime.[43]

Dissemination, exploitation and sustainability of results

In their stage 2 proposal, applicants must provide a draft plan for dissemination and the exploitation, including sustainability of results. A full plan as a distinct deliverable must be delivered within the first 6 months of the project[44], and updated during the project lifetime and could include identification of:

- Different types of exploitable results
- Potential end-users of the results
- Results that may need sustainability and proposed sustainability roadmap solutions

Enough resources should be foreseen for activities related to dissemination and exploitation, including the plan for the sustainability of the project results. This may involve engaging with suitable biological and medical sciences Research Infrastructures (RIs).[45]

Communication

The proposed communication measures for promoting the project and its findings during the period of the grant should also be described and could include a possible public event to showcase the results of the project.

[43] Guidance on data management is available at http://ec.europa.eu/research/participants/docs/h2020-funding-guide/cross-cutting-issues/open-access-data-management/data-management_en.htm
[44] As an additional dissemination obligation under Article 29.1 of the IMI2 Grant Agreement will apply.
[45] http://www.corbel-project.eu/about-corbel/research-infrastructures.html

References

[1] Cassini A, Högberg LD, Plachouras D, Quattrocchi A, Hoxha A, Simonsen GS, et al. Attributable deaths and disability-adjusted life-years caused by infections with antibiotic-resistant bacteria in the EU and the European Economic Area in 2015: a population-level modelling analysis. Lancet Infect Dis 2019; 19 (1): 56–66. https://doi.org/10.1016/S1473-3099(18)30605-4

[2] Birkegård AC, Halasa T, Toft N, Folkesson A and Græsbøll1 K. Send more data: a systematic review of mathematical models of antimicrobial resistance. Antimicrob Resist Infect Control 2018; 7:117. https://doi.org/10.1186/s13756-018-0406-1

[3] Magiorakos AP, Burns K, Rodríguez Baño J, Borg M, Daikos G, Dumpis U, et al. Infection prevention and control measures and tools for the prevention of entry of carbapenem-resistant Enterobacteriaceae into healthcare settings: guidance from the European Centre for Disease Prevention and Control. Antimicrob Resist Infect Control 2017; 6: 113. https://doi.org/10.1186/s13756-017-0259-z

Topic 3 : A platform for accelerating biomarker discovery and validation to support therapeutics development for neurodegenerative diseases

Topic details

Topic code	IMI2-2020-23-03
Action type	Research and Innovation Action (RIA)
Submission and evaluation process	2 stages
IMI2 Strategic Research Agenda - Axis of Research	Target validation and biomarker research (efficacy and safety)
IMI2 Strategic Research Agenda - Health Priority	Neurodegenerative diseases

Specific challenges to be addressed by public-private collaborative research

Neurodegenerative diseases, and in particular Alzheimer's disease (AD) and Parkinson's disease (PD), represent a huge economic and societal burden.

One of the key barriers to the development of treatments for neurodegenerative disease is an insufficient toolbox of biomarkers and associated clinical progression data to easily screen populations, diagnose patients, monitor progression and response to treatment, all of which would improve the efficiency of clinical trials.

Investments by both funders and pharmaceutical companies have created significant amounts of data and samples that could be used to accelerate biomarker discovery and development in a major way. However, these valuable resources remain in silos, and cannot easily be shared and accessed by the research community.

Key unmet needs limiting the use of samples and data for the discovery, development and validation of neurodegenerative disease biomarkers today include:

- Sample and data access for research use: There is currently insufficient access to high-quality, longitudinal, and well-characterised samples (including clinically well diagnosed and controls) and accompanying clinical data to meet current and future demands.
- Sample quality: A lack of standardisation in collecting and processing samples and linked datasets causes large disparities in sample quality and decreases the utility of banked samples for researchers.
- Transparency: There is currently no centralised resource documenting what sample types and accompanying clinical datasets are available across different organisations (public and private), and what access restrictions may be in place.
- Data sharing: Platforms and processes for sharing clinical data to accompany samples and then to enable reutilisation of derived data are lacking or inadequate in terms of interoperability.

Enabling the sharing of, and access to, high quality samples and data for accelerating biomarker discovery and validation has a twofold public health benefit. First of all, it would foster more efficient and effective translation of research into public health relevant outputs by boosting cooperation, reproducibility of research, and its cost efficiency. Secondly the availability of validated biomarkers would both speed up the development of novel therapies and their effective deployment at scale, decreasing the significant burden on public health of neurodegenerative diseases. This is expected be seen with a focus on the development of early detection diagnostic tools, that leverage potentially peripheral biomarkers in combination with a digital signature, which are

easy to access and use. This will be significantly facilitated by building a platform for sample sharing and broader data access.

The fields of bio-banking, data sharing, and biomarker analysis are in constant and rapid evolution from technological, legal and ethical perspectives. Many different stakeholder groups have the relevant experience, know-how and resources but these are not currently shared or leveraged at scale. A synergistic, public-private partnership effort is needed to successfully tackle these challenges, and solve the current fragmentation, dispersion and lack of sustainability. A concerted initiative to create a scalable and self-sustaining public-private federated bio-banking infrastructure has never been tried before, nor have all the elements necessary for its success, such as upscaling and sustainability, been previously identified. The Innovative Medicines Initiative (IMI) framework offers an ideal model to create such an initiative at the necessary scale in terms of resourcing and the integration of all necessary stakeholder groups.

Scope

At the short proposal stage, applicants are expected to address all five objectives of this Call topic, providing the outline and strategy for implementing them as analysed below. These will be fine-tuned and fully developed at the full proposal stage jointly with the industry consortium.

1. Create a set of agreed principles to enable sharing and access to data and samples, taking into consideration all the established legal and ethical research standards and principles (e.g. General Data Protection Regulation (GDPR), legal, intellectual property (IP), ethical, regulatory, societal issues) and their practical implementation.

Applicants are expected to address all considerations (e.g. operational, GDPR, national legislation, ethical, intellectual property, social) for delivery, sharing and access of both the retrospective and prospective data and samples with the whole research community including drug developers. In particular, they must convincingly formulate how to ensure best practices and to enable the effective use of samples and data, respecting the wishes, intent and privacy of research participants. A first set of agreed principles needs to be available by the end of Phase one of the project (end of year one), to be further worked upon during the project duration, with an aim of agreeing on a final version of principles by the end of the funding period. These need to be effectively disseminated to the broader research community.

2. Establish a network that can house high quality data and samples, which could have federated and centralised elements. This must build on existing ongoing and relevant cohorts (see below). The overall solution has to be interoperable (e.g. with other global data platforms), scalable and suitable for a broad variety of both data types (including digital), and samples, from public and private (e.g. proprietary clinical trials) sources, whether they be part of the consortium or provided from external donors. The overall solution has to be interoperable (e.g. with other global data platforms), scalable and suitable for a broad variety of both data types (including digital), and samples, from public and private (e.g. proprietary clinical trials) sources, whether they be part of the consortium or provided from external donors.

Applicants need to demonstrate in their proposal the strategy and capacity to build, grow and deliver by end of the funding period a self-sustainable platform for high quality samples and data, sharable and accessible by the broader research community, including drug developers.

Applicants need to be aware that activities related to building a biorepository or data management and sharing platform from scratch are out of scope for this topic. Instead, they must build upon existing resources (including ongoing longitudinal cohorts or studies), knowledge and infrastructures to deliver a novel solution able to seamlessly incorporate existing retrospective samples and data with prospective samples and data collections. The industry consortium will make available a data platform (e.g., Alzheimer's Disease (AD) Workbench[46] via the

[46] To register as a user of the Alzheimer's Disease Workbench please go to the following web site : https://portal.addi.ad-datainitiative.org/ and follow the steps in this guide: https://knowledgebase.aridhia.io/article/registering-for-a-workspaces-account/

Alzheimer's Disease Data Initiative), which will soon start. The AD Workbench provides not just for storage but also for computational needs, tools, and a virtual analytics environment, among others. Thus, applicants are expected to propose solutions for adapting AD Workbench to create an instance of the data platform in Europe to achieve the objectives of the topic. Any data platform to be used in addition to and/or in combination with the AD Workbench must be open source and fully interoperable.

Ideally, the starting infrastructures for sample and data hosting would have been successfully utilised in international public-private multi-stakeholder settings and must be scalable and interoperable. The final platform created by the project could be based on a primary solution from the applicants, which needs to be interoperable with existing other solutions (and in particular AD Workbench) or could be primarily based on AD Workbench. In developing the final platform applicants must also consider that it has to be fit for purpose, i.e. capable of incorporating samples and data contributed by the industry consortium from previous clinical trials, plus, and importantly, samples and paired data collected in future clinical trials. Applicants need to demonstrate how the know-how and experience of the industry consortium and the industry-provided data platform is integrated for optimal operation and sustainability of the network platform.

The value of the datasets needs to be maximised through the creation or utilisation of e.g. a data environment in the cloud, which collects and harmonises existing data from academic cohorts and pharmaceutical studies that are already available with newly created ones. This should facilitate uniform data sharing and reutilisation with interoperability, for data analysis, artificial intelligence (AI) and machine learning applications. The platform is expected to enable secondary use of data acquired on samples including high-dimensionality data such as genomes, proteomes and metabolomes.

It is expected that under the 'agreed principles to enable sharing and access to data' in this network, components of data sharing and data return for partners or external research collaborators will be included, to ensure that those novel/derived data are generated based on data or samples provided.

3. Establish fair and transparent governance and processes specifically to enable sharing and access to data and samples.

Applicants must establish a credible sample and data access committee. They need to identify and apply clear and transparent rules of appointment of its members and ensure that there is relevant stakeholder representation (including patients).

In addition, and starting from the agreed principles (see objective 1), the consortium must develop an agreed charter to be followed by the access committee to enable consistent access to samples and data. The applicants also need to formulate a strategy to efficiently and effectively dynamically incorporate the learnings from the project activities into the project's governance and processes for data sharing and access, to keep it fit for purpose.

4. Test the above with the defined case studies and apply the learnings to fine-tune processes and use the outcomes to grow the platform.

To demonstrate the utility of the established entity, case studies must be proposed using data and samples to support biomarker discovery and validation. These need to include (but are not limited to):

- the amyloid-tau-neurodegeneration (ATN) system, which has been proposed as a very suitable staging and prediction system, but whose measurement still relies on complex markers which do not lend themselves easily to screening and testing of large numbers of elderly people;

- the complement pathway, which is a specific component of the inflammation response that is now recognised as a key factor in a wide range of chronic neurodegenerative conditions and has been genetically linked to Alzheimer's disease; furthermore, there continues to be increasing attention towards digital biomarkers (see point 3);

- digital biomarkers with the potential for monitoring neurodegenerative diseases given the ubiquitous nature of consumer electronics and powerful computational platforms.

As such, successful proposals have to include pilot case studies that at minimum target all the above described.

Applicants have to include the well substantiated description of:

- cohorts with early Alzheimer's disease, which will allow the evaluation of the ATN system, comparing more complex and expensive markers like cerebrospinal fluid amyloid β (Aβ) & tau, amyloid-positron emission tomography (PET) and magnetic resonance imaging (MRI) with potential liquid biopsy (blood, saliva,..) markers as alternate biomarkers and;

- cohorts with Parkinson's disease to investigate the impact/relation of the complement system on diagnosis, severity and progression. This should be especially in light of new classes of minimally invasive neurodegenerative disease biomarkers (e.g. autoantibodies, DNA methylation, exosomes) and sample matrices (e.g. saliva).

Since high quality is of paramount importance, applicants need to demonstrate:

- that the retrospective samples are of high quality and accompanied by high-quality, curated, standardized, and interoperable datasets, and;

- they have a strategy and robust methodology for ensuring high quality of the prospective data and sample collection. Prospective collection must be based on well-defined clinical cohorts, with bio-samples and digital biomarker data. This must build on state-of-the-art standards and processes with updates and new developments to allow moving to the next level and achieving the project objectives.

It is critical that they show how the know-how and experience of the industry consortium is leveraged in the full consortium to ensure the consistency and quality of samples, accompanying assays/standard operating procedures (SOPs) and data. In view of the expected use of samples and data for regulatory biomarker validation, the perspective of regulators should be included from day one of activities.

Applicants need to document that both samples and data described in their proposal are accessible and sharable with the whole public-private partnership from the start of the project activities, with the potential for broader availability by the end of the project. In addition, applicants must addressed how the retrospective sample and data collections will be further expanded and enriched both in size and type as a result of the activities of the project. This must importantly include digital data and longitudinal follow up at individual level, which is both sharable and scalable.

5. This platform must be a self-sustainable entity by the end of the project.

Applicants need to formulate how the network platform will achieve self-sustainability by the end of the project. Considering the challenges and demands for achieving this objective, relevant activities need to be in place from the beginning of the project and it is expected that a sufficient amount of the total IMI2 JU funding will be allocated to this important work-stream. To demonstrate self-sustainability, first of all applicants need to address how the established network will be able to handle the logistics required to receive, handle, process, store, and deliver samples at scale, both existing ones as well as new sample sets, as the initiative reaches maturity.

To respond to the rapid changes in the field, the consortium needs to perform an analysis of gaps and requirements to efficiently build and operate the platform and make it self-sustainable. This is to be part of a white paper, concluded by the end of the first year of activities (the first phase of the project). With the support of an advisory board (to be in place by month three of activities and including all necessary expertise and stakeholder representation, e.g. regulators, industry, patients, among others) the consortium will appraise original plans, available assets and expertise to adapt them as necessary. This may require some re-tuning in areas and activities of critical need and related budgeting to ensure achievement of the project objectives and progress to self-sustainability by end of the funding period. Significant changes will be taken on-board according to the relevant grant agreement procedure.

Applicants need to present a strategy and plan of activities to further grow the platform and ensure steady sample availability by attracting and integrating data and samples from novel cohorts and clinical trials beyond those

provided by consortium members. The plans need to be documented by previous record of success. These plans need to be based on a thorough analysis of both blocking factors and success ingredients for making the platform attractive to the donors of data and samples. These latter should/could also be the end-users, to create a virtuous self-sustaining cycle. Starting from multiple neurodegeneration cohorts (in Alzheimer's disease and Parkinson's disease) the potential for future expansion to other indications (e.g. other tauopathies), beyond the funding period, should be considered. Applicants should also demonstrate the suitability of the platform for integrating unusual samples (e.g. faeces, saliva) and unusual data sets (e.g. dietary surveys, microbiota profiles).

Applicants need to propose and develop a business model for a sustainable network or platform. The result needs to reach the stage of a first concrete application. This must include all important considerations for making the platform attractive for its users, usable, useful and thus used. A strategy has to be implemented both for maintaining a constant stream of data and samples from external donors and for attracting sample users. This must include a mechanism for the integration of data obtained from the sample analysis back into the platform for secondary use by the research community. Implementation of a fee system for access to data and samples might be considered to secure continued operation. A mechanism for making the model sustainable needs to be developed from the start, including e.g. consideration of potential revenues / income (via sample and data access fees) and be operational already within its lifespan.

To enable the achievement of the project's ambitious objectives, the applicants need to propose a strategy for effective public-private governance and management of activities within timelines and budget. The project leaders will have to agree on and deliver the complete project work-plan in two consecutive phases; a preparatory one (first year) and a subsequent full implementation phase (second phase of four years). This includes the initial allocation, monitoring and necessary adaptation of resources to work-streams during the course of the project. The complete project work plan needs to be in place before Grant Agreement signature.

The timing of activities needs to be proposed considering that the project will consist of two phases: a first starting phase of one year, and a further full implementation phase of four years. Applicants are expected to propose key activities to reach the milestones for both phases at the time of submission of their short proposal, to be further refined by the full consortium in the stage 2 full proposal.

Considering the overall objectives and the challenges implied for their achievement, it is expected that the Phase 1 activities will require around 15 % of the budget, with the remaining amount for the activities of Phase 2. Applicants need to also ensure sufficient budget is allocated to the key activities supporting the objective of self-sustainability by end of the project.

The fundamental components of the proposed business model need to be clearly outlined and tested in the second phase to enable sustainability beyond the 60 months. The results of this testing must provide tangible evidence to illustrate that the business model can then be deployed successfully to enable continuation of the platform and services specifically beyond the lifespan of the funded project.

In Phase 1 of the action, the consortium is expected to achieve critical milestones that will inform Phase 2 activities, including any relevant change in areas and activities of critical need and related budgeting. Therefore, the work plan of Phase 2 may have to be adapted in light of the outcome of the activities of Phase 1.

Starting Phase 2 activities (and final allocation to activities of relevant IMI2 JU contribution) will be endorsed by an internal review by the consortium supported by the advisory board of the project (milestone review).

Thus, for the success of this initiative, it will be paramount to have mechanisms that allow integrating novel elements and knowledge identified by the gap analysis in Phase 1. This will allow for upscaling and operational validation to ensure successful self-sustainability during the action. This will be enabled by the Phase 1 & Phase 2 milestone-based approach for activities and their budgeting.

To enable this process, each of the work streams must define critical milestones as a minimum at the end of the first year of activities (phase 1 of the project), mid-term (will be assessed by the reviewers in the mid-term review organised by IMI2 JU), and at the end of the funding period. Milestones have to be clear decision points for go/no go decisions and re-orientation of specific activities and their resources. They must be based on measurable and time-bound deliverables. Robust mechanisms for checks and corrections have to be agreed across the public-

private partnership and be in place from the beginning of the project, both at overall project coordination level and work stream level.

Expected key deliverables

It is expected that applicants already address all deliverables in the short proposal (within the available duration and budget) and demonstrate a relevant strategy for achieving them, through partnership with the industry consortium. These will be fine-tuned by the full consortium to lead to a final set of agreed deliverables in the full proposal.

The listed key deliverables link directly to the topic objectives as listed below. The applicants need to propose complementary additional relevant and measurable deliverables well aligned with the activities described in the scope section and considering the two-phase, milestone-based strategy.

Associated with objective 1) Create a set of agreed principles to enable sharing and access to data and samples, taking into consideration the established legal and ethical research standards and principles (e.g. IT, GDPR, legal, ethical, regulatory, societal) and their practical application

- Establish an advisory body: this body needs to represent diverse experts (e.g. in bio-banking, data sharing, information technology and artificial intelligence, regulatory advice, GDPR, ethical and societal issues, the patient voice, intellectual property, national legislations across Europe and globally, business models and sustainability) within and outside the consortium.
- Delivery of an initial white paper that addresses gaps and requirements (including European regulatory considerations, as part of the above described areas of expertise) to establish a network that can house high quality data and samples and enable sharing and access for supporting discovery and validation of biomarkers.
- Delivery of final white paper with updated agreed principles to enable sharing and access to data and samples with clear identification of the cohorts participating. This needs to incorporate all learnings generated by the project activities including relevant regulatory guidance in the context of validation of biomarkers.

Associated with objective 2) Establish a network that can house high quality data and samples, which could have federated and centralised elements

- Establish a framework to leverage (or integrate with) existing/proposed data platforms, which need to be scalable to accommodate retrospective and prospective data, and a strategy for its dynamic fine-tuning as the initiative grows.
- An established interoperable scalable network of biobanks to accommodate retrospective and prospective samples and a strategy for its dynamic fine-tuning as the initiative grows.

Associated with objective 3) Establish governance and processes to enable sharing and access

- Establish a credible sample and data access committee:
    - with clear and transparent rules of appointment;
    - including relevant stakeholder representation (including patients);
    - with an agreed charter (from the overall consortium) to enable consistent access to samples and data.
- Establish a process for efficiently linking to regulatory procedures (e.g. Innovation Task Force and/or Scientific Advice by European Medicines Agency (EMA)) for maximum impact on drug development and/or biomarker validation. Include the consideration of regulators or, at a minimum, a regulatory expert in the advisory committee.

Associated with objective 4) Test the above with case studies

- Produce reports on the performed case studies testing the established network, and demonstrating the utility of the data, biomarkers and biorepository. These need to appraise the value of leveraging samples and data towards:
    1. demonstration of utility of samples with a standardised assay of current neurodegenerative disease biomarkers;
    2. new biomarker identification and analysis interrogating the complement system for neurodegenerative diseases. This needs to include an appraisal on the utility in the regulatory context considering as relevant e.g. Innovation Task Force and Scientific Advice.[47]
- Case studies:
    - Evaluate the ATN (amyloid-tau-neurodegeneration) system in cohorts with early Alzheimer's disease, to allow comparison of the more complex and expensive markers like cerebro-spinal fluid (CSF) amyloid β (Aβ) & tau, amyloid-PET and MRI with potential liquid biopsy (blood, saliva,..) markers as alternate biomarkers;
    - Interrogate the complement pathway biomarkers across a panel of neurodegenerative diseases. This could start potentially using first a discovery stage complement proteomics unbiased approach, that could be followed by confirmatory studies with standard lab-based assays on larger sample panel, in order to identify potential patient subgroups. This needs to include regulatory advice, e.g. from EMA Innovation Task Force[48];
    - Include at least one cohort with longitudinally collected digital biomarkers.
- Generation of harmonised sample and datasets: Novel, prospective samples and datasets must be incorporated in the platform and must be harmonised and interoperable with data resources already included from the start of the operation.

Associated with objective 5) This network must be a self-sustainable entity by the end of the project

- Draft sustainability plan: A first draft of a detailed sustainability plan (financial and business) needs to be developed to demonstrate sustained operation after funding period;
- Finalised and implemented sustainability plan: Self-sustainability of the entity needs to be demonstrated via a finalised and implemented sustainability plan.

Suggested allocation to Phase 1 of activities (thus to be achieved by end of 1st year of activities):

- Associated with objective 1) Create a set of agreed principles to enable sharing and access to data and samples taking into consideration all established legal and ethical research standards and principles (e.g. GDPR, legal, ethical, regulatory, societal) and their practical implementation:
    - Establish an advisory body: This body needs to represent diverse experts (e.g. in bio-banking, data sharing, information technology and artificial intelligence, regulatory advice, GDPR, ethical and societal issues, the patient voice, intellectual properties, national legislations across Europe and globally, business models and sustainability) within and outside the consortium;
    - Deliver a white paper that addresses gaps and requirements to establish a network that can house high quality data and samples, and enable sharing and access (see objective 1).
- Associated with objective 4) Test the above with case studies:

[47] https://www.ema.europa.eu/en/human-regulatory/research-development/scientific-advice-protocol-assistance/qualification-novel-methodologies-medicine-development
[48] https://www.ema.europa.eu/en/human-regulatory/research-development/innovation-medicines#ema's-innovation-task-force-(itf)-section

- Gauge the ATN (amyloid-tau-neurodegeneration) system in cohorts with early Alzheimer's disease, to allow comparison of the more complex and expensive markers like CSF Aβ & tau, Amyloid-PET and MRI with potential liquid-biopsy (blood, saliva...) markers as alternate biomarkers.

Expected impact

In their proposals, applicants need to describe how the outputs of the project will contribute to the following impacts and include wherever possible baseline, targets and metrics to measure impact.

In particular, short proposals must address:

- how the self-sustainable network platform composed of a European biobank operation, and accompanying data platform, will positively fuel and impact basic research and development and drug development campaigns;
- how the public-private partnership providing infrastructure to enable worldwide sample and data sharing will have a substantial impact on the development and regulatory validation of biomarkers/diagnostics, and how in turn this would likely have a cascading effect on accelerating therapeutic development.

In their proposals, applicants need to outline how the project plans to leverage the public-private partnership model to maximise impact on innovation, research & development; regulatory, clinical and healthcare practices, as relevant. This could include a strategy for the engagement with patients, healthcare professional associations, healthcare providers, regulators, HTA agencies, payers etc., where relevant. A clear plan on how to involve the public and patients in the project from the beginning until the end of the project, as well as a demonstration of their involvement in the formulation of the proposal (short and full proposal) is a requirement and has to be included in the proposal. This is especially important given the need to engage ongoing cohorts for this project to be successful.

In addition, applicants need to describe how the project will impact on competitiveness and growth of companies including SMEs.

In their proposals, applicants must outline how the project will:

- manage research data including use of data standards[49];
- disseminate, exploit, and sustain the project results - this may involve engaging with suitable biological and medical sciences research Infrastructures[50];
- communicate the project activities to relevant target audiences.

In addition, the following additional dissemination[51] obligations must be considered to maximise impact.

Dissemination needs to include (1) publication and actively engaging the stakeholder community to implement the agreed principles for data/sample sharing and access; and (2) demonstrating the value of the platform (key to support its sustainability) as impact of the enabled data/sample usage.

Potential synergies with existing consortia

Synergies and complementarities must be considered with relevant national, European and non-European initiatives (including suitable biological and medical sciences research infrastructures) in order to incorporate

[49] Guidance on data management is available at http://ec.europa.eu/research/participants/docs/h2020-funding-guide/cross-cutting-issues/open-access-data-management/data-management_en.htm
[50] http://www.corbel-project.eu/about-corbel/research-infrastructures.html
[51] Article 29.1 (Additional dissemination obligations) of the IMI2 Grant Agreement will apply

resources, past achievements, available data and lessons learnt where possible, thus avoiding unnecessary overlap, and duplication of efforts and funding.

Industry consortium

The industry consortium is composed of the following EFPIA partners:

- Gates Venture (co-lead)
- UCB (co-lead)
- Janssen
- Novartis
- Roche
- Sanofi
- SVAR Lifescience
- Takeda

The industry consortium will contribute the following expertise:

- Project leadership, governance and project management resource and capabilities.
- The identification and transfer of samples into the biorepository will be supported, including accompanying patient / participant data.
- Provide the necessary scope of legal, technical, and other required resources (Full Time Employees) to enable successful transfer of samples and subsequent utility of the platform for users.
- Testing of the consistency and quality of sample handling, storage, and distribution using some of the now standard biomarkers used in the field such as Aβ40, Aβ42, Tau, phosphorylated Tau (p-Tau), synuclein, neurofilaments (NFL) etc.
- Interaction to ensure banking of samples will aid in disease understanding and modelling. For example, existing sample collections from previous clinical trials entertained by EFPIA-companies may be used to:
    - define and refine criteria to incorporate, use, distribute samples and return obtained data back into the database for further use by third parties;
    - refine legal requirements and documents (inform consent forms, etc) to standardise how samples will be retrieved in future trials to be incorporated in such repositories.
- Support for research activities focusing on the utility of the biorepository to identify biosignatures related to the dysregulation of as-yet under-researched mechanisms in neurodegeneration, e.g. the complement system (see case studies appraising biobank operational scheme).
- Supporting validation of biomarkers to accelerate the development of diagnostics.
- Supporting development of sample collection, quality assurance/quality control, sample storage and handling protocols.
- Facilitation of transfer of capabilities and knowledge to reach the ultimate goal of self-sustainability of the biobanking entity.

The industry consortium plans to contribute the following assets:

- Existing samples from clinical trials including accompanying data and information. The transfer of such samples into the biorepository will be supported.
- Assays, standard operating procedures, and necessary material (e.g. antibodies) to perform diagnostics.

- Research assay with CSF and plasma markers of neurodegeneration and neuroinflammation including but not limited to:
  - CSF: Aβ42, total Tau (tTau), (pTau), Aβ40, neurofilaments (NFL), soluble triggering receptor expressed on myeloid cells 2 (STREM2), tyrosine (Y), lysine (K) and leucine (L)-40 glycoprotein (YKL40), glial fibrillary acidic protein (GFAP), Alpha Synuclein, Neurogranin, interleukin-6 (IL-6), S100b;
  - plasma/ serum: Aβ42 high sensitivity, Aβ40, tTau, NFL, STREM2, YKL40, IL-6, S100b, GFAP, brain derived neurotrophic factor (BDNF), growth differentiation factor-15 (GDF-15), insulin like growth factor binding protein 7 (IGFBP7), neuron-specific enolase (NSE).

These assays are high-performance, non-commercial assays, and would be made available fee for service at a contract research organisation (Covance) and would require advance planning to ensure capacity and availability (> 6 Months).

- Diagnostic assays to evaluate the function of the patient's complement system via classical, alternative and lectin pathway in serum.
- Contribute datasets from retrospective (and ongoing) interventional and/or observational studies to the data platform.
- AD Work bench – access and leverage AD Work bench data platform for the project.
- In addition, the Gates Ventures will provide synergy and point of contacts with its other funded initiatives including Diagnostics Accelerator[52], Dementia Discovery Fund[53], Early Detection of Neurodegenerative diseases[54], and a yet to be publicly announced initiative on data sharing and interoperability (Alzheimer's Disease Data Initiative) for the benefit of the Alzheimer's disease patients. The AD Data Initiative has developed a set of solutions to enable interoperability across a representative sample of data platforms.

Indicative duration of the action

The indicative duration of the action is 60 months.

This duration is indicative only. At stage 2, the consortium selected at stage 1 and the predefined industry consortium may jointly agree on a different duration when submitting the stage 2 proposal.

Indicative budget

The financial contribution from IMI2 JU is a maximum of EUR 9 680 000.

The indicative in-kind and financial contribution from EFPIA partners is EUR 9 720 000.

The total financial contribution available from the EFPIA partners for the activities in relation to the objectives of this action is EUR 3 000 000.

The allocation of the EUR 3 000 000 financial contribution will be decided by the full consortium at stage 2 when preparing the stage 2 proposal.

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

[52] https://www.alzdiscovery.org/research-and-grants/diagnostics-accelerator
[53] https://theddfund.com/
[54] https://edon-initiative.org/

Expertise and resources expected from applicants at stage 1

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

The stage 1 applicant consortium is expected, in the submitted short proposal, to address all the objectives and key deliverables of the topic, taking into account the expected contribution from the industry consortium which will join at stage 2 to form the full consortium.

This may require mobilising, as appropriate the following expertise.

All relevant areas of expertise that are necessary to deliver on all of the project deliverables. This needs to include entities with a proven track record of successful experience in the following or equivalent areas of experience, including key considerations of SMEs.

- Technology and solid understanding of technical architectures for biobanks and bio-repository know-how for long-term collection, storage and distribution of large numbers of samples, including:
    - capacity to allow online identification and ordering of samples including infrastructure to accept, add, and retrieve data obtained with and attached to samples; this includes modalities for covering handling, maintenance, and distribution costs of the repository which will support the transformation of the action into a self-sustainable operation in a European and worldwide context;
    - legal expertise;
    - data / information technology infrastructure expertise;
    - expertise and networks to procure samples through existing or (clinical) networks that are to be established;
    - experience in standardisation procedures (e.g. via European Committee for Standardisation (CEN)) including QC of samples;
    - experience with federated and/or centralised laboratory information management system (LIMS) architecture, security and standards to monitor the status of the repository and maintain and amend information available to each specimen.
- Expertise regarding establishing and managing a data platform that:
    - utilises requisite standards and common data models;
    - facilitates data access;
    - can incorporate new data generated using samples from the repository;
    - with appropriate protections and security to protect sensitive healthcare data;
    - is suitable for a public-private partnership context.
- Knowledge in establishing and maintaining a harmonised online data portal / interface that:
    - can interrogate available datasets and samples via federated approaches to unify available clinical datasets;
    - is interoperable between biobanks, clinical data systems, and across the biorepository network involved in the action, including requesting samples for analysis.
- Experience relevant to biomarker discovery and validation, ideally including the expertise below to ensure the success of the described pilot case studies:
    - experience with early AD biomarkers;
    - experience in complement pathway biomarker analysis, both unbiased (such as large-scale targeted proteomics), and more standard biomarker assays for large-scale analysis of larger case panels;

- experience in digital biomarkers and digital signatures via connected devices and wearables e.g. for early detection and/or disease progression.

- EU & worldwide legal, ethical and regulatory expertise pertaining to:
  - legal requirements specifically to sharing, access and usage of health data in Europe at a minimum;
  - the use of human samples (sampling, storage, distribution across regions), bio-banking and patient consent/secondary use / ethics;
  - data sharing, access and consent related to sensitive health-related data and their secondary use;
  - regulatory expertise in how to engage and influence outcomes with regulators in line with targeted project deliverables.

- Business, financial, and economics experience to transform the bio-sample repository into a self-sustainable business:
  - experience and expertise in developing a strategy for ensuring the translation of the project results / bio-sample analysis to drug development, regulatory / health technology assessment (HTA) settings (e.g. through scientific advice/ qualification advice /opinion, etc.), clinical and healthcare practices and/or decision-making processes;
  - general project management (ability to consistently set and achieve milestones on time and within budget; managing varying interests of multiple stakeholders) and professional communication expertise (expertise in communication tools and systems for project management purposes).

Applicants are also encouraged to consider having a patient group involvement within the consortium to ensure that the input of patients is covered, including not limited to, but including consent and other aspects e.g. 'Henrietta Lacks' representation (https://www.nature.com/news/deal-done-over-hela-cell-line-1.13511).

The size of the consortium should be proportionate to the objectives of the topic while ensuring its manageability.

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

- A pre-existing and functional sample repository, preferentially with a background in the neurodegenerative disease therapeutic area (Alzheimer's disease and related tauopathies, Parkinson's disease), that could already be made available for distribution at the beginning of the action;
- Active cohorts with early stage neurodegenerative disease (e.g. Alzheimer's disease and Parkinson's disease);
- An established distribution pipeline to deliver samples to customers and be operational at within first year of the action;
- Existing sample and data sets (provided e.g. from industry partners or provided by third parties) that will be contributed to this network.

Considerations for the outline of the project work plan

In their stage 1 proposals, applicants need to:

- Give due visibility on data management; dissemination, exploitation and sustainability; and communication activities. This must include the allocation of sufficient resources for these tasks which will be further developed in stage 2 proposal.
- Propose a work plan that efficiently enables the implementation of activities following the two Phases as in the Scope section.
- Consider including a strategy for ensuring the translation of the projects results to drug development, regulatory/HTA settings (e.g. through scientific advice/ qualification advice /opinion, etc.), clinical and healthcare practices and/or decision-making processes.

Suggested architecture

Please consider a work plan that includes all activities and elements related to scope and deliverables.

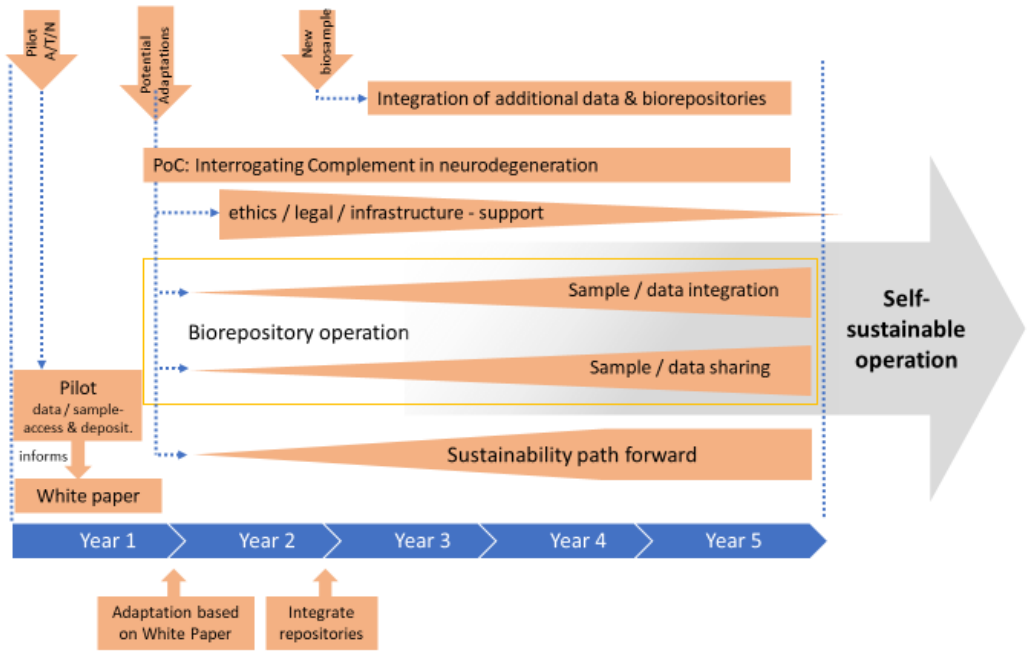


Figure 1 – draft structure of activities

Additional considerations to be taken into account at the stage 2 full proposal

At stage 2 of the IMI review process, the consortium selected at stage 1 and the predefined industry consortium jointly submit the full proposal developed in partnership. The full proposal is based upon the selected short proposal at stage 1.

In the spirit of the partnership, and to reflect how IMI2 JU call topics are built on identified scientific priorities agreed together with EFPIA beneficiaries/large industrial beneficiaries, these beneficiaries intend to significantly contribute to the programme and project leadership as well as project financial management. The final architecture of the full proposal will be defined by the participants in compliance with the IMI2 JU rules and with a view to the achievement of the project objectives. The allocation of a leading role within the consortium will be discussed in the course of the drafting of the full proposal to be submitted at stage 2. To facilitate the formation of the final consortium, until the roles are formally appointed through the consortium agreement, the proposed project leader from among EFPIA beneficiaries/large industrial beneficiaries shall facilitate an efficient negotiation of project content and required agreements. All beneficiaries are encouraged to discuss the project architecture and governance and the weighting of responsibilities and priorities therein.

Data Management

In their stage 2 proposal, applicants must give due visibility to data management including use of data standards. A full 'data management plan' (DMP) as a distinct deliverable must be delivered within the first 6 months of the

project. The DMP needs to be kept up to date with the needs of the project and as such be updated as necessary during its lifetime.[55]

Dissemination, exploitation and sustainability of results

In their stage 2 proposal, applicants must provide a draft plan for dissemination and the exploitation, including sustainability of results. A full plan as a distinct deliverable must be delivered within the first 6 months of the project.[56], and updated during the project lifetime and could include identification of:

- Different types of exploitable results;
- Potential end-users of the results;
- Results that may need sustainability and proposed sustainability roadmap solutions.

Sufficient resources need to be foreseen for activities related to dissemination and exploitation, including the plan for the sustainability of the project results. This may involve engaging with suitable biological and medical sciences research infrastructures (RIs).[57]

Communication

The proposed communication measures for promoting the project and its findings during the period of the grant must also be described and could include a possible public event to showcase the results of the project.

[55] Guidance on data management is available at http://ec.europa.eu/research/participants/docs/h2020-funding-guide/cross-cutting-issues/open-access-data-management/data-management_en.htm
[56] As an additional dissemination obligation under Article 29.1 of the IMI2 Grant Agreement will apply.
[57] http://www.corbel-project.eu/about-corbel/research-infrastructures.html

Topic 4: Optimal treatment for patients with solid tumours in Europe through Artificial Intelligence

Topic details

Topic code	IMI2-2020-23-04
Action type	Research and Innovation Action (RIA)
Submission and evaluation process	2 stages
IMI2 Strategic Research Agenda - Axis of Research	Adoption of innovative clinical trial paradigms
IMI2 Strategic Research Agenda - Health Priority	Cancer

Specific challenges to be addressed by public-private collaborative research

Demands of cancer care in Europe continue to increase significantly, with the number of incident cancer cases in Europe projected to increase by 14.1% by 2030[58]. This leads to a growing demand for innovative cancer treatments among patients, payers, physicians, and society. At the same time, the understanding of the complex biology of cancer is growing, and as a result, pharmaceutical companies are developing a multitude of new therapeutic agents. These include, but are not limited to, novel kinase inhibitors, immunotherapy combinations, and cell therapies.

This trend for new, effective therapies creates more treatment options for patients. However, it confronts physicians with an increasingly expanding number of potential therapeutic options, which each need to be understood and adopted effectively. Numerous factors such as genetic analysis, specific tumour biology, and biomarkers have a growing influence on clinical decision-making. To become familiar with the huge volume of available information, physicians need to learn continuously about medical guideline changes and marketed treatments. In conclusion, future decision-making processes will become ever-more complex, with the potential outcome of sub-optimal or even incorrect treatment choices being made. Furthermore, some patients have disease characteristics for which evidence of guideline recommendations is scarce and physicians lack information about real-world treatment outcomes. Hence, the challenges to be addressed are assisted guideline-based decision-making and the discovery of knowledge about treatment outcomes in real-world settings. As the latter challenge requires analysis of large data sets, the application of Artificial Intelligence (AI) will be a key technology.

To ensure the challenges can be properly addressed, and ensure the innovations reach the physicians and patients, a public-private partnership is necessary, including the following actors:

- **patient organisations and regulatory authorities** to specify the requirements and boundaries of AI-driven data processing, data security and privacy as well as individual data ownership
- **medical societies** to provide the network of participating in- and out-patient clinics to enable data access
- **medical experts/institutions** to specify AI approaches, validate the decision support and set the requirements for general acceptance
- **life-science companies** to contribute study data for the evaluation of therapeutic approaches, as well as expertise in data mining and data-set merging

[58] https://gco.iarc.fr/tomorrow/home

- **SMEs** for infrastructure set-up, data management and data security, AI-driven data processing and merging of unstructured information, visualisation and user experience design.

Scope

The scope of this call topic is to establish guideline-based decision support and platform solutions to generate knowledge discovery for breast, lung and prostate cancer with applicability to other indications, in several European (EU member states and H2020 associated countries) 'model' regions. The model regions serve as platforms to show general feasibility of the decision-support tool and lay the foundation for further expansion to other European regions. The results obtained from these model regions are expected to be of relevance to countries with different socioeconomic backgrounds. The funded action will focus only on breast, lung and prostate cancer. These indications show a high number of cases per year, a high, unmet medical need, multiple available therapeutic options and a fast-evolving treatment environment. Expansion to other indications is not part of the funded action but a proposed solution should allow for expansion afterwards. The three core objectives of this call topic are as follows:

Objective 1: Establish a guideline-based decision support for prioritised indications

Development of a decision-support tool that automatically extracts relevant clinical information from electronic health records (EHRs) and facilitates guideline-compliant treatment approaches for the defined solid tumours.

Objective 2: Establish a structured and interoperable data platform to unlock real-world-data potential in an oncology network

A major requirement for the provision of patient-specific treatment is the availability and the harmonisation of extensive patient data across in-patient (e.g. academic centres, teaching hospitals) and out-patient (community and private practices) settings - stored in a structured format, ready to be used and interoperable. The successful consortium should address this need by involving relevant and available regional/national networks of in-/out-patient clinics providing access to their data, for instance with the inclusion of medical societies.

Easy-to-use new platforms that enable the gathering and granular storage of clinical data to offer a foundation for data analysis and knowledge discovery need to be established. The real-world data platforms should include prospective data from electronic health records, structured data from (non)interventional studies provided by members of the pre-identified industry consortium as well as potentially registry data.

Objective 3: Leverage the real-world-data gathered by the action to establish an AI-knowledge base and support treatment decisions for prioritized indications

The funded action will develop a disease-specific (breast, lung and prostate cancer) AI system that facilitates the discovery of novel medical knowledge. This includes hypothesis generation about optimal treatment sequences for patients and prognostic features that can be validated in clinical research. The output will strongly support building the European health data space and improve the quality and acceptance of AI-generated evidence in decision making in research and healthcare delivery. It will also set the foundation for explainable AI approaches necessary for personalised treatment.

During the funded action, members of the industry consortium plan to contribute scientifically relevant pre-existing data and/or data from prospective studies including activities for generating such data that are part of broader industry clinical studies and making such data fit for purpose.

Expected key deliverables

In order to address the call topic challenges, the selected action must ensure that current medical knowledge is quickly translated into clinical practice. It must deal with patients who do not fully match the reasoning paths of guidelines due to certain characteristics for which evidence is limited. Finally, it must be able to decipher how current treatment approaches affect patient outcomes in the real world.

The collaborative public-private consortium is expected to address these challenges in a three-step process. First, a guideline-based decision-making tool that automatically extracts and validates relevant clinical information from EHRs needs to be developed. Second, a database for real-world treatment outcomes needs to be created. Third, AI-technology is to be applied to analyse the data and facilitate novel knowledge discovery.

Overarching considerations:

- Ensure adherence to existing regulatory guidelines and (e.g. GDPR, Convention on Human Rights and Biomedicine (Oviedo Convention), WMA Declaration of Helsinki: Ethical Principles for Medical Research Involving Human Subjects, WMA Declaration of Taipei on Ethical Considerations regarding Health Databases and Biobanks);
- Patient informed consent for data collection and data sharing;
- Real-world data must be provided from identified countries having access to cancer treatments suggested by treatment guidelines;
- A business model for a platform that is 'sustainable by design' for public health applicability;
- Provision of a detailed concept for its sustainability, maintenance and commercialisation;
- Present concepts and strategies about how their respective proposals will have an impact on competitiveness and industrial leadership of Europe in a sustainable way, e.g. via SME engagement.

A guideline-based decision-support tool:

- Develop a decision model based on national and/or international clinical guidelines for the three indications; breast, lung and prostate cancer;
- Implement the decision model and integrate into existing IT infrastructures;
- Establish methods to acquire and process decision-relevant clinical information automatically from EHRs;
- Include mechanisms to quickly adapt guideline changes or updates, and scale to incorporate guidelines from additional countries after the project ends.

Data platform:

- Integration of multi-language user frontends;
- Implementation of secure and interoperable cloud-based data storage;
- Integration into existing clinical IT infrastructures across various geographies to address socioeconomic barriers and IT infrastructure differences;
- Integration of system mechanics that address individual data ownership and transferable data access and usage permissions via extended rights;
- Consideration of different viewpoints on the data based on the stakeholder group:
  - Physicians; a transparent decision-support and intuitive result visualisations;
  - Patients; data ownership and permission management;
  - Patient organisations patient-centric viewpoints;
  - SMEs; programming interfaces.
- Relevant data sources can be derived from electronic health records, (non)Interventional study data or registry data and may include, for example:
  - Patient demographics;
  - Lab panel;
  - Pathological cancer classification;

- Genomic data;
- Treatment sequences;
- Radiology and nuclear medicine reports.

- Documentation of outcomes data like progression-free survival, overall survival, quality of life and adverse events;
- A description of how generated data will be shared with other institutions to further evaluate the generated results and enable transnational comparison throughout the different healthcare systems;
- Applicants are allowed to bring in an existing platform that is then tailored to the needs of the project.

Deliverables of the AI-supported knowledge discovery:

- Healthcare providers should be able to monitor the impact of the solutions regarding personalised medical treatment as well as the associated cost and outcome;
- Integration of verified knowledge (e.g. outcomes data such as progression-free survival, overall survival, quality of life and adverse events) into the indication-specific knowledge base;
- Process of knowledge discovery needs to be guided by a scientific review committee;
- Consortium members and third parties must be able to request data analyses after approval of the scientific review committee;
- Integration of simulation features based on the knowledge base, e.g. to simulate therapy response, side-effects, quality of life or other outcome-related factors based on prediction modelling on top of the retrospective case data.

Expected impact

In their proposals, applicants should describe how the outputs of the project will contribute to the following impacts and include wherever possible baseline, targets and metrics to measure impact.

- An explainable AI-based knowledge discovery platform should enable the development of data-driven solutions with the goal to sustainably improve oncologic treatments throughout the EU and beyond;
- The results obtained from these model regions are expected to be of relevance to countries with different socioeconomic backgrounds;
- The platform should allow oncologists to save valuable time due to the automatic data gathering and facilitated guideline-based assessment;
- In addition, physician-patient communication and shared decision making should be supported which might improve proactive therapy involvement to accomplish increases in individual quality of life as well as overall patient satisfaction;
- The platform may also allow research questions from various stakeholders to be answered through data analysis and data pooling as well as data extraction. Besides overall survival, this could include real-world quality of life (QoL) and safety evaluations of new therapies as well as novel combinations under real world conditions. This can potentially contribute to value-based healthcare assessments at EU level;
- The solutions provided by a public-private consortium will significantly benefit European society: patients receive optimal personalised treatment; physicians are supported in complex decision-making processes; and payers as well as pharmaceutical companies receive information about real world treatment outcomes as a foundation for value-based healthcare approaches;
- The topic is well aligned with the EU Commission's strategy to develop a European Health Data Space and Europe's Beating Cancer Plan.

In their proposals, applicants should outline how the project plans to leverage the public-private partnership model to maximise impact on innovation, research & development, as well as regulatory, clinical and healthcare practices,

where relevant. This could include a strategy for engagement with patients, healthcare professional associations, healthcare providers, regulators, Health Technology Assessment (HTA) agencies, payers etc., where relevant.

In addition, applicants should describe how the project will impact the competitiveness and growth of companies including SMEs.

In their proposals, applicants should outline how the project will:

- Manage research data including use of data standards[59];
- Disseminate, exploit, and sustain the project results. This may involve engaging with suitable biological and medical sciences Research Infrastructures[60];
- Communicate the project activities to relevant target audiences.

Potential synergies with existing consortia

Synergies and complementarities should be considered with relevant national, European and non-European initiatives (including suitable biological and medical sciences research infrastructures) in order to incorporate past achievements, available data and lessons learnt where possible, thus avoiding unnecessary overlap, and duplication of efforts and funding.

Industry consortium

The industry consortium is composed of the following EFPIA partners:

- Pfizer (lead)
- Abbvie
- Amgen
- Bayer
- Roche

The industry consortium plan to contribute the following expertise and assets:

- Personnel with expertise in oncology solid tumours, AI algorithm implementation, real-world data;
- Real-world data from (non)interventional studies supplementing the public partner cohorts. Relevant data may include, for example, outcome results like progression-free survival, overall survival, quality of life and adverse events as well as patient demographics and treatment sequences.

Indicative duration of the action

The indicative duration of the action is 60 months.

This duration is indicative only. At stage 2, the consortium selected at stage 1 and the predefined industry consortium may jointly agree on a different duration when submitting the stage 2 proposal.

[59] Guidance on data management is available at http://ec.europa.eu/research/participants/docs/h2020-funding-guide/cross-cutting-issues/open-access-data-management/data-management_en.htm
[60] http://www.corbel-project.eu/about-corbel/research-infrastructures.html

Indicative budget

The financial contribution from IMI2 JU is a maximum of EUR 10 460 000.

The indicative in-kind contribution from EFPIA partners is EUR 11 400 000.

The EFPIA contribution includes EUR 3 500 000 financial contribution. The allocation of this financial contribution will be decided by the full consortium at stage 2 when preparing the full proposal.

Due to the global nature of the participating industry partners and IMI2 JU Associated Partners, it is anticipated that some elements of the contributions will be non-EU/H2020 Associated Countries in-kind contributions.

Expertise and resources expected from applicants at stage 1

The stage 1 applicant consortium is expected, in the submitted short proposal, to address all the objectives and key deliverables of the topic, taking into account the expected contribution from the industry consortium which will join at stage 2 to form the full consortium.

The stage 1 submitted short proposals should include suggestions for creating a full proposal architecture which could be in line with the suggested architecture described below, though this architecture is only a suggestion.

This may require mobilising, as appropriate the following expertise:

- Expertise in medical oncology with a special focus on the three prioritised indications: breast, lung and prostate cancer;
- Expertise from patient organisations as well as regulatory expertise to address data security and privacy as well as individual data ownership and AI-driven data processing;
- Large-scale medical data management and processing expertise to ensure proper data modelling according to current technical and infrastructural standards;
- Expertise in interoperable IT system design e.g. implementing Health Level 7 Fast Healthcare Interoperability Resources (HL7 FHIR);
- Expertise in technical interface development regarding current clinical technologies and systems such as EHR, Picture Archiving and Communication Systems (PACS) or Laboratory Information Management Systems (LIMS);
- Advanced database and transfer security, client- and server-side encryption (E2E), system threat modelling and prevention;
- User experience design and accessibility considering the broad spectrum of potential users;
- Application development for different server- and client-side systems (e.g. web applications and mobile operating systems);
- Big data analysis;
- Strategies to deal with unstructured data;
- Strategies for handling unfavourable data sets (e.g. incomplete or missing data);
- Methodologies of proper semantic and contextual modelling of patient and disease characteristics;
- Unification, pre-processing, and validation of multimodal clinical data sources.

The size of the consortium should be proportionate to the objectives of the topic while ensuring its manageability.

Furthermore, at stage 1, the applicant consortium should also provide a strategy for allocating the amount of EFPIA Financial contribution – mentioned under indicative budget. The allocation will be decided by the full consortium at stage 2 when preparing the full proposal.

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

Considering the development of AI-supported data analysis and knowledge modelling, applicants will need to provide extended competences regarding:

- Network of clinics (in- and/or out-patient) with access to patient level electronic health records.

Considerations for the outline of project work plan

In their stage 1 proposals applicants should:

- Give due visibility on data management, dissemination, exploitation and sustainability, and communication activities. This should include the allocation of enough resources for these tasks which will be further developed in stage 2 proposal;
- Consider including a strategy for ensuring the translation of the projects results to drug development, regulatory/ Health Technology Assessment (HTA) settings (e.g. through scientific advice / qualification advice / opinion, etc.), clinical and healthcare practices, and/or decision-making processes.

Suggested architecture

The project challenges are summarized in Figure 1.

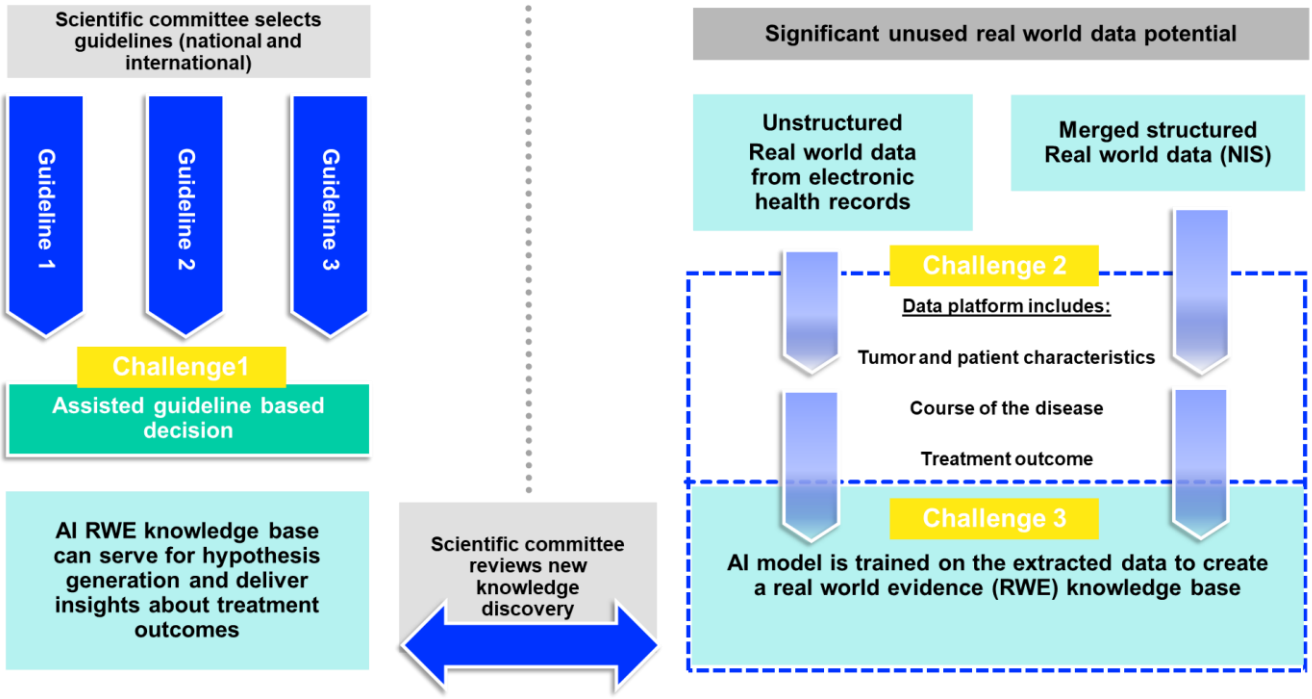


Figure 2 – Overview of project challenges.

Work package 1 – Project management

The goals of this work package are to:

- Ensure alignment between the beneficiaries as well as smooth internal and external communication;
- Monitor compliance with the work plan;
- Monitor planned resources and time schedule;
- Coordinate fulfilment of all administrative milestones;

- Ensure legal and data privacy requirements are met during the project lifetime.

The expected applicant consortium contribution should include project management, ensuring the implementation of the coordinating tasks and running the day-to-day operation, such as project tracking and reporting, meetings, internal communication, website creation, budget management, etc.

Work package 2 – Informed consent, general requirement analysis, governance, and regulation

The goals of this work package are to:

- Obtain patient informed consent;
- Technical and medical requirement analyses to specify the clinical need and required technical infrastructure;
- Design of governance principles for both data platform and AI component including legal structures in participating countries and sites;
- Definition of ethical principles towards the application of AI in a medical context;
- Conceptualisation of long-term operation and monetisation strategies;
- Requirements for data privacy adherence (e.g. GDPR).

Work package 3 – Guideline-based decision support tool

The goals of this work package are:

- Identification of relevant treatment guidelines for the targeted indications by a scientific committee;
- Development of model-based representations of those guidelines;
- Allowing instantiation of the decision models with real-world patient data;
- Integration of automatic reasoning methods for the individual patient case;
- Integration of an automatic or assisted evaluation pipeline for model updates and adjustments.

Work package 4 – Platform technical and infrastructural requirement analysis

The goals of this work package are:

- Specification of the technical platform infrastructure;
- Consideration of necessary tools for data analysis and knowledge discovery;
- Specification of all necessary technical interfaces;
- Evaluation of data storage and management strategies;
- Establishment of a resource plan including strategies for resource scaling;
- Development of a data and operations security framework.

Work package 5 – Platform implementation and evaluation

The goals of this work package are:

- Generation of user personas based on the relevant platform stakeholders;
- Integration of data analysis tools or integration of compatibility features for external applications;
- Development of automated testing and deployment pipelines;

- Conduction of a user study to evaluate visual and functional platform components accordingly to the generated personas;
- Platform and interface documentation for users and third-party developers.

Work package 6 – (Non)interventional study data and real-world data gathering, preparation and integration

The goals of this work package are:

- Aggregation and evaluation of available study data sources;
- Consideration of all legal and ethical aspects relating to the data sets;
- Assessment of gathered data pools regarding quality and impact of the contained data;
- Quality assurance in terms of data preparation;
- Establishment of a processing pipeline for unstructured entities;
- Strategies to deal with inconsistent or missing information.

Work package 7 – Artificial Intelligence knowledge base implementation

The goals of this work package are:

- Development of a suitable knowledge representation scheme;
- Development of pre-processing features for data integration (e.g. validation);
- Integration of explainability and traceability mechanisms that allow for linking individual discoveries to the respective evidence and its derivation;
- Integration of system-assisted validation features for a committee of experts (e.g. peer-review) that verifies individual findings before knowledge base integration.

Work package 8 – Dissemination and communication

Work package 9 – Exploitation and sustainability of the results

Additional considerations to be taken into account at the stage 2 full proposal

At stage 2, the consortium selected at stage 1 and the predefined industry consortium jointly submit the full proposal developed in partnership. The full proposal is based upon the selected short proposal at stage 1.

In the spirit of the partnership, and to reflect how IMI2 JU call topics are built on identified scientific priorities agreed together with EFPIA beneficiaries/large industrial beneficiaries, these beneficiaries intend to significantly contribute to the programme and project leadership as well as project financial management. The final architecture of the full proposal will be defined by the participants in compliance with the IMI2 JU rules and with a view to the achievement of the project objectives. The allocation of a leading role within the consortium will be discussed in the course of the drafting of the full proposal to be submitted at stage 2. To facilitate the formation of the final consortium, until the roles are formally appointed through the consortium agreement, the proposed project leader from among EFPIA beneficiaries/large industrial beneficiaries shall facilitate an efficient negotiation of project content and required agreements. All beneficiaries are encouraged to discuss the project architecture and governance and the weighting of responsibilities and priorities therein.

Data Management

In their stage 2 proposal, applicants should give due visibility to data management including use of data standards. A full 'data management plan' (DMP) as a distinct deliverable must be delivered within the first 6 months of the project.

The DMP needs to be kept up to date with the needs of the project and as such be **updated as necessary during its lifetime.**[61]

Dissemination, exploitation and sustainability of results

In their stage 2 proposal, applicants must provide a draft plan for dissemination and the exploitation, including sustainability of results. A full plan as a distinct deliverable must be delivered within the first 6 months of the project[62], and updated during the project lifetime and could include identification of:

- Different types of exploitable results;
- Potential end-users of the results;
- Results that may need sustainability and proposed sustainability roadmap solutions.

Sufficient resources should be foreseen for activities related to dissemination and exploitation, including the plan for the sustainability of the project results. This may involve engaging with suitable biological and medical sciences Research Infrastructures (RIs).[63]

Communication

The proposed communication measures for promoting the project and its findings during the period of the grant should also be described and could include a possible public event to showcase the results of the project.

[61] Guidance on data management is available at http://ec.europa.eu/research/participants/docs/h2020-funding-guide/cross-cutting-issues/open-access-data-management/data-management_en.htm
[62] As an additional dissemination obligation under Article 29.1 of the IMI2 Grant Agreement will apply.
[63] http://www.corbel-project.eu/about-corbel/research-infrastructures.html

Topic 5: Shortening the path to rare disease diagnosis by using newborn genetic screening and digital technologies

Topic details

Topic code	IMI2-2020-23-05
Action type	Research and Innovation Action (RIA)
Submission and evaluation process	2 stages
IMI2 Strategic Research Agenda - Axis of Research	Innovative medicines
IMI2 Strategic Research Agenda - Health Priority	Rare/orphan diseases

Specific challenges to be addressed by public-private collaborative research

Unmet medical need:

Approximately 5,000-8,000 distinct rare diseases (RD) affect 6-8% of the EU population i.e. between 27 and 36 million people[64]; 263-446 million people are affected globally [1]. Considerable public funding has been invested in research for rare diseases for more than 12 years, with a significant share coming from the EU framework programmes[65]. However, despite scientific advances, in Europe, the fact remains that fewer than 10% of RD patients receive treatment and only 1% are managed using an approved treatment[66]. Delivering effective treatments to RD patients where the prevalence is low has been described as one of the major global health challenges of the 21st century. There is a need for a strategic approach to address some of the major challenges faced by the RD Community, endorsed by IMI2 JU.

Challenges:

Even though RDs span a plethora of multisystemic syndromes, involving virtually every single organ or physiological function, most RD patients face common problems. These major hurdles can be summarised as delayed diagnosis, lack of R&D, and lack of access to or reimbursement of innovative medicines[67].

One of the main challenges for RDs is related to diagnosis because RDs are characterised by a broad diversity of syndromic disorders and symptoms that vary from disease to disease and from patient to patient suffering from the same disease. In isolation, these symptoms can be very common, leading to misdiagnosis. Altogether, this leads to a lengthy and burdensome path to diagnosis that can take, on average, take eight years[68], often involving pointless treatments, creating a heavy human and societal burden that could be avoided by earlier diagnosis.

Benefit to Public Health:

Early detection of rare genetic diseases would enable early intervention (when available), follow-up, and genetic counselling (such as family planning). This would result in improved clinical and patient oriented outcomes. Overall, this project will increase public understanding around RDs, and therefore foster rare disease R&D. A better

[64] https://ec.europa.eu/health/non_communicable_diseases/rare_diseases_en
[65] https://ec.europa.eu/health/ern_en
[66] https://www.eurordis.org/about-rare-diseases
[67] https://www.eurordis.org/sites/default/files/publications/Fact_Sheet_RD.pdf
[68] http://download2.eurordis.org.s3.amazonaws.com/documents/pdf/Undiagnosed-International-Joint-Recommendations.pdf

understanding of rare diseases would also potentially lead to better rare disease policies, as well as reduced healthcare inefficiencies & disparities.

Public Funding:

Strategic collaboration with public partners is required as this programme is central at the cusp of public health policy. To address the challenges and undertake a project of such a transformational nature, an active partnership from a range of contributors across the public and private sectors is necessary. A project of this nature and scope requires a synergistic effort across academia, industry partners and other relevant stakeholders, in order to potentially positively impact the lives of up to 30 million RD patients in the EU and their families. As mentioned above, RDs are diverse and complex, which calls for a vast and diverse group of collaborators to leverage the required spectrum of knowledge, expertise, and network, as detailed in the section entitled "Expertise and resources expected from applicants at stage 1". Positive results will lead the consortium to make recommendations with regards to wider government run programme(s). Perspectives from Public Partners will ensure that proposed solutions are fit-for-purpose, and truly value-added for all stakeholders. The establishment of a public-private partnership offers a unique mechanism for all parties to engage in delivering the range of input and expertise necessary for achieving the project aims and ensuring that a practical and long-term sustainable plan follows this action.

Scope

It has been recently estimated that between 3.5 to 5.9 % of the general population has a RD (excluding rare cancers) and 72% of those RDs have an identified genetic origin [1]. Therefore, RD genetic screening might yield significant results. In addition, 70% of those RD patients are children [1], which points towards newborn screening[69]. In 2003, the cost of sequencing a human genome was a billion dollars. Today, it is under a thousand dollars and falling. With the advent of gene / genome sequencing, along with the ever-increasing availability of digital tools enhancing ways to collect, store, process and interpret massive amounts of data ("big data"), there is an unprecedented opportunity to transform the landscape of RD diagnosis as it is today.

In order to address the RD conundrum, the overall objective of this call topic is to shorten the path to RD diagnosis by using newborn / paediatric (infants during their first weeks of life) genetic screening; and, via application of advanced digital technologies that enable rare disease diagnosis / identification. The latter might require consolidation of existing fragmented efforts.

The specific objectives are:

1. Assessment and development of a comprehensive, strategic overview of existing converging RD resources e.g. databases, registries (such as the EU RD platform[70]), natural history projects, platforms, reference networks, rare disease academic centers of excellence (e.g. European Reference Networks (ERNs)[71]), and initiatives for evaluation / identification of potential collaboration and synergies;
2. Federation of available RD databases into a RD metadata repository amenable to machine learning or other advanced digital tools;
3. Co-creating a sustainable strategy for newborn genetic screening and pilot it. This could start directly after achieving objective 1;
4. Based on the output of objectives 1 & 2:
    a) Repurposing of pre-existing diagnosis AI algorithm to identify early onset RD patients in electronic health records (EHRs). This will include at least 3 pilots in better-known rare diseases (with the understanding that solutions and algorithms developed or adapted should be amenable or made amenable to be

[69] https://www.eurordis.org/sites/default/files/publications/fact-sheet-new-born-screening.pdf
[70] https://eu-rd-platform.jrc.ec.europa.eu/_en
[71] https://ec.europa.eu/health/ern_en

emulated for larger sets of better-known RDs) where more robust data is available to train and test the AI algorithm(s), and / or;

b) Design and development of new AI algorithm(s) to achieve the above goal.

5. Based on insights generated by objectives 1, 2 & 4, either repurposing or development of a broad AI RD diagnosis "symptom checker" to help undiagnosed RD patients going from one health care provider (HCP) to another. In addition, exploration of further viable options to implement the symptom checker in actionable solutions for HCPs and patients.

Expected key deliverables

The consortium would have the following role:

- Responsible for making it possible to interconnect all the different sources of data;
- Curate data to make it interoperable and reusable; the applicants should follow the data standards developed by the European Joint Programme on Rare Diseases (EJP RD)[72] and the EU RD platform for research and registries data, as well as use European Patient Identifiers (EUPID) to track the diagnosis history and involvement in clinical studies;
- Ensure the algorithms are compliant with existing/emergent governance and validation policies;
- Ensure the algorithms are compliant with the Guidelines for Trustworthy Artificial Intelligence adopted by the High-Level Expert Group on AI[73]
- Make the algorithms available to the hospitals to run on their existing systems and, at the same time, use the data generated by the algorithms to improve diagnosis (through prediction and identification of potential new diagnostic/predictive/monitoring biomarkers).

The key deliverables are as follows:

1. **Addressing objective 1**: All listed deliverables are required in order to perform the subsequent "steps", must include GDPR / data ethics considerations, and follow FAIR principles:
    - Comprehensive landscape analysis of ongoing relevant initiatives and pre-existing resources with strategic recommendations about potential for collaboration. This includes a Cochrane systemic literature review, or equivalent;
    - Landscape analysis of relevant available data sources with analysis of usability readiness (data integrity, validity, re-consenting requirements, etc.) within the timeframe and budget scope of this project;
    - Definition of a pre-competitive business model to access rare disease data to purchase, license, or negotiate data sharing agreements. The consortium should be able to either bring the data or ensure access to data in a sustainable way with a long-term plan. For the data, as for all background brought into the project, access rights (according to IMI2 JU's intellectual property (IP) policy[74]) should be respected during and after the project (access rights of other beneficiaries and of third parties);
    - Analysis of regulatory, ethics and data privacy dimension requirements with strategic recommendations for subsequent work packages.

2. **Addressing objective 2:**

[72] https://www.ejprarediseases.org/
[73] https://ec.europa.eu/digital-single-market/en/news/ethics-guidelines-trustworthy-ai
[74] https://www.imi.europa.eu/apply-funding/general-overview/intellectual-property

- Federating of available RD databases into a RD metadata repository amenable to machine learning or other advanced digital tools;
- Co-creating new or identify available pre-existing optimal AI approach / platforms (considering access rights etc.), able to identify early-onset rare disease patients. Access rights should be considered not only during but also after the project, as per IMI2 JU IP policy;
- Integration of platforms with de-identified data and control of access rights for each data point to improve the use of big data analytics by several partners;
- Ensuring platform interoperability: readiness to integrate and aggregate new data from different sources or operate with other platforms, e.g. patient-reported outcomes or biobank databases;
- Ensuring adoptability and acceptance of such tools from the public, regulators and HCPs by engaging in dialogue with relevant stakeholders.

3. **Addressing objective 3:**

- RD gene panel for the purpose of newborn screening (NBS): List of criteria for inclusion / exclusion in the panel (scientific, technical, sustainable, and ethical) aligned with the overarching goals of action;
- Fully developed RD genetic NBS protocol (and / or kit), tested and validated, with post-diagnosis planning recommendations (genetic counselling, referral, etc.);
- As a complementary approach, development of a whole exome sequencing (WES) implementation protocol (with criteria) for infants (up to 1-2 months old) with unexplained symptoms, including all considerations mentioned in the deliverables above. These two sequential approaches should be strategically mapped for feasibility and acceptability, according to the opinions of all stakeholders, but also on a case–by-case basis, driven by family decision (both approaches in b and c should be developed);
- Post-pilot metrics and data on feasibility, health economics, scalability, improved outcomes for patients; benefits to patients & families. This will contribute to the input that feeds into health policy and ethics discussions.

4. **Addressing objective 4:**

- Repurposing and / or development of digital diagnosis algorithms trained on the RD metadata repository to be used in electronic health records to continuously screen for patients with early signs of better-known RDs and facilitate referral for genetic testing or further testing;
- This algorithm should be tested; based on this pilot, recommendations should be formulated for public health authorities.

5. **Addressing objective 5:**

- Review and analysis of options for a potential artificial intelligence phenotypic recognition tool (digital “clinical symptom checker” support tool) trained on the federated RD database to help RD patients cycling through HCPs. The intent is that the tool(s) will be publicly available afterwards, open source, with the associated HCP training curriculum. The tool should be designed in such a way that it would be used by both HCPs and patients;
- In addition, generation of a strategic report regarding potential further viable options to implement the symptom checker in actionable solutions for HCPs and patients. This could include mapping further potential functionalities within the symptom checker and / or other avenues to leverage the symptom checker capabilities.

6. **Overall output:**

- Publication plan, data dissemination and communication plan, recommendations to public health governing bodies, multi-stakeholder engagement strategythat includes the EMA, FDA and other regulatory bodies.

Expected impact

In their proposals, applicants should describe how the outputs of the project will contribute to the following impacts and include, wherever possible, baseline, targets and metrics to measure impact.

The Rare Disease conundrum:

Despite the recent rise in RD research and development, most RDs remain under-studied, and therefore under-treated / cared for. This can be attributed for the most part to:

- Patients are not identified / diagnosed;
- Lack of epidemiological data;
- No natural history of disease data;
- No validated endpoint / patient-reported-outcomes (PROs);
- Patient are rare, experts are even rarer.

This has the pernicious additional effect of blunting interest in diagnosis / screening initiatives, as it would lead to patients being diagnosed with no concrete medical or clinical option. This poses an ethical challenge, which unfortunately feeds the conundrum. This has been identified as a major problem for the rare disease community.

This Call topic anticipates the following benefits:

- For patients:
    - Decreased time to the right diagnosis;
    - Improved patient journey;
    - Better healthcare;
    - Increased quality of life;
    - Decreased irreversible organ damage;
    - Access to their own healthcare data.
- For healthcare
    - Implementation of digital transformation in healthcare;
    - Paradigm change in rare disease diagnosis;
    - Improved diagnostic tools;
    - Improved understanding of disease;
    - Higher accuracy in clinical decisions;
    - Better care delivery;
    - Integrated care among different specialties.
- For research
    - Advances in utilisation of digital technologies;

- Increased disease knowledge for future research;
- Improved data availability for future research.

- For society
    - Decreased burden for family and carers;
    - Increased trust in the healthcare system;
    - Better use of data for public health;
    - Improved value-based healthcare.

In their proposals, applicants should outline how the project plans to leverage the public-private partnership model to maximise impact on innovation, research & development; regulatory, clinical and healthcare practices, as relevant. This could include a strategy for engagement with patients, healthcare professional associations, healthcare providers, regulators, health technology assessment (HTA) agencies, payers etc., where relevant.

In addition, applicants should describe how the project will impact the competitiveness and growth of companies including SMEs.

In their proposals, applicants should outline how the project will:

- Manage research data including use of data standards[75] and, to the extend relevant, the data standards developed by the European Joint Programme on Rare diseases[76] (EJP RD) and the EU RD platform for research and registries data respectively, as well as the use of EUPID;
- Disseminate, exploit, and sustain the project results. This may involve engaging with suitable biological and medical sciences research infrastructures;[77]
- Communicate the project activities to relevant target audiences.

Potential synergies with existing consortia

Synergies and complementarities should be considered with relevant national, European and non-European initiatives (including suitable biological and medical sciences research infrastructures) in order to incorporate past achievements, available data and lessons learnt where possible, thus avoiding unnecessary overlap, and duplication of efforts and funding.

Industry consortium

The industry consortium is composed of the following EFPIA partners:

- Pfizer (lead)
- Illumina
- Lysogene
- Novartis / Avexis
- Novo Nordisk

[75] Guidance on data management is available at http://ec.europa.eu/research/participants/docs/h2020-funding-guide/cross-cutting-issues/open-access-data-management/data-management_en.htm
[76] https://www.ejprarediseases.org/
[77] http://www.corbel-project.eu/about-corbel/research-infrastructures.html

- ProQR
- Roche
- Sanofi
- Takeda

The industry consortium plans to contribute the following expertise and assets:

- Project leadership and programme oversight, genetic research, medical affairs, data science / analytics & AI, epidemiology, regulatory, public relations / policy, commercial nnovation;
- Scientific affairs, innovation, PPP management support, medical affairs, public affairs;
- Genetic diseases / digital medical innovation, newborn screening, diagnostics, personalised medicine / healthcare, public policy, immunodeficiency

One of the foreseeable rate-limiting factors for the success of this project is the availability of robust disease natural history data, of high enough quality that it can be used for machine learning (training data sets). Therefore, during the funded action, members of the industry consortium plan to contribute scientifically relevant activities for generating data in prospective activities that are part of broader industry clinical studies. Namely, data provided by members of the industry consortium will include (but will not be limited to) rare disease clinical trial data. This data will be either control data (such a placebo) or baseline data. For the purpose of this project, such data will serve as "natural history data", to be used for machine learning covered by objectives 2, 4, and 5.

The relevant activities will be included in the project's Description of the Action and are necessary for achieving its objectives. The introduction of the data constitutes an in-kind contribution which entails access rights to these project results in line with IMI2 JU intellectual property (IP) rules. The estimated in-kind contribution for the prospective activities to generate these data and samples is EUR 3 500 000.

Indicative duration of the action

The indicative duration of the action is 60 months.

This duration is indicative only. At stage 2, the consortium selected at stage 1 and the predefined industry consortium may jointly agree on a different duration when submitting the stage 2 proposal.

Indicative budget

The financial contribution from IMI2 JU is a maximum of EUR 11 940 000.

The indicative in-kind contribution from EFPIA partners is EUR 12 600 000.

The EFPIA contribution includes EUR 1 000 000 financial contribution; the allocation of this financial contribution will be decided by the full consortium at stage 2 when preparing the full proposal.

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

Expertise and resources expected from applicants at stage 1

The stage 1 applicant consortium is expected, in the submitted short proposal, to address all the objectives and key deliverables of the topic, taking into account the expected contribution from the industry consortium which will join at stage 2 to form the full consortium.

The stage 1 submitted short proposals should include suggestions for creating a full proposal architecture, which could be in line with the suggested architecture described below, though this architecture is only a suggestion.

This may require mobilising, as appropriate the following expertise:

The consortium should include (but not limited to) the following key stakeholders:

- Patient Organization, Academia, SMEs, Public Health Decision Makers, Regulators.

The consortium should mobilise the following expertise:

- In order to achieve objective 1 and to deliver associated deliverables, the consortium should have the required expertise and capabilities to networking with EU, local Healthcare & Data Protection Regulators. Expertise will be needed in the fields of regulatory affairs, policy and politics, health economics, HTA / pharmaco-economy, regulatory sciences, legal / IP / licensing, rare disease expertise, international rare disease Patient Advocacy, patient journey, Innovation, public health, expertise in high & low-income EU health systems, public health systems Implementation.
- In order to attain goals described for objective 2, 4 & 5 and to deliver associated deliverables, the consortium should have the required following expertise and capabilities: Data Exchange & Building Digital Infrastructure, User experience, Data security and Data Anonymisation, Methodology development, Data Management, Data Science, Data standards, Data translation, Pharmaco-epidemiology, Biostatistics, Bioinformatics, Software Engineering, Data stewardship, Business and governance model development (Including sustainability), Medical, Legal General Data Protection Regulation (GDPR) Compliance, Data ethics, Privacy, Medical Insurance, Medical Training, Data Quality assurance, IT, Cyber security, Federated data
- In order to attain goals described for objective 3 and to deliver associated deliverables, the consortium should have the required following expertise and capabilities: Genetics, Genomics, Molecular Biology, Whole Exome and Whole genome Sequencing (WES / WGS), Gene panel, In silico panel, Bioethics, Genetic Counseling;
- In addition, the following general expertise / capabilities will be required: Project Management, Study / Trial Operation Manager, Medical / Scientific Writing, Communications, Public Outreach.

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

- Ideally, the consortium should welcome the participation of partners who could and would be willing to contribute RD phenotypic data that could be integrated in the meta-data repository that would train the AI algorithm(s), as well as partners able to contribute pre-developed rare disease recognition algorithm(s).

Considerations for the outline of project work plan

In their stage 1 proposals applicants should:

- Give due visibility on data management; dissemination, exploitation and sustainability; and communication activities. This should include the allocation of sufficient resources for these tasks which will be further developed in stage 2 proposal;
- Consider including a strategy for ensuring the translation of the projects results to drug development, regulatory/ HTA settings (e.g. through scientific advice/ qualification advice /opinion, etc.), clinical and healthcare practices and/or decision-making processes.

Suggested architecture

Work packages:

It is suggested that each of the 5 objectives described under section "SCOPE" (with associated goals and deliverable) becomes a work package (WP).

In addition, consideration should be given to a project management WP that would:

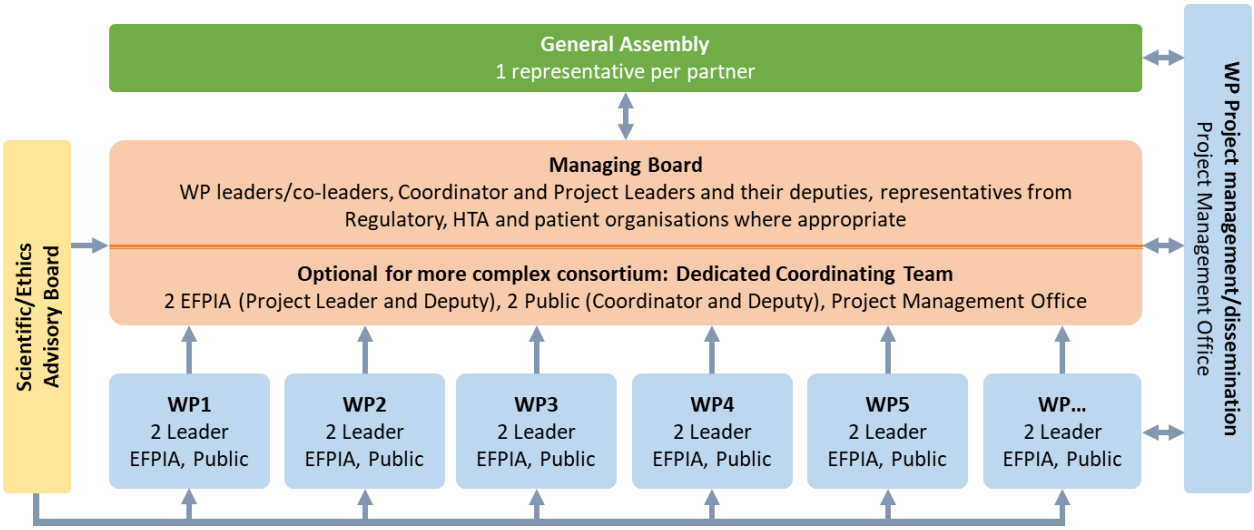
- Ensure alignment between the participants as well as smooth internal and external communication;

- Monitor compliance with the work plan;
- Monitor planned resources and time schedule;

- Coordinate fulfilment of all administrative milestones;
- Ensure legal and data privacy requirements are met during the project lifetime.

Applicant consortium is expected to contribute to project management, ensuring the implementation of the coordinating tasks and running the day-to-day operation, such as project tracking and reporting, meetings, internal communication, website creation, budget management, etc.

Example Architecture:



Additional considerations to be taken into account at the stage 2 full proposal

At stage 2, the consortium selected at stage 1 and the predefined industry consortium jointly submit the full proposal developed in partnership. The full proposal is based upon the selected short proposal at stage 1.

In the spirit of the partnership, and to reflect how IMI2 JU call topics are built on identified scientific priorities agreed together with EFPIA beneficiaries/large industrial beneficiaries, these beneficiaries intend to significantly contribute to the programme and project leadership as well as project financial management. The final architecture of the full proposal will be defined by the participants in compliance with the IMI2 JU rules and with a view to the achievement of the project objectives. The allocation of a leading role within the consortium will be discussed in the course of the drafting of the full proposal to be submitted at stage 2. To facilitate the formation of the final consortium, until the roles are formally appointed through the consortium agreement, the proposed project leader from among EFPIA beneficiaries/large industrial beneficiaries shall facilitate an efficient negotiation of project content and required agreements. All beneficiaries are encouraged to discuss the project architecture and governance and the weighting of responsibilities and priorities therein.

Data management

In their stage 2 proposal, applicants should give due visibility to data management including use of data standards. A full 'data management plan' (DMP) as a distinct deliverable must be delivered within the first 6 months of the project. The DMP needs to be kept up to date with the needs of the project and as such be updated as necessary during its lifetime.[78]

Dissemination, exploitation and sustainability of results

In their stage 2 proposal, applicants must provide a draft plan for dissemination and the exploitation, including sustainability of results. A full plan as a distinct deliverable must be delivered within the first 6 months of the project[79], and updated during the project lifetime and could include identification of:

- Different types of exploitable results;
- Potential end-users of the results;
- Results that may need sustainability and proposed sustainability roadmap solutions.

Sufficient resources should be foreseen for activities related to dissemination and exploitation, including the plan for the sustainability of the project results. This may involve engaging with suitable biological and medical sciences Research Infrastructures (RIs).[80]

Communication

The proposed communication measures for promoting the project and its findings during the period of the grant should also be described and could include a possible public event to showcase the results of the project.

References

[1] Nguengang Wakap, S., et al., Estimating cumulative point prevalence of rare diseases: analysis of the Orphanet database. Eur J Hum Genet, 2020. 28(2): p. 165-173.

[78] Guidance on data management is available at http://ec.europa.eu/research/participants/docs/h2020-funding-guide/cross-cutting-issues/open-access-data-management/data-management_en.htm
[79] As an additional dissemination obligation under Article 29.1 of the IMI2 Grant Agreement will apply
[80] http://www.corbel-project.eu/about-corbel/research-infrastructures.html

Topic 6: Behavioural Model of Factors Affecting Patient Adherence

Topic details

Topic code	IMI2-2020-23-06
Action type	Research and Innovation Action (RIA)
Submission and evaluation process	2 stages
IMI2 Strategic Research Agenda - Axis of Research	Patient-tailored adherence programmes.
IMI2 Strategic Research Agenda - Health Priority	Other

Specific challenges to be addressed by public-private collaborative research

Patient non-adherence to prescribed treatment is an issue that affects patient health outcomes and healthcare system costs worldwide. It is estimated that it contributes to 200 000 premature deaths in the EU each year [1]. The annual costs in Europe of avoidable hospitalisations, emergency care and adult outpatient visits are assessed at EUR 125 billion[1] and there are similar figures in the US [2]. In addition, poor patient outcomes and resulting lower productivity affect the wider society, estimated in the US as 2.3 times direct healthcare costs [2]. Addressing the issues of adherence would significantly improve both individual patient outcomes and reduce societal costs.

Reported adherence rates for on-market drug products vary from 7% to 87% [3] and average 50% [4]. Non-adherence may also include non-pharmaceutical treatments (e.g. digital therapeutics, non-pharmaceutical respiratory devices, lifestyle changes) and over-use of medication, for example, patients are known to increase their intake of pain relief medication above their prescribed dose [5].

Many researchers have approached the topic of adherence[3] but insights have necessarily been limited to specific sub-topics due to the breadth of the field. Consequently, whilst there are pockets of knowledge, both published and unpublished, there are also areas and interactions that are not fully understood. Although a number of app-based solutions for non-adherence have been developed, their effectiveness is highly variable [6]. Unless the underlying problem is well-defined and understood, the probability of developing effective solutions with broad and consistent impact is low. In addition, for a solution to be effective, it must be used. Therefore, the patient burden must be minimised and the solution must be simple to apply to ensure broad implementation. An optimised solution is required balancing personalisation (complexity) and simplicity of use. This may include population segmentation according to behavioural phenotypes [7].

A disease-agnostic solution has the potential to achieve the necessary simplicity. Although there are some factors which appear to be disease-specific (e.g. stigma of the disease) these may exist more generally in the population and merely be weighted more strongly in specific conditions. There are also many significant factors which are not associated with any single disease state and which vary minimally between them, such as a patient's health beliefs, need for control, social environment or education level. This indicates the potential for a disease-agnostic baseline model.

Consequently, there is a need to generate a more comprehensive theoretical and empirical understanding of the underlying causes of these patient behaviours and any interactions. This topic proposes the creation of a generalised model, grounded in behavioural theory, which integrates significant factors affecting non-adherent behaviour. Factors should include patient motivation, which is critical to adherence [8], and is particularly under-represented in the literature compared to more quantitative factors such as education level. This would provide a robust definition of the problem – a foundation for understanding and predicting patient behaviour – and guidance to develop and implement cost-effective tools and solutions for patients, healthcare professionals (HCPs) and other healthcare stakeholders which directly target the causes of non-adherence and, ultimately, improve patient outcomes and reduce health system costs.

As medication adherence includes three distinct elements: 1) initiation of therapy, 2) implementation of the dosing regimen, and 3) persistence with treatment **Error! Reference source not found.**, it is anticipated that these three issues can be addressed by the proposed model.

Creating the necessary understanding for an effective model will require broad engagement and skills, particularly since we are targeting a disease agnostic model. The perspectives of patients, healthcare providers, academic experts, behavioural scientists, digital and data analytics experts and regulatory bodies will be essential to maximise the benefits and ensure all sectors of society are well served.

The establishment of a public-private partnership offers the opportunity to generate the necessary breadth of data and bring together the breadth of expertise needed to address these challenges.

Scope

The aims of the Call topic are to:

- develop a comprehensive understanding of the factors which affect patient needs and adherence, independently from the therapeutic area (i.e. generic or disease-agnostic), in a real-world context (as opposed to clinical setting);
- identify the most significant factors;
- evaluate existing models and then either create an open access behavioural model or further develop an existing model;
- collect additional real-world data to refine the model;
- provide tools that will enable healthcare stakeholders to cost-effectively develop and implement solutions to address patient needs and improve adherence rates.

The project will require a phased approach as the results of earlier activities may influence the focus and definition of later stages.

The scope of the project will include a definition of adherence and collate the factors affecting adherence. The relative impact and significance of factors shall be assessed and a gap analysis performed against theory to identify areas for research during the project. The review stage should therefore include an evaluation of available models of non-adherence behaviour. One potential model identified during the development of this text is the Subjective Experienced Health Methodology (SEHM) [10]. The evaluation of models should consider the extent to which significant factors are included and the applicability and availability of models for ongoing development to achieve the project aims.

Based on this research, a behavioural model will be created or selected and refined. In parallel, adherence modules will be added to existing patient studies to fill identified gaps in the data.

While disease-agnostic, the model should be able to increase the prediction power and accuracy when applying additional, disease-specific inputs. The model should be sufficiently flexible to allow future development as population needs change.

It is envisaged that there will be a strong data analysis component (e.g. through Machine Learning (ML) or Artificial Intelligence (AI), if applicable) in the evaluation of data and generation of tools to assess the proposed model. This will identify any factors not demonstrated in the literature and identify patterns within the data. The model should clearly indicate the primary causes of patient motivations and should provide guidance for aligning patient needs with solutions. Feedback from this activity will be used to develop and optimise the model.

Given the quantity of data that will be collected or generated, consideration will be required for data storage and management solutions.

Once developed or refined, the model will be validated for multiple ages (including paediatric), ethnicities and conditions. It is anticipated that this shall be achieved using the following therapeutic areas, dependent on access to patients provided by members of the consortium:

- Cardiovascular;
- Oncology;
- Immunology;
- Neurology;
- Endocrinology and
- Rare Disease.

It should be noted that this list is not exhaustive. Where opportunities arise to validate in other additional therapeutic areas, these should be explored. The objective of this phase is to demonstrate the consistency and effectiveness of identifying patient needs and predicting adherence rates.

Finally, an implementation strategy of this model will be determined (e.g. guidelines for use, Application Programming Interface or API approach). To ensure that any future tools generate genuine benefit for both patients and HCPs, a phase of work is required to assess how the interface could be simplified for patients, potentially sharing common data between companies or a common interface framework to engage with patients in a single location.

The implementation of stand-alone, patient-facing solutions (e.g. digital platforms) is out of scope of this Call topic. Modelling the behaviour of HCPs is also out of scope.

During the funded action, members of the industry consortium plan to contribute scientifically relevant pre-existing data and/or data from prospective studies including activities for generating such data that are part of broader industry clinical trials and/or patient studies and making such data fit for purpose.

Expected key deliverables

- Searchable database of published and available (to the consortium) unpublished sources of data on treatment adherence causes;
- Definition of adherence and methodology for assessing data, including consideration of bias;
- Statistical analysis and prioritisation of relative significance of factors on treatment adherence and persistence;
- Evaluation of available treatment adherence models, assessing strengths and weaknesses of selected models, considering the balance between personalisation and simplicity of implementation. This deliverable will then be used by the consortium to choose one model to refine/build a new model for validation;
- Methods to measure key factors and adherence levels which can feasibly be used with patients, considering minimum burden to patient;
- Disease-agnostic model of patient behaviour considering all factors identified above;
- Development of tools to collect data from patients and to quantify behavioural factors, for use in validating the model and in future applications of the model;
- Evaluation of trends within the data which indicate population sub-groupings with similar causes of non-adherent behaviour, and which could be used to cost-effectively identify suitable support types for patients;
- Model validation to demonstrate effective understanding of patient needs and prediction of adherence rates;
- Guidance on applying the model to develop solutions to address patient needs and, hence, adherence rates;
- Educational tools for patient organisations and support groups, pharmacies and healthcare providers;

- Requirements assessment for data-sharing solutions to minimise patient burden and data entry duplication. Potential proof-of-concept solution to demonstrate how a single patient input can be shared with multiple companies.

Expected impact

The model and supporting guidance developed under the project have the potential to transform the way healthcare stakeholders engage with patients to optimise their understanding of their condition and their adherence levels throughout their healthcare journey.

In their proposals, applicants should describe how the outputs of the project will contribute to the following impacts and include wherever possible baselines, targets and metrics to measure impact:

- Positive impact on healthcare at a societal level through enhanced adherence, targeted use of resources, and improved overall patient outcomes;
- Validated foundation to compile and understand factors affecting patient non-adherence to treatment regimens and the relative weighting of these factors;
- Identification of sub-groups of the population with similar causes of non-adherent behaviour such that solutions can be tailored to population needs and applied in a cost-effective manner to multiple treatment conditions;
- Model for the basis of a consistent approach to non-adherence across the industry; a framework for future development of patient-centric solutions, with the capacity for the model to evolve with the future needs of patient populations;
- Guidance, based on the validated model, for identifying patient needs and tailoring support tools for patients and HCPs which most closely address patient adherence needs and improve patient outcomes and quality of life;
- The data collected during the project will provide a broad and deep resource for future understanding of adherence.

The model and associated tools and guidance will provide open access resources that healthcare stakeholders can use to independently:

- Collect a minimum dataset from patients e.g. via questionnaire or online tool;
- Use data and the model to estimate risk of patient non-adherence;
- Use data and the model to identify patient needs for good adherence – potentially linked to a sub-group of similar patients;
- Use as a baseline to create their own specific toolkits;
- Create support solutions for delivery to patients or patient sub-groups, based on patient needs e.g. patient education, practical tools such as dose histories, links to HCPs or patient groups for emotional support. Potential to create multiple tools or resources but only deliver those that are most valuable to the individual patient;
- Repeat assessments to identify changing patient attitudes and needs

In their proposals, applicants should outline how the project plans to leverage the public-private partnership model to maximise impact on innovation, research & development, as well as regulatory, clinical and healthcare practices, where relevant. This could include a strategy for engagement with patients, healthcare professional associations, healthcare providers, regulators, Health Technology Assessment (HTA) agencies, payers etc., where relevant.

In addition, applicants should describe how the project will impact the competitiveness and growth of companies including SMEs.

In their proposals, applicants should outline how the project will:

- Manage research data including use of data standards;[81]
- Disseminate, exploit, and sustain the project results. This may involve engaging with suitable biological and medical sciences Research Infrastructures;[82]
- Communicate the project activities to relevant target audiences.

In addition, the following additional exploitation[83]/dissemination[84] obligations must be considered to maximise impact:

It is expected that the model, guidance and any development tools will be made available through an open source process to achieve the aims of maximising the number of patients receiving support.

Potential synergies with existing consortia

Synergies and complementarities should be considered with relevant national, European and non-European initiatives (including suitable biological and medical sciences research infrastructures[77]) in order to incorporate past achievements, available data and lessons learnt where possible, thus avoiding unnecessary overlap, and duplication of efforts and funding.

Industry consortium

The industry consortium is composed of the following EFPIA partners:

- Pfizer (lead)
- Astellas
- Janssen
- Merck KGaA
- Novonordisk
- Resmed
- Servier
- Takeda

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

- Link2Trials

The industry consortium (EFPIA and Associated Partner) plan to contribute the following expertise and assets as in-kind contributions:

- Curation and re-analysis of existing in-house study data or data summaries to show adherence rates and links to causes of non-adherence;
- Expertise in behavioural science to support model development/refinement;
- Development of methods to collect and assess treatment adherence rates;

[81] Guidance on data management is available at http://ec.europa.eu/research/participants/docs/h2020-funding-guide/cross-cutting-issues/open-access-data-management/data-management_en.htm
[82] http://www.corbel-project.eu/about-corbel/research-infrastructures.html
[83] Article 28.1 (Additional exploitation obligations) of the IMI2 Grant Agreement will apply
[84] Article 29.1 (Additional dissemination obligations) of the IMI2 Grant Agreement will apply

- Study design, planning and management experience;
- Access to planned patient studies for data generation, model development, testing and validation activities. Identification of planned industry-sponsored phase 4 or other planned real-world studies to which an adherence module could be appended. Industry studies will provide access to patients for the selected medical conditions as a minimum. Further assessment areas may be added depending on the availability of suitable studies. Studies will be sponsored and funded by the respective company including the cost of full-time equivalents (FTEs) and other expenses to run the studies, including but not limited to contract research organisations (CRO) and investigator costs;
- Data analysis, including statistical analysis of study results and advanced analytics/machine learning expertise to identify trends;
- Project leadership and programme oversight;
- Regulatory, General Data Protection Regulation (GDPR), legal and medical expertise.

Indicative duration of the action

The indicative duration of the action is 60 months.

This duration is indicative only. At stage 2, the consortium selected at stage 1 and the predefined industry consortium may jointly agree on a different duration when submitting the stage 2 proposal.

Indicative budget

The financial contribution from IMI2 JU is a maximum of EUR 5 950 000.

The indicative in-kind contribution from EFPIA partners and IMI2 JU Associated Partner is EUR 5 950 000. This contribution comprises an indicative EFPIA in-kind contribution of EUR 5 700 000 and an indicative IMI2 JU Associated Partner in-kind contribution EUR 250 000.

Due to the global nature of the participating industry partners and IMI2 Associated Partner it is anticipated that some elements of the contributions will be non-EU/H2020 Associated Countries in-kind contributions.

Expertise and resources expected from applicants at stage 1

The stage 1 applicant consortium is expected, in the submitted short proposal, to address all the objectives and key deliverables of the topic, taking into account the expected contribution from the industry consortium, which will join at stage 2 to form the full consortium.

The stage 1 submitted short proposals should include suggestions for creating a full proposal architecture (which could be in line with the suggested architecture described below, though this architecture is only a suggestion.)

This may require mobilising, as appropriate the following expertise:

- Published expertise in patient experience, factors which affect treatment adherence, e.g. scientific and research organisations;
- Expertise to provide insight across countries and therapeutic areas as well as insight from different HCPs (e.g. physicians, pharmacists, nurses) and stakeholders (e.g. patients, healthcare providers, healthcare policy makers, and pharmaceutical researchers);
- Academic and commercial expertise in building and evaluating behavioural models and frameworks and the factors which drive treatment adherence behaviour;
- Reporting capabilities in agreement with the ABC taxonomy and the EMERGE guidelines;
- Study design and management expertise;

- Expertise in the use and analysis of real-world data on treatment adherence to contribute to and validate the model, including machine learning to identify data patterns and trends;
- SMEs with implemented solutions (i.e. hardware and software) to measure and manage medication adherence, ideally with own datasets and published evidence;
- Experience of patient communication, patient interfaces and app development for individualisation of therapies and patient empowerment;
- Legal and data privacy (e.g. GDPR) expertise;
- Access to health authorities, healthcare professionals, patients, patient advocacy groups and policy makers for their input into the implementation of the model, either as partner of the consortium or seeking advice;
- Information technology, data management, website management expertise;
- Expertise in clinical compliance/ICH GCP (International Council for Harmonisation – Good Clinical Practice) aspects;
- Project management, project administration/coordination, budget management and communication expertise;

NB It is not a requirement that public partners recruit patients unless it is for patient studies to which they have access.

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

- Evidence-based digital tools to systematically collect adherence factors and dosing rate data from all participants included in studies and to identify relevant patterns in the adherence data.

Considerations for the outline of project work plan:

In their stage 1 proposals applicants should

- Give due visibility to data management; dissemination, exploitation and sustainability; and communication activities. This should include the allocation of sufficient resources for these tasks which will be further developed in stage 2 proposal;
- Consider including a strategy for ensuring the translation of the project results to drug development, regulatory/ HTA settings (e.g. through scientific advice/qualification advice/opinion, etc.), clinical and healthcare practices and/or decision-making processes.

Suggested architecture

Work package 1 – Review of existing data and state of the art

The goals of this work package are to:

- Agree on a definition of adherence;
- Collate published adherence work and unpublished data from members of the consortium demonstrating significant factors that impact patient behaviour with respect to treatment adherence. The work should consider medical, psychological and social factors, variation during the patient journey, and both over- and under-utilisation;
- Create a searchable database of data on treatment adherence causes;
- Carry out statistical analysis and prioritisation of relative significance of factors on treatment adherence and persistence;
- Identify published and unpublished models of patient behaviour with respect to treatment adherence and adherence levels;

- Evaluate available adherence models, assessing strengths and weaknesses of selected models. This deliverable will then be used by the consortium to choose one model to refine/build a new model for validation;
- Perform gap analysis against behavioural theories to identify factors that are missing or not well substantiated.

Work package 2 – Model Development / Model Refinement

The goals of this work package are to:

- Develop a disease-agnostic model of patient behaviour considering all factors identified in WP1;
- Refine the model using the additional data collected in WP3 and any data analysis techniques to identify trends, patient groupings or surrogate measures for adherence;
- Develop methods to measure key factors and adherence levels that can feasibly be used with patients, considering minimum burden to patient.

Work package 3 – Generation of additional data

The goals of this work package are to:

- Generate additional data to fill the gaps identified in WP1 and contribute to WP2 for the model refinement;
- Develop tools to collect data from patients and to quantify behavioural factors and potential solution types, for use in refining and validating the model and future model implementation;
- Use existing industry-sponsored real-world studies and append a module on adherence factors and measurement to generate a breadth of data across different conditions.

Work package 4 – Model validation

The goals of this work package are to:

- Identify suitable studies (e.g. existing Phase 4 clinical studies, real-world studies) to test the model predictions of patient needs and adherence rates;
- Validate the behavioural model for at least six therapeutic areas covering the most significant medical, psychological and social factors identified in WP1;
- Develop prototype solutions as required to support validation activities.

Work package 5 – Implementation strategy

The goals of this work package are to:

- Develop guidance on how to apply the model to develop solutions to address patient needs and, hence, adherence rates, for use by industry partners, academia or healthcare practitioners;
- Consider how patients with multiple conditions may interact with likely adherence solutions. Consider concepts for future tools that could share data or interfaces to minimise the burden on the patient. Determine the requirements for such tools, including the needs of patients, healthcare providers, regulators and industry;
- Prepare a proof of concept of such tools.

Work package 6 – Project management, incl. sustainability plan, regulatory, legal & data privacy

The goals of this work package are to:

- Ensure alignment between the beneficiaries as well as smooth internal and external communication;
- Monitor compliance with the work plan;
- Monitor planned resources and time schedule;
- Coordinate fulfilment of all administrative milestones;

- Prepare a sustainability plan for the deliverables that shall be maintained and/or developed after the completion of the project. The plan shall be produced in parallel with model development;
- Ensure legal and data privacy requirements are met during the project lifetime.

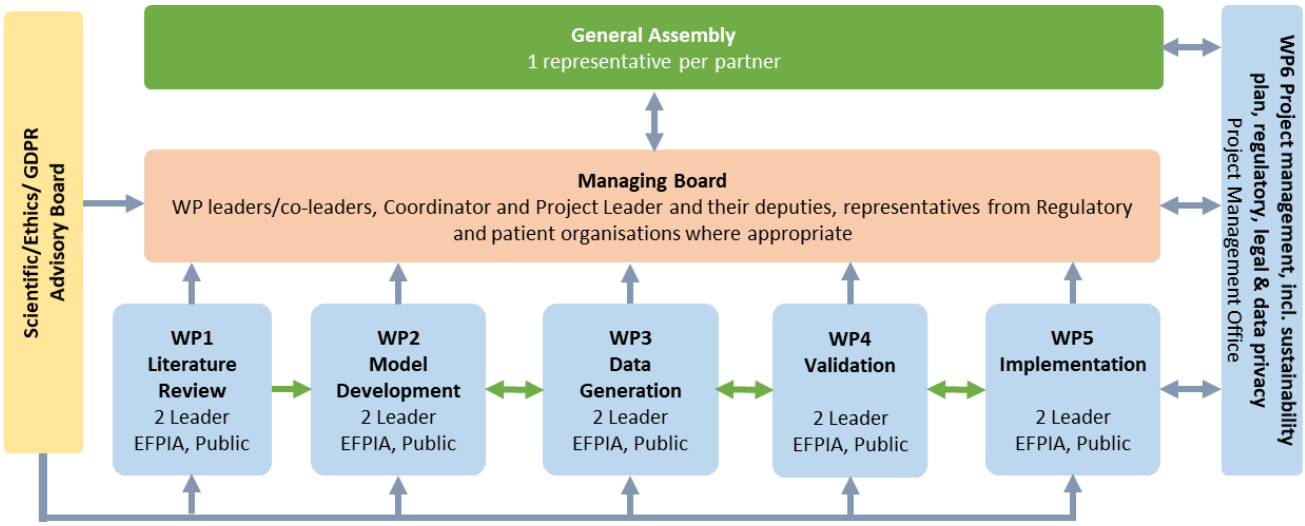


Figure 1 – Suggested WP architecture

Additional considerations to be taken into account at the stage 2 full proposal

At stage 2, the consortium selected at stage 1 and the predefined industry consortium jointly submit the full proposal developed in partnership. The full proposal is based upon the selected short proposal at stage 1.

In the spirit of the partnership, and to reflect how IMI2 JU call topics are built on identified scientific priorities agreed together with EFPIA beneficiaries/large industrial beneficiaries, these beneficiaries intend to significantly contribute to the programme and project leadership as well as project financial management. The final architecture of the full proposal will be defined by the participants in compliance with the IMI2 JU rules and with a view to the achievement of the project objectives. The allocation of a leading role within the consortium will be discussed in the course of the drafting of the full proposal to be submitted at stage 2. To facilitate the formation of the final consortium, until the roles are formally appointed through the consortium agreement, the proposed project leader from among EFPIA beneficiaries/large industrial beneficiaries shall facilitate an efficient negotiation of project content and required agreements. All beneficiaries are encouraged to discuss the project architecture and governance and the weighting of responsibilities and priorities therein.

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[85] Guidance on data management is available at http://ec.europa.eu/research/participants/docs/h2020-funding-guide/cross-cutting-issues/open-access-data-management/data-management_en.htm

Dissemination, exploitation and sustainability of results

In their stage 2 proposal, applicants must provide a draft plan for dissemination and the exploitation, including sustainability of results. A full plan as a distinct deliverable must be delivered within the first six months of the project.[86], and updated during the project lifetime and could include identification of:

- Different types of exploitable results;
- Potential end-users of the results;
- Results that may need sustainability and proposed sustainability roadmap solutions.

Sufficient resources should be foreseen for activities related to dissemination and exploitation, including the plan for the sustainability of the project results. This may involve engaging with suitable biological and medical sciences Research Infrastructures (RIs).[87]

Communication

The proposed communication measures for promoting the project and its findings during the period of the grant should also be described and could include a possible public event to showcase the results of the project.

[86] As an additional dissemination obligation under Article 29.1 of the IMI2 Grant Agreement will apply
[87] http://www.corbel-project.eu/about-corbel/research-infrastructures.html

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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 conditions shall apply to this IMI2 JU Call for Proposals:

Applicants intending to submit a Short proposal in response to the IMI2 Call 23 should read this topics text, the IMI2 JU Manual for submission, evaluation and grant award and other relevant documents (e.g. IMI2 JU Model Grant Agreement).

Call Identifier	**H2020-JTI-IMI2-2020-23-two-stage**
Type of actions	**Research and Innovation Action (RIA)**
Publication Date	**23 June 2020**
Stage 1 Submission start date	**23 June 2020**
Stage 1 Submission deadline	**29 September 2020 (17:00:00 Brussels time)**
Stage 2 Submission deadline	**17 March 2021 (17:00:00 Brussels time)**
Indicative Budget	
From EFPIA companies and IMI2 JU Associated Partners	47 360 000 EUR
From the IMI2 JU [88]	47 790 000 EUR

Call Topics

IMI2-2020-23-01 **Returning Clinical Trial Data to Study Participants within a GDPR compliant and approved ethical framework**	The indicative contribution from EFPIA companies is EUR 4 930 000 The financial contribution from IMI2 JU is a maximum of EUR 3 260 000	Research and Innovation Action (RIA) 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.
IMI2-2020-23-02 **Modelling the impact of monoclonal antibodies and vaccines on the reduction of antimicrobial resistance**	The indicative contribution from EFPIA companies is EUR 2 760 000 The financial contribution from IMI2 JU is a maximum of EUR 6 500 000	Research and Innovation Action (RIA) 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.

[88] In case the budget of this given line cannot be consumed (totally or partially) the corresponding budget will be allocated to the topics under the other budget lines.

IMI2-2020-23-03 **A platform for accelerating biomarker discovery and validation to support therapeutics development for neurodegenerative diseases**	The indicative contribution from EFPIA companies is EUR 9 720 000 The financial contribution from IMI2 JU is a maximum of EUR 9 680 000	Research and Innovation Action (RIA) 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.
IMI2-2020-23-04 **Optimal treatment for patients with solid tumours in Europe through Artificial Intelligence**	The indicative contribution from EFPIA companies is EUR 11 400 000 The financial contribution from IMI2 JU is a maximum of EUR 10 460 000	Research and Innovation Action (RIA) 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.
IMI2-2020-23-05 **Shortening the path to rare disease diagnosis by using newborn genetic screening and digital technologies**	The indicative contribution from EFPIA companies is EUR 12 600 000 The financial contribution from IMI2 JU is a maximum of EUR 11 940 000	Research and Innovation Action (RIA) 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.
IMI2-2020-23-06 **Behavioural Model of Factors Affecting Patient Adherence**	The indicative contribution from EFPIA companies is EUR 5 700 000 The indicative IMI2 JU Associated Partners contribution is EUR 250 000 The financial contribution from IMI2 JU is a maximum of EUR 5 950 000	Research and Innovation Action (RIA) 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 the IMI2 JU Calls for Proposals. They are based on the General Annexes to the Horizon 2020 Work Programme 2018-2020[89].

LIST OF COUNTRIES AND APPLICABLE RULES FOR FUNDING

By way of derogation[90] 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:

[89] http://ec.europa.eu/research/participants/data/ref/h2020/other/wp/2018-2020/annexes/h2020-wp1820-annex-ga_en.pdf

[90] 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

(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.

Participating legal entities listed in (b) above established in a third country may receive funding from the IMI2 JU provided their participation is deemed essential for carrying out the action by the IMI2 JU or when such funding is provided for under a bilateral scientific and technological agreement or any other arrangement between the Union and the country in which the legal entity is established[91].

STANDARD ADMISSIBILITY CONDITIONS, PAGES LIMITS AND SUPPORTING DOCUMENTS

Part B of the General Annexes to the Horizon 2020 Work Programme 2018-2020 shall apply *mutatis mutandis* for the actions covered by this Calls for Proposals.

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

- at stage 1 of a two-stage call, the limit for RIA/IA short proposals is 30 pages;
- at stage 2 of a two-stage call, the limit for RIA/IA full proposals is 70 pages.

STANDARD ELIGIBILITY CONDITIONS

Part C of the General Annexes to the Horizon 2020 Work Programme 2018-2020 shall *apply mutatis mutandis* for the actions covered by this Calls for Proposals.

In addition, under all two-stage submission procedures the following additional condition[92] applies:

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

TYPES OF ACTION: SPECIFIC PROVISIONS AND FUNDING RATES

Part D of the General Annexes to the Horizon 2020 Work Programme 2018-2020 shall apply *mutatis mutandis* for the actions covered by this Calls for Proposals.

TECHNOLOGY READINESS LEVELS (TRL)

Part G of the General Annexes to Horizon 2020 Work Programme 2018-2020 shall apply *mutatis mutandis* for the actions covered by this Calls for Proposals.

[91] In accordance with Article 10(2) of the Regulation (EU) No 1290/2013 and Article 1 of Commission Delegated Regulation (EU) No 622/2014
[92] Article 9(5) of the Regulation (EU) No 1290/2013 of the European Parliament and of the Council of 11 December 2013 laying down the rules for participation and dissemination in "Horizon 2020"

EVALUATION RULES

Part H of the General Annexes to the Horizon 2020 Work Programme 2018-2020 shall apply *mutatis mutandis* for the actions covered by this Call for proposals with the following additions:

Award criteria and scores:

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

Type of action	Excellence *The following aspects will be taken into account, to the extent that the proposed work corresponds to the topic description in the call for proposals and referred to in the IMI2 JU annual work plan:*	Impact *The following aspects will be taken into account:*	Quality and efficiency of the implementation *The following aspects will be taken into account:*
RIA **1st stage** **Evaluation of two-stage evaluation** **IMI2 JU Call 23**	▪ Level to which all the objectives of the Call topic text are addressed; ▪ Soundness of the concept and credibility of the proposed methodology; ▪ Extent that the proposed work is beyond the state of the art and demonstrates innovation potential; ▪ Appropriate consideration of interdisciplinary approaches and use of stakeholder knowledge.	▪ Demonstration of how the outputs of the project will contribute to each of the expected impacts mentioned in the relevant Call topic text; ▪ Outline of how the project plans to leverage the public-private partnership model to achieve greater impact on innovation within research and development, regulatory, clinical and healthcare practices, as relevant; ▪ Impacts on competitiveness and growth of companies including SMEs; ▪ Quality of the proposed outline to: ○ Disseminate, exploit and sustain the project results; ○ Manage research data; ○ Communicate the project activities to relevant target audiences.	▪ Quality and effectiveness of the work plan outline, including extent to which the resources assigned to work packages are in line with their objectives and deliverables; ▪ Appropriateness of the outline management structures and procedures; ▪ Appropriateness of the allocation of tasks, ensuring that all participants have a valid role and adequate resources in the project to fulfil that role; ▪ Complementarity of the participants and extent to which the consortium as whole brings together the necessary expertise; ▪ Strategy to create a successful partnership with the industry consortium as mentioned in the Call topic text.

Type of action	Excellence *The following aspects will be taken into account, to the extent that the proposed work corresponds to the topic description in the Call for proposals and referred to in the IMI2 JU annual work plan and, for two stage procedures, is consistent with the stage 1 proposal:*	Impact *The following aspects will be taken into account:*	Quality and efficiency of the implementation *The following aspects will be taken into account:*
RIA **2nd stage** **Evaluation of two-stage evaluation** **IMI2 JU Call 23**	▪ Level to which all the objectives of the Call topic text are addressed; ▪ Soundness of the concept and credibility of the proposed methodology; ▪ Extent that the proposed work is beyond the state of the art and demonstrates innovation potential; ▪ Appropriate consideration of interdisciplinary approaches and use of stakeholder knowledge.	▪ Demonstration of how the outputs of the project will contribute to each of the expected impacts mentioned in the relevant Call topic text; ▪ Demonstration of how the project plans to leverage the public-private partnership model to achieve greater impact on innovation within R&D, regulatory, clinical and healthcare practices, as relevant; ▪ Impacts on competitiveness and growth of companies including SMEs; ▪ Quality and effectiveness of the proposed measures to: ○ Disseminate, exploit and sustain the project results; ○ Manage research data; ○ Communicate the project activities to relevant target audiences.	▪ Quality and effectiveness of the work plan, including extent to which the resources assigned to work packages are in line with their objectives and deliverables; ▪ Appropriateness of the management structures and procedures, including management of risk and innovation; ▪ Appropriateness of the allocation of tasks, ensuring that all participants have a valid role and adequate resources in the project to fulfil that role; ▪ Complementarity of the participants and extent to which the consortium as whole brings together the necessary expertise; ▪ Clearly defined contribution and effective integration of the industrial partners to the project.

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

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

Under IMI2 JU Call 23, for the evaluation of proposals under a two-stage submission procedure, at both stages (Stage 1 and Stage 2):

- the threshold for individual criteria will be 3;
- the overall threshold, applying to the sum of the three individual scores, will be 10.

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

The full evaluation procedure is described in the IMI2 JU Manual for submission, evaluation and grant award in line with the Horizon 2020 Rules for Participation.[93]

Under the two-stage evaluation procedure, and on the basis of the outcome of the first stage evaluation, the applicant consortium of the highest ranked short proposal (first stage) for each topic[94] will be invited to discuss with the relevant industry consortium the feasibility of jointly developing a full proposal (second stage).

Under the stage 2 preparation process, the applicant consortia of the second and third-ranked short proposals (stage 1) for each topic may be invited by the IMI2 JU, in priority order, for preliminary discussions with the industry consortium if the preliminary discussions with the higher ranked proposal and the industry consortium fail. IMI2 JU may explore this possibility if the first ranked applicant consortium and the industry consortium jointly notify the IMI2 JU that the preparation of a joint full proposal is not feasible. If this is the case, the first ranked consortium and the industry consortium shall notify IMI2 JU without delay, not later than within 30 days from the invitation to submit the stage 2 proposal. This notification must be accompanied by a joint report clearly stating the reasons why a stage 2 proposal is considered not feasible in order for IMI2 JU to take the decision whether to invite the lower ranked consortium. In the absence of a joint notification within the deadline, it is deemed that the first ranked applicant consortium and the industry consortium are going to submit the joint stage 2 proposal. Accordingly, the second and third-ranked short proposals will be formally rejected.

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

As part of the panel deliberations, 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.

The IMI2 JU evaluation procedure is confidential. The members of the applicant consortia shall avoid taking any actions that could jeopardise confidentiality.

[93] https://www.imi.europa.eu/sites/default/files/uploads/documents/apply-for-funding/call-documents/imi2/IMI2_ManualForSubmission_v1.7_November2018.pdf

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

INDICATIVE TIMETABLE FOR EVALUATION AND GRANT AGREEMENT

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

BUDGET FLEXIBILITY

Part I of the General Annexes to the Horizon 2020 Work Programme 2018-2020 shall apply mutatis mutandis for the actions covered by this Call for proposals.

ACTIONS INVOLVING FINANCIAL SUPPORT TO THIRD PARTIES

Part K of the General Annexes to the Horizon 2020 Work Programme 2018-2020 shall apply mutatis mutandis for the actions selected under topics covered by this Call for proposals.

CONDITIONS RELATED TO OPEN ACCESS TO RESEARCH DATA

Part L of the General Annexes to the Horizon 2020 Work Programme 2018-2020 shall apply mutatis mutandis for the actions covered by this Call for proposals.

However, should a project 'opt-out' of these provisions, a Data Management Plan must still be prepared. A template for the Data Management Plan is available on the IMI2 JU website.

SUBMISSION TOOL

Proposals in response to a topic of the IMI2 JU Call for proposals must be submitted online, before the call deadline, by the coordinator via the Submission Service section of the relevant topic page available under Funding & tender opportunities – Single Electronic Data Interchange Area (SEDIA).

No other means of submission will be accepted.

OTHERS

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

https://ec.europa.eu/research/participants/data/ref/h2020/other/legal/templ/h2020_tmpl-clinical-studies_2018-2020_en.pdf

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

Ethical issues should be duly addressed in each submitted proposal to ensure that the proposed activities comply with ethical principles and relevant national, Union and international legislation. Any proposal that contravenes ethical principles or which does not fulfil the conditions set out in the H2020 Rules for Participation, or in the IMI2 JU Call for proposals shall not be selected. [95]

All submitted proposals at stage 2 of two stages should be 'ethics ready'. The ethics self-assessment performed by applicants in their proposal must identify and deal correctly with any ethics issues that may arise from the research activities. Once submitted, all proposals recommended for funding will undergo an ethics review (screening) and in addition, a number of projects could be assessed for ethics compliance (ethics checks), if recommended by ethics experts.

In order to ensure excellence in data and knowledge management consortia will be requested to disseminate scientific publications on the basis of open access[96] (see 'Guidelines on Open Access to Scientific Publications and Research Data in Horizon 2020').

To ensure actions are implemented properly, at the time of the signature of the grant agreement, each selected consortia must have agreed upon a consortium agreement, i.e. the internal arrangements regarding their operation and co-ordination.

Two-stage full proposals must contain a draft plan for the exploitation and dissemination of the results.

Applicants intending to submit a proposal in response to the IMI2 JU Calls should also read the topic text, the IMI2 JU Manual for submission, evaluation and grant award, and other relevant documents[97] (e.g. IMI2 JU model Grant Agreement).

[95] Article 19 of Horizon 2020 Framework Programme and Articles 13 and 14 of the Horizon 2020 Rules for Participation.
[96] 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
[97] http://www.imi.europa.eu/apply-funding/call-documents/imi2-call-documents

List of acronyms

Acronym	Meaning
AD	Alzheimer's Disease
AI	Artificial Intelligence
AIDS	Acquired immune deficiency syndrome
AMR	Anti-Microbial Resistance
AP	Associated Partner
API	Application Programming Interface
ATN	Amyloid-Tau-Neurodegeneration
Aβ	Amyloid beta
BDNF	Brain Derived Neurotrophic Factor
BOD	Burden of Disease
CBN	Capability Building Network
CDC	Centers for Disease Control and Prevention
CEA	Cost-effectiveness analysis
CEN	European Committee for Standardization - French: Comité Européen de Normalisation
CPDL	Clinical Practice Data Linkage
CPE	Carbapenemase Oroducing Enterobacteriaceae
CPRD	Clinical Practice Data Linkage
CRE	Cerbapenem Resistant Enerobacteraceae
CRO	Contract Research Organisation
CSF	Cerebro-spinal fluid
CTR	Clinical Trial Regulation
DALYs	disability-adjusted life years
DMP	Data Management Plan
DNA	Deoxyribonucleic acid
DPA	Data Protection Authority
DS	Drug-sensitive
E2E	Client- and Server-side Encryption
ECs	Ethics Committee
EC	European Commission
ECDC	European Center for Disease Control and Prevention
EDPB	European Data Protection Board
EEHRxF	European Electronic Health Record Exchange Format
EFPIA	European Federation of Pharmaceutical Industries and Associations
EHR	Electronic Health Record

Acronym	Meaning
EJP RD	European Joint Programme on Rare Diseases
EMA	European Medicines Agency
EU	European Union
EUCROF	European Contract Research Organisation Federation
EUPID	European Patient Identifiers
FAIR	Findable, Accessible, Interoperable, Useable
FHIR	Fast Healthcare Interoperability Resources
FTEs	Full-time equivalent
GCP	Good Clinical Practice
GDF-15	Growth Differentiation Factor-15
GDPR	General Data Protection Regulation
GFAP	Glial Fibrillary Acidic Protein
GLP	Global laboratory practice
GMP	Global manufacturing practice
GP	General Practitioner
HCP	Healthcare Professional
HIV	Human immunodeficiency viruses
HL7	Health Level 7
HTA	Health & Technology Assessment
IARC	International Agency for Research on Cancer
ICF	Informed Consent Form
ICH	International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use
ICH-GCP	International Council for Harmonisation – Good Clinical Practice
IGFBP7	Insulin like Growth Factor Binding Protein 7
IL-6	Interleukin-6
IMI JU	Innovative Medicines Initiative Joint Undertaking
IMI2 JU	Innovative Medicines Initiative 2 Joint Undertaking
IP	Intellectual Property
IRB	International Review Board
IRP	Integrated Research Platform
IT	Information Technology
LIMS	Laboratory Information Management System
mAbs	Monocolonal Antibodies
MDR	Multi-drug Resistant

Acronym	Meaning
ML	Machine Learning
MRI	Magnetic resonance imaging
MRSA	Methicillin Resistant Staphylococcus aureus
NBS	New-born Screening
NCE's	New Chemical Entities
ND4BB	New Drugs for Bad Bugs
NFL	Neurofilaments
NSE	Neuron-Specific Enolase
NTM	Non-tubercular mycobacteria
PACS	Picture Archiving and Communications System
PBNs	Company-specific Portfolio Building Networks
PD	Parkinson's disease
PDAI	Patient Data Return Initiative
PET	Positron emission tomography
PHE	Public Health England
PI	Principal Investigator
PROs	Patient Reported Outcomes
pTau	Phosphorylated Tau
QA/QC	Quality Assurance/Quality Control
QALYs	Quality-adjusted life year
QoL	Quality of life
R&D	Research & Development
RD[s]	Rare Disease[s]
RI	Research Infrastructure
RIA	Research and Innovation Action
RoI	Return on Investment
SEHM	Subjective Experienced Health Methodology
SME	Small and Medium-sized Enterprises
SOPs	Standard Operating Procedures
STREM2	Soluble Triggering Receptor Expressed on Myeloid cells 2
TB	Tuberculosis
TBDA	TB Drug Accelerator
TBDDN	Tuberculosis Drug Development Network
tTau	Total Tau
US	United States

Acronym	Meaning
USD	US dollars
WES	Whole Exome Sequencing
WGS	Whole Genome Sequencing
WHO	World Health Organization
WMA	World Medical Association
WP	Work Package
XDR-TB	Extensively Drug-Resistant Tuberculosis
YLK40	Tyrosine (Y), lysine (K) and leucine (L)-40 glycoprotein