Amended Annual Work Plan and Budget for 2019

In accordance with Article 16 of the Statutes of the IMI2 JU annexed to Council Regulation (EU) No 557/2014 of 6 May 2014 and with Article 31 of the Financial Rules of the IMI2 JU.
The amended Annual Work Plan will be made publicly available after its adoption by the Governing Board.

Sole annex to the Decision of the Governing Board of the Innovative Medicines Initiative 2 Joint Undertaking no. IMI2 GB-DEC-2019-12 adopted on 21.06.2019

IMI reference: IMI2/INT/2019-00638

NOTICE

Please note that until the UK leaves the EU, EU law continues to apply to and within the UK, when it comes to rights and obligations; this includes the eligibility of UK legal entities to fully participate and receive funding in Horizon 2020 actions such as those called for in this work plan. Please be aware however that the eligibility criteria must be complied with for the entire duration of the grant. If the UK withdraws from the EU during the grant period without concluding an agreement with the EU ensuring in particular that British applicants continue to be eligible, they will no longer be eligible to receive EU/JU funding and their participation may be terminated on the basis of Article 50 of the grant agreement.

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Chronology and list of reviews

Version	Date of the adoption by the Governing Board	Items
Version 1.0	12.12.2018	Annual Work Plan and Budget for 2019
Version 1.1	18.01.2019	Corrigendum of Annex I – page 64 4th bullet point under Scope of topic 1 has been updated to clarify the objective
Version 2.0	21.06.2019	Update of the following sections: ▪ 2.2.2 Scientific priorities for 2019 ▪ 2.2.4 Activities to support and monitor ongoing projects ▪ 2.2.6 Stakeholders' engagement and external collaborations ▪ 2.3 Call management rules ▪ 2.4.1 Communication and events ▪ 2.4.2 Procurement and contracts ▪ 4. Budget ▪ List of acronyms Insertion of Annex II - IMI2 Call 18 topics text Insertion of Annex III - IMI2 Call 19 topics text

1 Introduction

In 2019, IMI2 JU will continue to focus on its core activity of launching Calls for proposals for projects that address key challenges highlighted in the IMI Strategic Research Agenda in areas such as diabetes/metabolic disorders, neurodegeneration, immunology, infection control (including vaccines), translational safety, digital health, and oncology.

In addition, the IMI2 JU Programme Office will continue implementing the recommendations of the experts' panel on the interim evaluation of IMI2 JU. This will include continuing with the strategy to attract more small and medium-sized enterprises (SMEs) to IMI2 JU, as well as putting greater efforts into identifying our projects' most important outputs and communicating on them to a wider audience.

To ensure that IMI2 JU projects include a broad range of stakeholders, IMI2 JU will continue to reach out to priority groups like SMEs, patients, and regulators. IMI2 JU will also engage proactively with potential Associated Partners from the philanthropic and public sectors, as well as companies from other industry sectors (e.g. ICT, imaging, medical technology, animal health, nutrition, etc.).

Throughout the year, the IMI2 JU Programme Office will strive to deliver work of the highest quality, following strict ethical standards, adhering to the principle of sound financial management and within the context of a robust internal control framework.

In the long term, these activities will help IMI2 JU to achieve its goals of accelerating and improving medicines development and ensuring that new discoveries are rapidly transformed into benefits for both the wider medical research community, and healthcare systems and patients.

Pierre Meulien

Executive Director

2 Annual Work Plan Year 2019

2.1 Executive Summary

The main goals of IMI2 JU in 2019 are set out as follows.

- Launch three new Calls for proposals based on scientific priorities set out in section 2.2.2. Additional call topics might be considered according to very urgent public-health needs.
- Successfully manage and connect a growing portfolio of projects.
- Expand the basis of external collaborations and partnerships to best meet the challenges of speeding up the development of, and patient access to, innovative medicines and optimise the innovation framework.
- Implement an ambitious communication strategy to demonstrate, in a spirit of openness and transparency, the added value of the partnership to EU citizens. Our focus on the impacts of our projects and the results of the socio-economic impact study on completed IMI1 projects will contribute to meeting this objective.
- Improve and upgrade various aspects of our operating systems, including efficient management of IMI2 project cycle using common Horizon 2020 IT tools.
- Carry out and implement audits and controls over beneficiaries that receive IMI2 JU funding and companies' in-kind contributions.

2.2 Operations

2.2.1 Objectives & indicators - risks & mitigations

The key objectives for IMI2 JU operations in 2019 are identified by the Governing Board in the Annual Work Plan and by the Management at operational level.

Key operational objectives for 2019 are as follows:

1.	**execute Strategic Research Agenda priorities by initiating competitive Calls for proposals bringing together the different stakeholders involved in health research (including SMEs, regulators and patient organisations) and by fostering cross-project collaboration;**
2.	**ensure sound budget implementation through the effective and efficient management of Calls for proposals, grant award process, close monitoring of projects and error rate;**
3.	**demonstrate the EU added value of IMI2 JU through assertive communication to target audiences with emphasis on the openness, transparency, relevance, and coherence of IMI2 JU activities;**
4.	**involve industry from related sectors other than the pharmaceutical industry (diagnostics, medical technologies industry, imaging, digital industry, food and nutrition, etc.) in IMI2 JU projects through proactive outreach strategies;**
5.	**ensure IMI2 JU internationalisation and build productive linkages to major international efforts to address Global Challenges (AMR, Alzheimer and other dementias, autism, cancer, diabetes, emerging infectious diseases, etc.);**
6.	**improve and broaden access to IMI project outcomes in collaboration with IMI2 projects by embedding dissemination in all stages of the project lifecycle.**

IMI2 KPIs

Reporting on measuring and outcomes on the following ten Key Performance Indicators will be provided yearly as part of the IMI2 JU Annual Activity Reports for year 2019 and beyond.

KPI	Definition	Comment	Relates to	Baseline	Target
1	Number of relevant priority areas in the WHO 'Priority Medicines for Europe and the World 2013 Update' reflected in the IMI2 Strategic Research Agenda (SRA) and addressed by IMI2 projects.	Based on the SRA and including the WHO priority medicines therapeutic areas: - expressed as a number of areas reflected in the IMI2 portfolio; - complemented by the number and budget of grant agreements that delivered them.	IMI2 Regulation objective b1: b1: 'increase the success rate in clinical trials of priority medicines identified by the WHO'	0	12
2	The number of project-developed assets which complete a significant milestone during the course of an IMI2 project.	Assets are defined as new drug or diagnostic candidates, targets, biomarkers or other tools that can be shown to have reached a significant milestone or pass a significant stage gate.	IMI2 Regulation objective b1, b2, b4, b5 and b6: b1: 'increase the success rate in clinical trials of priority medicines identified by the WHO' b2: 'reduce the time to reach clinical proof of concept in medicine development…' b4: 'develop diagnostic and treatment biomarkers for diseases clearly linked to clinical relevance and approved by regulators' b5: 'reduce the failure rate of vaccine candidates in phase III of clinical trials through new biomarkers for initial efficacy and safety checks' b6: 'improve the current drug development process by providing the support for the development of tools, standards and approaches to assess efficacy, safety and quality of regulated health products'	0	50

KPI	Definition	Comment	Relates to	Baseline	Target
3	New or improved guidelines, methodologies, tools, technologies or solutions accepted by regulatory authorities for use in the context of R&D, specifically for: - new tools for preclinical drug development; - biomarkers and tools developed to predict clinical outcomes; - improved protocols to design and process of clinical trials; - new biomarkers developed for the efficacy and safety of vaccine candidates.	- Measured by the number of the formal qualification procedures completed (letters of support, qualification opinions received). - Complemented by number of qualification procedures launched. - Expressed as net figure. - Complemented by the number and budget of grant agreements that delivered them.	IMI2 Regulation objective b1, b2, b4, b5 and b6: b1: 'increase the success rate in clinical trials of priority medicines identified by the WHO' b2: 'reduce the time to reach clinical proof of concept in medicine development…' b4: 'develop diagnostic and treatment biomarkers for diseases clearly linked to clinical relevance and approved by regulators' b5: 'reduce the failure rate of vaccine candidates in phase III of clinical trials through new biomarkers for initial efficacy and safety checks' b6: 'improve the current drug development process by providing the support for the development of tools, standards and approaches to assess efficacy, safety and quality of regulated health products'	0	10 (for completed procedures)

KPI	Definition	Comment	Relates to	Baseline	Target
4	New taxonomies of diseases and new stratifications (such as the definition of patient subpopulations, development, validation and use of new diagnostics) developed.	- Expressed as net figure. - As published and/or implemented by industrial partners and evidenced in annual reporting. - Complemented by the number and budget of grant agreements that delivered them.	IMI2 Regulation objective b3 and b4: b3: 'develop new therapies for diseases for which there is a high unmet need…' b4: 'develop diagnostic and treatment biomarkers for diseases clearly linked to clinical relevance and approved by regulators'	0	30
5	Contribution (in-kind or in-cash) from non-pharma actors (e.g. non-pharma industries, foundations, charities, professional organisations).	Expressed as total amount in EUR.	IMI2 Regulation objective a: a: 'to support… the development and implementation of pre-competitive research and of innovation activities of strategic importance to the Union's competitiveness and industrial leadership…'; and IMI2 Regulation recital 8: 'The initiative should consequently seek to involve a broader range of partners, including mid-caps, from different sectors, such as biomedical imaging, medical information technology, diagnostic and animal health industries.'	0	EUR 300 Million

KPI	Definition	Comment	Relates to	Baseline	Target
6	Share of IMI projects whose resources/outputs are made accessible beyond the consortia partners (with or without fee), such as major databases, bio-banks, *in silico* tools, training materials, clinical trial networks, guidance etc.	- Complemented by the number and budget of grant agreements that delivered them. - Accessibility to be evidenced by online availability (with or without fee), and documented by project reports.	IMI2 Regulation objective a, b2 and b6: a: 'to support… the development and implementation of pre-competitive research and of innovation activities of strategic importance to the Union's competitiveness and industrial leadership…' b2: 'reduce the time to reach clinical proof of concept in medicine development' b6: 'improve the current drug development process by providing the support for the development of tools, standards and approaches to assess efficacy, safety and quality of regulated health products'	0	50%
7	Co-authorships and cross-sector publications between European researchers on IMI2 projects (sectors include academia, small and mid-sized companies, pharma, regulators, patient organisations, etc.).	- Expressed as net figure - Complemented by the number and budget of grant agreements that delivered them.	IMI2 Regulation objective a: a: 'to support… the development and implementation of pre-competitive research and of innovation activities of strategic importance to the Union's competitiveness and industrial leadership…'	0	1500

KPI	Definition	Comment	Relates to	Baseline	Target
8	New tools and processes generated by IMI2 projects that have been implemented by the industry participants of IMI projects.	- New tools and processes: e.g. animal models, standards, biomarkers, SOPs, use of screening platforms and clinical trial networks. - Expressed as net figure. - Complemented by the number and budget of grant agreements that delivered them. - Assessment based on yearly reporting by industrial partners until the project close-out meetings.	IMI2 Regulation objective a, b2 and b6: a: 'to support… the development and implementation of pre-competitive research and of innovation activities of strategic importance to the Union's competitiveness and industrial leadership…' b2: 'reduce the time to reach clinical proof of concept in medicine development' b6: 'improve the current drug development process by providing the support for the development of tools, standards and approaches to assess efficacy, safety and quality of regulated health products'	0	50
9	Share of projects involving patient organisations and healthcare professionals' associations (as consortium partners, members of advisory boards, members of stakeholder groups etc.).	- Complemented by the number and budget of grant agreements that delivered them.	IMI2 Regulation objective a, and b1: a: 'to support… the development and implementation of pre-competitive research and of innovation activities of strategic importance to the Union's competitiveness and industrial leadership…' b1: 'increase the success rate in clinical trials of priority medicines identified by the WHO'	Share of IMI1 projects involving patient organisations: (participants /advisory boards etc. 40%)	80%

10	Support to SMEs: share of SMEs participating as formal IMI project beneficiaries.	- To be complemented by the number of SMEs benefitting from IMI project support in other ways.	H2020 priority; IMI2 Regulation recital 9 '(…) should seek to foster the capacity of smaller actors such as research organisations, universities and SMEs for participating in open innovation models and to promote the involvement of SMEs in its activities, in line with its objectives'	Share of SMEs participating as formal IMI1 project beneficiaries: 15.96%	20%

To ensure the monitoring of the above-mentioned 10 Key Performance Indicators, IMI2 JU has established a performance evaluation plan which aims at identifying appropriate sources of information, a suitable framework as well as consistent processes and tools.

Risks & mitigations

Risks are a strategic element of planning activities as their identification enables management to customise the objectives and prioritise actions.

The annual risk assessment exercise towards the Annual Work Plan (AWP) 2019 objectives has identified 8 corporate risks that might potentially challenge their achievement. These risks are documented in the internal Risk Register of the IMI2 JU, which incorporates a description of the respective action plans, detailing the action owners and individual deadlines. In practice, the outcome of the risks assessment indicates that:

1. Some risk factors persist, as they are typically associated with IMI2 JU nature of public-private partnership and its mission – which aim at supporting volatile activities such as the development and implementation of pre-competitive research and innovation in the pharmaceutical sector. For these risks, the mitigating actions envisaged in the past will continue to be applied in 2019.

2. On the other hand, the 2019 annual objectives could be challenged by some specific risks, whose factors will be continuously monitored and mitigated by the Programme Office where needed. These relate to:

   - the impact of the external environment (e.g. Brexit) on programme implementation and operational activities[1];
   - the implementation of IMI2 JU communications strategy to demonstrate, in a spirit of openness and transparency, the benefit of the partnership to EU citizens; this should contribute to mitigating possible negative perception or misconceptions about IMI2 JU objectives;
   - avoiding delays in defining annual scientific priorities and call topics through a fixed plan of call development stages, as well as the enhancement of the quality of key operations (i.e. Horizon 2020 implementation, project extension, etc.), financial management and staff allocation; this should avoid any mismatch between the ambition of the programme and limited resources available affecting the implementation of the programme;
   - ensuring proactive outreach strategies and exploring alternative approaches to ensure and boost industry participation and contribution;
   - carrying on with the new SME strategy, and exploring and drafting potential call topics adapted to SME needs and activities to address the low rate of SME participation.

[1] The plans/activities of the year will take into account and reflect the needs which are related to Brexit. Notwithstanding the need to cater for individual specificities to the Joint Undertaking, these actions are being coordinated by the Secretariat-General of the European Commission with a view to ensuring coherence in the design and timing of these measures.

2.2.2 Scientific priorities for 2019

The IMI2 JU activities for 2019 are fully in line with the objectives as set out in Article 2 of the IMI2 JU Regulation. In particular, they aim at the development and implementation of pre-competitive research and innovation activities of strategic importance to the EU's competitiveness and industrial leadership, and address specific Horizon 2020 societal challenges, in particular improving European citizens' health and well-being.

These activities will be developed within the general framework of the Scientific Research Agenda (SRA) for IMI2 JU (see http://www.imi.europa.eu/about-imi/strategic-research-agenda). The SRA identifies a set of scientific priorities, where IMI2 JU attempts to pilot new ideas in a real life, safe harbour environment. The IMI2 JU model maximises collaboration and synergies among all stakeholders; drives innovation in business models to support the transition from blockbusters to personalised medicines by testing new approaches across multiple companies and projects simultaneously; and it pilots new types of collaboration between companies with different innovation cycles to optimise the success in delivering IMI2 JU objectives. The SRA furthermore identifies data and knowledge management as key enabling technologies, as well as education and training, and excellence in clinical trial implementation as key implementation strategies.

In order to achieve its objectives, IMI2 JU continues to seek the involvement of a broader range of partners from different sectors (e.g. biomedical imaging, medical information technology, diagnostics and/or animal health industries among others). The actions resulting from the 2019 priorities will generate results that will have a high impact and facilitate the maximum number of stakeholders to join forces. The outcome and impact of these actions should bring great benefits to patients and society-at-large. There will also be engagement with regulatory agencies and other health bodies fostering the approval of research outcomes. 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 an expected high impact on public health.

SMEs have an important role in strengthening the competitiveness and industrial leadership in the EU. In addition, SME involvement might offer a complementary perspective to industry and the academia, and help deliver the long-term impact of IMI2 JU. Thus, in 2019, IMI2 JU will continue its efforts to increase the engagement of SMEs in all its activities and to encourage their involvement in applicant consortia.

For 2019, IMI2 JU has identified seven scientific priorities, broken down into several topics, taking into account the advice that the Strategic Governing Groups (SGGs) provided to the IMI2 JU Governing Board. As described in the following pages, each priority area will be implemented via the launch of one or more topics, which will generate multi-stakeholder actions, potentially including (or even driven by) Associated Partners. Further details regarding the expected multi-stakeholder actions are elaborated under the individual topics. Topics for 2019 have been prioritised based on criteria that include the highest impact on reducing attrition in drug development, speeding up patient access, improving health outcomes and enhancing the biomedical research ecosystem.

Additional topics for 2019 might also be considered at a later stage in the case of very urgent public health needs, such as rapid response to emerging diseases. The Annual Work Plan 2019 would then be updated accordingly.

To implement the 2019 priorities, IMI2 JU will initiate three competitive Calls for proposals, each covering several topics (see table at the end of this section), with predefined launch dates foreseen for Q1 and Q2 in 2019.[2]

Topics launched based on this Annual Work Plan 2019 will seek synergies with other ongoing initiatives especially those funded under Horizon 2020 and at the national level, and those identified by the European Strategy Forum on Research Infrastructures (ESFRI), to ensure the consistency of approaches, to leverage other funding initiatives and to avoid duplication of effort and funding.

[2] Please see Article 1 (f) and (g) of the Statutes, annexed to the IMI2 JU Council Regulation

A. Diabetes/Metabolic disorders

Activities in 2019 will address the following topic.

1. **Optimising future obesity treatment.** This topic focuses on multifaceted profiling of patients with obesity in order to define clinically meaningful and relevant subgroups as a premise for optimising future prevention and treatment of obesity and its complications. The aim is to pool pre-existing observational and/or clinical data to establish a federated database with enough phenotypic granularity for a data-driven stratification of obesity into subgroups based on a set of operational parameters including subject characteristics, biomarkers and questionnaires. In addition, activities will address specifically type 1 and type 2 diabetes (T1D and T2D) as examples of co-morbid conditions in which obesity influences both clinical phenotype and treatment.

Expected impact:

- a common understanding and vocabulary among stakeholders to facilitate scientific, medical and political acknowledgement of obesity as a disease and the importance of prevention, personalising health and lifestyle interventions and weight management;
- potential high impact on future guidelines to treat diabetic and obese individuals;
- potential high impact on public health regarding population morbidity, co-morbidity and mortality, and public healthcare costs.

Type of actions:

Research and innovation actions

B. Translational safety

Activities in 2019 will address the following topics.

2. **Central repository of digital pathology slides to support the development of artificial intelligence tools.** Pathology is the cornerstone of the workup of many diseases such as cancer, autoimmune diseases, transplant rejection, but still relies on the interpretation of a tissue section by a qualified pathologist. Although the pathologist's report is currently the only accessible pathology data, slide scanners can capture the data of the entire tissue sections digitally. The systematic digitization of slides opens the field of digital pathology. It facilitates the consultations with expert pathologists and the search or review of large collections of slides. As digital modality, it allows to quantify features from tissues. The recent development of deep learning has propelled the field of digital pathology even further, opening the way to computer-assisted diagnosis. This has the potential to revolutionize medicine by allowing to discover new clinic-pathological entities and better identify treatments for specific groups of patients.
   In drug development, digital pathology would apply to unbiased evaluation of preclinical safety or clinical efficacy. Regulators could conduct faster review of pathology data and could have a transversal view across projects/sponsors.
   The scope would comprise: (1) centralised repository for digitalized slides, including secured archival of pathology data (2) the initial population of such a repository with preclinical safety studies, clinical trials, and clinical collections, (3) a legal and regulatory framework to enable exchange of studies and cases series while preserving patient's privacy, and (4) tools for access, visualisation, quality control (QC) and data mining (open source).

The slides would be collected from preclinical safety studies and clinical trials (source: industrial and academic partners) and could be associated with clinical findings and biomarkers. The partners would provide electronic versions (scans) of pathology slides used in upcoming preclinical safety studies, and clinical trials.

Expected impact:

- catalyse research in digital pathology and support the collaborative development of artificial intelligence in pathology;
- help identify sub-types in common diseases, possibly unveiling new clinico-pathological entities amenable to specific therapeutic interventions;
- better prediction and understanding of toxicities of drugs;
- reduce use of animals in toxicology studies;
- reduced costs and enhanced commercial viability of drug development.

Types of action:

Research and innovation actions

C. Big data, digital health, clinical trials and regulatory research

Activities in 2019 will address the following topics:

3. **Health Outcomes Observatories – empower patients with tools to measure their outcomes in a standardised manner creating transparency of health outcomes.** This topic will support activities to provide a legal and ethical framework for the management of patient reported outcomes (PROs), collect process, integrate and make health data available in an ethical manner, and contribute to standardising and integrating health data. The objective of this project is to work collaboratively with patient associations and empower individual patients to monitor their outcomes in a standardised manner. The data, when collected, will provide transparency of patient outcomes on specific diseases on a per country or regional basis. This will provide the evidence required for making informed decisions on resource allocation. At the same time, it will also create a unique value proposition for patients to collect their health data.

4. **Improving patient access, understanding and adherence to healthcare information: an integrated digital health information project.** This topic addresses two critical challenges associated with the use of medicinal products in Europe: lack of adherence to the health-authority-approved product information, and poor understanding of this information in relation to treatment. Such challenges affect multiple stakeholders across Europe, and it is of utmost importance that these diverse perspectives are captured to ensure that any future solution is fit-for-purpose for citizens, healthcare providers, health authorities and industry alike. It embraces all medicinal products registered in European Member States. It is assumed that the paper version of the package leaflet (PL) will continue to exist according to current legislation. However, the delivery method for the product information will be examined (e.g. printing the PL at the pharmacy instead of always in the pack) as well as options for reconstruction of the health-authority-approved text in ways which are more personalised to an individual's needs. The overall objective is to optimise provision of information on medicines to users across the EU so that adherence to the product information is improved, and users' understanding of their medicine is increased. These two challenges are related and have profound implications for patient safety and well-being, as well as widespread effects within healthcare systems and industry across the EU.

Expected impact:

- improved quality of care through better and more transparent evidence of patient measures and outcomes
- easier access to trusted health information, tailored to be relevant to the specific needs of the patient;
- faster translation of insights from real-world health data to biomedical research and development approaches;
- enhanced drug efficacy and effectiveness via a better understanding and adherence to medicines.

Type of actions:

Research and innovation actions

D. Oncology

Activities in 2019 will address the following topic.

5. **Establishing international standards in the analysis of patient reported outcomes and health-related quality of life data in cancer clinical trials**. There is an increased emphasis on patient-centred care, health-related quality of life (HRQL), and other patient-reported outcomes (PRO), that quantify how a patient feels and/or functions. These parameters may acquire an even more prominent role as important endpoints in cancer clinical trials. However, so far, no standardization in the use and analysis of HRQoL and PRO data in cancer clinical trials is given. Such a lack of standardisation can lead to variations in the analysis of data and could result in two identical trials being analysed in different ways, leading to different conclusions. In particular, in oncology such a lack of standardization can undermine the credibility of the HRQoL and PROs since this can lead to differences in interpretation of the findings depending on how the data were analysed. Thus, this topic aims to develop and recommend international standards for the analysis of HRQOL data from cancer clinical trials.

Expected impact:

- better assessment of the risks and benefits of cancer therapies and fostering of patient-centred cancer care.
- a large positive impact on treatment outcomes, to support the adequate reimbursement of innovations in this field.

The Oncology area is also addressed in the “Supporting the development of chimeric antigen receptor T cells” topic in the “E. Facilitating the translation of advanced therapies to patients in Europe” section below.

Type of actions:

Research and Innovation Actions

E. Facilitating the translation of advanced therapies to patients in Europe

Activities in 2019 will address the following topics.

6. **Accelerating research & innovation for advanced therapy medicinal products.** This topic aims to accelerate the research and innovation of Advanced Therapy Medicinal Products (ATMPs) by filling gaps in our knowledge-base in, and tools for, gene and cell therapy. This will provide medicines developers and regulators with the information they need to more swiftly move these potentially transformative medicines forward so that they can benefit patients in need. The main focus of this topic is to develop a product characterisation framework (rather than delineating the methodologies for achieving such a framework) thus limiting the scope to the pre-competitive space. This topic intends to utilise both therapeutically relevant systems, as well as model systems that rely on the use of marker transgenes. In order to develop such a framework, there is a need for a coordinated and substantive effort to acquire and analyse the currently available data and then design preclinical and clinical studies to fill the knowledge gaps. This information will help to address gene/cell therapy risks and also guide product developers and regulators to determine and implement an appropriate and effective characterisation framework to enable efficient and safe development of gene/cell therapies.

7. **Supporting the development of engineered T cells**. CAR-T cell therapies (chimeric antigen receptor T-cell therapy) are complex medicinal products. Their translation from basic and pre-clinical research to clinical trials therefore poses many challenges that slow down clinical development. The objective of the topic is to develop pre-clinical models to better predict safety and efficacy. Definition of a regulatory frame for the translation of pre-clinical findings into the clinic and standardisation of monitoring methods will be also addressed.

Expected impact:

- to enhance research and development of advanced therapies in the EU and the Horizon 2020 Associated Countries as a fully-fledged industrial activity to make the EU more competitive and make advanced therapy products available to all patients in need;
- the development of safer and more effective engineered T-cell therapies;

Type of action:

Research and innovation actions

F. Other enablers of research topics

Activities in 2019 will address the following topics.

8. **Open access chemogenomics library and chemical probes for the druggable genome.** The objective is to generate potent, well-characterised functional modulators for a significant number of targets from the human druggable genome and, at the same time, lay the foundation for identifying an entire set of open-access tool compounds for the entire druggable human genome, which is currently estimated to consist of at least 3000 genes.

9. **Intelligent prediction and identification of environmental risks posed by human medicinal products.** Building on *in silico*, *in vitro* and *in vivo* tools and models developed in the project 'Intelligent assessment of pharmaceuticals in the environment', this topic aims to upgrade them to include other targets and endpoints. The aim is to maximise their predictive capability through machine learning and artificial intelligence approaches, including validation of their capacity to identify environmental concerns much earlier than within the current models in order to inform greener medicines development.

Expected impact:

- a resource for the entire chemical biology community;
- access to the highest quality tool compounds as starting points for probe development or drug discovery.
- seeding a massive community target prioritisation and target deconvolution effort via the availability of an unprecedented high-quality broader compound library;
- innovative approaches to ensure the environmental safety of human medicinal products;
- reduction of costs via increased efficiency of drug discovery.

Type of action:

Research and innovation actions

G. Restricted Call to maximise the impact of IMI2 JU objectives and scientific priorities

The drug development process is a highly challenging field of research, which can only be tackled using a sequential approach where the next step can only be decided based on the results of the previous one.

In such context, the Innovative Medicines Initiative 2 Joint Undertaking (IMI2 JU) provides the unique framework required to drive major and fundamental innovations by enabling unique collaborative partnerships among public and private stakeholders. Such partnerships have the potential to deliver well beyond the initially expected outputs. The efficient harnessing of such unique outcomes would be extremely valuable for the achievement of the IMI2 JU objectives, as well for the benefits of the citizens and the public health.

Certain IMI2 JU topics, launched under IMI2 JU Calls for proposals that are now closed, anticipated in their corresponding Work Plans the need for a stepwise approach. Thus, these Work Plans informed potential applicants that IMI2 JU at a later stage could publish a subsequent, restricted Call for proposals, addressing the consortia selected under initial topics.

The scope of the restricted Call will be to support follow-upresearch activities in those exceptional cases where it is necessary to enable successful consortia to build upon the remarkable achievements of their initial action, move onto the next scientific step of the challenge, and maximise the impacts of the initial action results.

Applicants will have to demonstrate how the proposed follow-up research activities relate to an area with a high un-met need in the context of public health and industrial challenges, as relevant, and the very high relevance for addressing successfully the IMI2 JU objectives and scientific priorities.
Activities supported by this Call will fall beyond the scope of the initial actions and could not be implemented within their financial and temporal framework.
The applicants will need to demonstrate the specific circumstances justifying that only the initial consortium (with some justified modifications of the partners list, if any, to cover the expertise needed for the newly proposed activities) can carry out activities successfully. For instance, that the initial consortium represents a unique and effective partnership with the expertise, equipment, methodologies, or access to unique resources and IP rights, that are not available from another consortium. The applicants will also need to justify that proposed follow-up activities are needed to further maximise the public-private partnership value of IMI2 JU. as demonstrated both: 1) by the success of the initial public private partnership and 2) by a substantial amount of in-kind and financial contributions brought to the action by EFPIA constituent and affiliated entities and when relevant by IMI2 JU Associated Partners.

The restricted Call will be published as a single-stage Call in the second quarter of 2019.
This Call will be:

- restricted to the original consortia of actions funded under topics published in the IMI2 JU Annual Work Plan of 2014 and of 2015, since only these actions are sufficiently advanced in their implementation to be considered for follow-up research activities, and;
- limited to those actions derived from topics where the corresponding Work Plan already pre-informed potential applicants about the possibility of a later restricted Call.

Applicant consortia will be competing for a maximum total EU contribution as indicated in the Calls for proposal table at the end of this section.

Expected impact:

- accelerate the impact of action breakthroughs to the next stage of drug development;
- significant impact on patients as novel treatments and patient pathways emerge;
- significant impact on EU industrial leadership;
- significant benefit for society and EU added value;
- further maximisation of the IMI2 JU public-private partnership value proposition.

Type of action:

Research and innovation actions

Calls for Proposals

Call number and topics	Call launch timing	IMI2 JU funding (in EUR)[3]	In-kind contribution from EFPIA entities and Associated Partners (in EUR)
IMI2 Call 17 *Diabetes/Metabolic disorders* ▪ Optimising future obesity treatment *Other enablers of research topics* ▪ Open access chemogenomics library and chemical probes for the druggable genome ▪ Intelligent prediction and identification of environmental risks posed by human medicinal products	22 January 2019	40,786,000	43,108,139
IMI2 Call 17 process			
Two-stage call with predefined submission deadline. Indicative Call deadline for **short proposals**: **25 April 2019** Indicative Call deadline for **full proposals: 7 November 2019** Research and innovation actions (RIA)			

Call number and topics	Call launch timing	Indicative IMI2 JU funding (in EUR),[4]	Indicative in-kind contribution from EFPIA entities and Associated Partners (in EUR)
IMI2 Call 18 *Translational safety* ▪ Central repository of digital pathology slides to support the development of artificial intelligence tools *Big data, digital health, clinical trials and regulatory research* ▪ Health Outcomes Observatories – empower patients with tools to measure their outcomes in a standardised manner creating transparency of health outcomes[5] ▪ Improving patient access, understanding and adherence to healthcare information: an integrated digital health information project	26 June 2019	74,866,000[6]	85,871,760

[3] The maximum possible rate of co-financing is 100 %.

[4] The maximum possible rate of co-financing is 100 %.

[5] Potential applicants must be aware that this topic, if exceptionally needed, may be subject to a restricted follow-up Call for proposals to be launched by IMI 2 JU at a later stage. This follow-up Call for proposals may be restricted to the consortium already selected under such topic, in order to enhance its results and achievements. The consortium will be entitled to open to other beneficiaries as appropriate. The detailed scope of the restricted Call shall be described in the relevant Annual Work Plan.

[6] It includes the carry-overs from 2018 for IMI2 JU, which correspond to 12,540,306 EUR. For further information, see the breakdown under Chapter 3 Budget 2019.

Call number and topics	Call launch timing	Indicative IMI2 JU funding (in EUR),[4]	Indicative in-kind contribution from EFPIA entities and Associated Partners (in EUR)
Oncology ▪ Establishing international standards in the analysis of patient reported outcomes and health-related quality of life data in cancer clinical trials *Facilitating the translation of advanced therapies to patients in Europe* ▪ Accelerating research & innovation for advanced therapy medicinal products ▪ Supporting the development of engineered T cells			
IMI2 Call 18 process			
Two-stage call with predefined submission deadline. Indicative Call deadline for **short proposals**: **26 September 2019** Indicative Call deadline for **full proposals**: **26 March 2020** Research and innovation actions (RIA)			

Call number and indicative topics	Call launch timing	Indicative IMI2 JU funding (in EUR)[7],[8]	Indicative in-kind contribution from EFPIA entities and Associated Partners (in EUR)
IMI2 Call 19 *Restricted Call* Restricted Call to maximise impact of IMI2 JU objectives and scientific priorities	26 June 2019	20,000,000	0
IMI2 Call 19 process			
One-stage call with predefined submission deadline. Indicative Call deadline for **full proposals: 26 September 2019** Research and innovation actions (RIA) Restricted Call			
Overall total IMI2 Calls		**135,652,000**	**128,979,899**

[8] The maximum possible rate of co-financing is 100 %.

Budget

The budget for the financial year 2019 is based on the currently available information.

A table overview of the operational budget for 2019 is set out below.

Heading Title 3	Budget 2019.0		Budget 2019 Amendment 1		Amended Budget 2019.1	
	Commitment Appropriation (CA)	Payment Appropriation (PA)	Commitment Appropriation (CA)	Payment Appropriation (PA)	Commitment Appropriation (CA)	Payment Appropriation (PA)
EU contribution to operational costs (fresh credits)	262,212,585	185,065,765	-139,100,891		123,111,694	185,065,765
Appropriations carried over from 2018	114,341,000		12,599,206[9]	29,829,799	126,940,206	29,829,799
EFPIA and Associated Partners contribution to operational costs		1,845,000				1,845,000
Total operational costs Title 3	**376,553,585**	**186,910,765**	**-126,501,685**	**29,829,799**	**250,051,900**	**216,740,564**

The difference between the total budget available for Title 3 (EUR 250,051,900) and the initial budget available for the IMI2 JU Calls for proposals in 2019 (EUR 376,612,485) is EUR 126,501,685. This amount is the result of the unused commitment appropriations from 2018 carried over to the 2019 budget (EUR 12,599,206) and the reduction of EU financial contribution (-EUR 139,100,891).

The decrease of the European Union's financial contribution to operational costs is due to the fact that the topics originally foreseen by EFPIA to be launched in 2019 have significantly reduced budgets than expected initially and some other topics do not have the maturity to move forward for IMI2 Call 18.

In the interest of ensuring sound financial management of public funds and efficient operational planning of the IMI2 JU, EUR 139,100,891 of 2019 commitment appropriations are returned to the EC.

[9] This amount corresponds to carry-overs form 2018 to 2019 and includes 55,838 EUR for IMI1 and 12,543,368 EUR for IMI2. For further information, see the breakdown under Chapter 3 Budget 2019.

A breakdown of the appropriations carried over is set out below.

Description	Commitment Appropriation (CA)	Payment Appropriation (PA)
unused operational appropriations IMI2 (H2020) carried over to operational budget 2019	**12,543,368**	**29,773,961**
IMI2 (H2020) Call 16 (2018)	*11,716,429*	
unused operational appropriations (2018) carried over for new Calls to be launched in 2019 (C1)	*12,176*	
unused operational appropriations IMI2 (H2020) from previous years (2017,2018) (C2)	*32,669*	
*unused operational appropriations carried over to 2019 (C8)**	*31,615*	
50% unused running costs (2018) carried over to operational budget 2019	*750,479*	
IMI1 (FP7) amounts recovered in 2018 from beneficiaries (C4) to be used only with respect to IMI1 related appropriations	**55,838**	**55,838**
IMI2 (H2020) Call 13 (2018) – already re-activated in AWP 2019	**114,341,000**	
TOTAL	**126,940,206**	**29,829,799**

* Unused operational appropriations following de-commitments of IMI2 (H2020) projects that are carried over to 2019. From that amount, EUR 3,062 is reserved in case we need to make an additional commitment to cover a late interest payment. As a result, EUR 12,540,306 is the carry-over amount dedicated to 2019 calls.

A table overview of the 2019 Budget is set out in Chapter 3 to this Annual Work Plan.

2.2.3 Call management (planning, evaluation, selection…)

Key activities in 2019 will comprise the launch of three competitive Calls for proposals implementing the 2019 scientific priorities with indicative launch dates on 22 January 2019 for the first call of the year and 26 June 2019 for the other two calls.

In the single-stage submission evaluation procedure, the submission deadline will be approximately three months from the publication of the Calls for proposals.

In the two-stage submission evaluation procedure, the submission deadline will be:
- for stage 1: approximately three months from the publication of the Calls for proposals;
- for stage 2: approximately eight months from the publication of the Calls for proposals.

In addition, the evaluation of short proposals and full proposals submitted in response to Calls launched under the AWP 2019 will be held according to the predefined timelines established in the relevant Call for proposals.

Timelines for the completion of the evaluation process and of preparation will be kept as lean as possible with the aim of completing the signature of the Grant Agreements within applicable time to grant (TTG), in compliance with the Horizon 2020 framework, i.e. a maximum of eight months from the final date of submission of the full proposals.[10]

For Call management, IMI2 JU will utilise the Horizon 2020 IT infrastructure available under Funding & tender opportunities - Single Electronic Data Interchange Area (SEDIA).

To maximise the efficiency of the calls management, the IMI2 JU will continuously explore and implement simplification and improved processes while maintaining the highest standards of the evaluation process.

2.2.4 Activities to support and monitor ongoing projects

In 2019, IMI will have 70 ongoing projects at different stages of their life cycle. In addition, 30 new projects that will start during the year when the IMI2 Calls launched in 2017 (IMI2 - Call 13), and 2018 (IMI2 - Calls 14, 15 and 16) complete the evaluation cycle and their Grant Agreements are signed. Most projects will submit to IMI2 JU a periodic report for the previous year summarising their progress and costs incurred. These reports form the basis for the Programme Office's ex-ante controls.

In addition to periodic reporting and associated feedback, IMI2 JU will continue to provide support and advice to the consortia, including on amendments to Grant Agreements.

Given the current planning and project durations, it is expected that IMI2 JU will organise 20 reviews for IMI2 projects.

The following table presents the number of ongoing projects per Call as well as a forecast of the reporting expected for 2019.

[10] Article 20 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'

The following table presents a forecast of the reporting expected for 2019.

		Project periodic report due in 2019						Of which		
IMI Calls	ongoing in 2019	1st RP[11] in 2019	2nd RP in 2019	3rd RP in 2019	4th RP in 2019	5th to 7th RP in 2019	Total reports	Reports due after 31/10/2018	finishing in 2019	Final report due 2019
IMI1 C1	0	0	0	0	0	0	0	0	0	0
IMI1 C2	0	0	0	0	0	0	0	0	0	0
IMI1 C3	0	0	0	0	0	0	0	0	0	0
IMI1 C4	0	0	0	0	0	0	0	0	0	0
IMI1 C5	0	0	0	0	0	0	0	0	0	0
IMI1 C6	0	0	0	0	0	1	1	0	0	0
IMI1 C7	1	0	0	0	0	1	1	0	0	1
IMI1 C8	2	0	0	0	0	3	3	0	0	1
IMI1 C9	2	0	0	0	1	1	2	0	0	1
IMI1 C10	1	0	0	0	1	1	2	0	0	0
IMI1 C11	9	0	0	0	1	7	8	0	0	1
Total IMI1	**15**	**0**	**0**	**0**	**3**	**14**	**17**	**0**	**0**	**4**
IMI2 C1	1	0	0	0	1	0	1	0	0	0
IMI2 C2	4	0	0	0	4	0	4	3	4	1
IMI2 C3	5	0	0	5	0	0	5	1	1	1
IMI2 C4	0	0	0	0	0	0	0	0	0	0
IMI2 C5	6	0	0	6	0	0	6	0	2	2
IMI2 C6	3	0	3	0	0	0	3	3	0	0
IMI2 C7	7	0	7	0	0	0	7	2	1	1
IMI2 C8	4	1	1	0	0	0	2	0	0	0
IMI2 C9	6	1	5	0	0	0	6	1	0	0
IMI2 C10	8	8	0	0	0	0	8	0	0	0
IMI2 C11	3	2	0	0	0	0	2	0	0	0
IMI2 C12	7	0	0	0	0	0	0	0	0	0
IMI2 C13	13	0	0	0	0	0	0	0	0	0
IMI2 C14	4	0	0	0	0	0	0	0	0	0
IMI2 C15*	8	0	0	0	0	0	0	0	0	0
IMI2 C16	5	0	0	0	0	0	0	0	0	0
Total IMI2	**84**	**12**	**16**	**11**	**5**	**0**	**44**	**10**	**8**	**5**
Total IMI	**99**	**12**	**16**	**11**	**8**	**14**	**61**	**10**	**8**	**9**

* For IMI2 Call 15 the number of projects is an estimate based on the number of topics included in the Call.

[11] Reporting Period

A key task will be to continue maximising efficiency, as well as facilitating, optimising, and monitoring the implementation of all these projects and seeking feedback for continuous improvement to IMI2 JU operations. To this end, further workshops to provide guidance on the management of financial and administrative aspects of the projects will be held for IMI2 JU beneficiaries. In addition, the IMI2 JU Programme Office will work with consortia to help them communicate on project progress and disseminate achievements.

2.2.5 Monitoring and analysis of projects' results

67 project periodic reports will be submitted in 2019 (for ongoing projects and those finalised in 2018 see column 8 in the table above – 'Project periodic report due in 2019 – Total reports'). These reports will be used to track progress against their stated objectives and deliverables as laid out in the relevant description of the action.

This reporting will also allow for an assessment of project achievements and the impact of results. In addition to the usual ex-ante controls, a combination of internal management information systems, external databases, independent evaluations and, if necessary, commissioned studies and surveys will be used to measure the progress and identify significant achievements of IMI projects.

In 2019, the analysis of the IMI2 JU project scientific outputs in terms of publications and collaboration among IMI researchers will be continued. Where feasible, monitoring and analysis approaches will be refined in line with observations from the European Court of Auditors (ECA) to ensure the highest possible standards.

2.2.6 Stakeholders' engagement and external collaborations

In 2019, IMI2 JU will continue to develop its relationships and engagement with key stakeholders such as patients, SMEs, regulators, payers and healthcare professions to ensure that its outputs are aligned with and address the needs of the society.

Patient engagement
Building on the experience of patient engagement so far, the IMI2 JU Programme Office will continue to work on developing an open and transparent system of patient engagement at all levels. The need for a consolidated framework for interaction with patients has been highlighted as one of the key elements reflecting IMI2 JU's patient engagement strategy. In this respect, IMI2 JU will create a Patient Expert Pool that will assist the JU to better include patients' perspectives in its activities and become more patient-centric.

Therefore, IMI2 JU foresees the launch of a Call for Expressions of Interest via its website in Q2 2019 aiming to identify patients/ patient informal carers interested in participating in IMI activities both at strategic and operational levels.

Drawing from this Patient Expert Pool, the IMI Programme office will invite expert patients/patient informal carers with the required profile, to perform a variety of roles and tasks depending on the need and topics discussed. Their input will contribute in shaping the IMI portfolio and improve quality of IMI projects through early and meaningful engagement.

Additionally, the Programme Office will continue to enhance, support and facilitate patient involvement in IMI2 JU projects and develop guidance for patients taking part in IMI2 JU activities. The JU will also lead efforts to ensure that patient engagement is embedded in procedures surrounding the preparation of Call topics, proposal evaluation as well as project reviews.

SMEs
Given their importance in driving employment and innovation in the EU and the Horizon 2020 Associated Countries, the IMI2 JU will remain engaged with SMEs and encourage their participation in IMI2 JU projects. In 2019, the IMI2 JU will continue to highlight SME opportunities in all topic texts and also embed SME participation at the earliest stages of topic development, for example through exploring call designs more appealing to SMEs.

The IMI2 JU will also continue to develop and disseminate targeted materials for SMEs and continue the SME outreach programme outlined in the IMI2 JU SME strategy. This includes partnering with other European, national and regional clusters to participate in events aimed at encouraging SMEs to apply and participate in IMI2 JU projects.

Regulators
The regulatory environment is key to ensuring that safe and effective medicines reach the market for the benefit of patients. IMI2 JU will continue to engage with all relevant regulatory authorities, in particular, the European Medicines Agency (EMA). When possible and relevant, IMI2 JU will continue to strengthen engagement with other international agencies and competent national authorities, through for instance interactions with the heads of agencies. Similarly, IMI2 JU will continue to strengthen engagement with relevant health technology assessment (HTA) bodies, through interactions with EUnetHTA for instance in order to progress the goal of end-to-end integration in medicine development. In addition, IMI2 JU will organise its 6th Regulatory Science Summit in 2019 to ensure that our projects have a real impact on patients' lives and global health.

Other industries and stakeholders
IMI2 JU will continue to explore how to mobilise industries and stakeholders outside of the pharmaceutical sectors. Through face-to-face meetings, workshops and presentations at conferences, IMI2 JU will engage with players in the ICT, imaging, diagnostic and health technology areas, to mention but a few. Likewise, important steps will continue to engage major players in the food and nutrition sector into discussions around potential programmes under the IMI2 JU umbrella. In addition to other industrial sectors, IMI2 JU will encourage the participation of charities and charitable foundations in its work programmes.

IMI2 JU and ECSEL JU (www.ecsel.eu) initiated in 2017 the first discussions to explore possibilities for cooperation between both JUs in the domain of smart health along three thematic areas: sensors and diagnostics, imaging, and patient monitoring platforms. As a continuation of the first concrete interactions set up in 2018, participation of both JUs in their respective governance bodies (e.g. participation of ECSEL in SGG Digital Health & Patient Centric Evidence Generation, Immunology, etc.), interactions during topics design and consultation process, as well as dedicated workshops, are planned in 2019. The objective is to further support synergies between the JUs' activities and potential collaborations between projects of the respective JUs.

As the healthcare challenges faced by society are global, IMI2 JU will continue exploring interactions and seeking synergies with EU and non-EU organisations (including technology hubs at national or regional level) when appropriate, for example in the area of antimicrobial resistance, mental health/neuroscience, microbiome, ATMP vaccines, bio preparedness or oncology. Where necessary, a workshop with IMI founding members and relevant experts will be organised in order to identify gaps and bring new ideas for future topics.

In order to share best practices between projects and develop potential synergies, IMI2 JU will encourage its projects to organise cross-project meetings for both IMI2-JU-funded and other initiatives. This is particularly important in helping disseminate information about IMI2 JU and ensuring harmonisation of approaches at both a European and global level.

IMI2 JU will host a workshop organised by the SGG oncology where experts will be invited to brainstorm on pre-identified themes in order to identify gaps and bring new ideas for future topics in oncology to be launched in upcoming Calls for proposals.

2.2.7 Dissemination and information about projects results

Although the responsibility for maximising the impact of their own research and innovation lies primarily with the project consortia, promoting the successes of IMI2 JU projects is a core element of both the IMI2 JU communications and dissemination strategies.

The IMI2 JU Programme Office identifies results and successes in a variety of ways, including through formal routes (project periodic reports, interim reviews) and informal routes (direct contacts with project participants, monitoring of project websites and social media, etc.). IMI2 JU will continue to support and supplement the dissemination of projects' public deliverables via a variety of channels, including the IMI2 JU and projects' websites, newsletter, social media (Twitter and LinkedIn), the press and events. Particular efforts will be invested in scaling up the online catalogue of accessible tools generated by our projects on the JU website.

In addition, IMI2 JU will continue to explore how to make better use of EU specific dissemination channels for the promotion of projects and their results by actively participating in the European Commission's Dissemination and Exploitation Network (D&E Net).

In 2019, the IMI2 JU expects to receive 13 final project reports. These reports will come from projects finishing in 2018 but reporting in 2019 (2 projects) and those finishing and reporting in 2019 (11 projects). In addition, 3 projects reaching their end date in 2019 will report in 2020. Capturing the outcomes and impacts of these projects presents IMI2 JU with a continuing challenge of ensuring that project results are disseminated widely and taken up by researchers in the field.

It is expected that at least 13 close-out meetings will be organised around the time of the final report submission. The IMI2 JU will prepare specific communication materials for each project based upon information provided in the respective final report and close out meeting.

Lastly, IMI2 JU will continue to fulfil its role/obligation to look after policy conformity, effectiveness and efficiency of the dissemination and exploitation at the level of each project.

2.2.8 Socio-economic impact study

An important part of evaluating the performance of IMI JU will be an assessment of the socio-economic impacts of the projects supported by the IMI1 programme. The efforts to assess this socio-economic impact will be continued using the previously developed methodology.

The final report will be ready for publication by the end of 2019 and will be disseminated to all stakeholders, including policymakers at the European level.

2.3 Call management rules

All proposals must conform to the conditions set out in the Horizon 2020 Rules for Participation (http://ec.europa.eu/research/participants/data/ref/h2020/legal_basis/rules_participation/h2020-rules-participation_en.pdf and the Commission Delegated Regulation with regard to IMI2 JU http://eur-lex.europa.eu/legal-content/EN/TXT/PDF/?uri=CELEX:32014R0622&from=EN.

The following general conditions shall apply to the IMI2 JU Calls for Proposals. They are based on the General Annexes to the Horizon 2020 Work Programme 2018-2020[12].

LIST OF COUNTRIES AND APPLICABLE RULES FOR FUNDING

By way of derogation[13] from Article 10(1) of Regulation (EU) No 1290/2013, only the following participants shall be eligible for funding from the Innovative Medicines Initiative 2 Joint Undertaking:

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

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

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

(ii) secondary and higher education establishments,

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

(c) the Joint Research Centre;

(d) international European interest organisations.

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[14].

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 Work Plan.

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;
- for a single-stage call, as well as at stage 2 of a two-stage call, the limit for RIA/IA full proposals is 70 pages.

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

[13] 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

[14] In accordance with Article 10(2) of the Regulation (EU) No 1290/2013 and Article 1 of Commission Delegated Regulation (EU) No 622/2014

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 Work Plan.

In addition, under all two-stage submission procedures the following additional condition[15] 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.

Furthermore, the IMI2 JU Call 19 for proposals, single-stage submission procedure, will be launched under the scientific priority 'Restricted Call to maximise the impact of IMI2 JU objectives and scientific priorities'. This Call intends to support further activities in those exceptional cases where it is necessary to enable successful consortia to build upon the achievements of their initial action in order to take full advantage of the impacts of the initial action results. In the context of the IMI2 JU 19 Call for proposals, the following additional condition[16] applies:

- the IMI2 JU Call 19 is restricted to the original consortia of actions funded under topics published in the IMI2 JU Annual Work Plan of 2014 and of 2015, since only these actions are sufficiently advanced in their implementation to be considered for follow-up activities, and;
- the IMI2 JU Call 19 is limited to those topics which already pre-informed potential applicants about the possibility for a later restricted Call.

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 Work Plan.

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 Work Plan.

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 Work Plan with the following additions:

The relevant call texts launched under this Work Plan must specify whether the Call for proposals is a single-stage or two-stage Call, and the predefined submission deadline.

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.

[15] 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"

[16] 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"

The Award criteria, scores and threshold for IMI2 JU Call 17 are as follows:

Type of action	Excellence	Impact	Quality and efficiency of the implementation
RIA **1st stage** **Evaluation** **IMI2 JU Call 17**	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 annual work plan: Clarity and pertinence of the proposal to meet all key objectives of the topic; Credibility of the proposed approach; Soundness of the concept, including trans-disciplinary considerations, where relevant; Extent that proposed work is ambitious, has innovation potential, and is beyond the state of the art; Mobilisation of the necessary expertise to achieve the objectives of the topic, ensure engagement of all relevant key stakeholders	The following aspects will be taken into account, to the extent to which the outputs of the project should contribute at the European and/or international level: The expected impacts of the proposed approach as mentioned in the Call for proposals Added value from the public-private partnership approach on R&D, regulatory, clinical and healthcare practice as relevant; Strengthening the competitiveness and industrial leadership and/or addressing specific societal challenges; Improving European citizens' health and wellbeing and contribute to the IMI2 objectives[17].	The following aspects will be taken into account: Coherence and effectiveness of the outline of the project work plan, including appropriateness of the roles and allocation of tasks, resources, timelines and approximate budget; Complementarity of the participants within the consortium (where relevant) and strategy to create a successful partnership with the industry consortium as mentioned in the topic description in the Call for proposal; Appropriateness of the proposed management structures and procedures, including manageability of the consortium.
RIA **2nd stage** **Evaluation** **IMI2 JU Call 17**	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 annual work plan and is consistent with the stage 1 proposal: Clarity and pertinence of the proposal to meet all key objectives of the topic; Credibility of the proposed approach;	The following aspects will be taken into account, to the extent to which the outputs of the project should contribute at the European and/or international level: The expected impacts of the proposed approach as mentioned in the Call for proposals; Added value from the public-private partnership approach on R&D, regulatory, clinical and healthcare practice as relevant;	The following aspects will be taken into account: Coherence and effectiveness of the project work plan, including appropriateness of the roles and allocation of tasks, resources, timelines and budget; Complementarity of the participants within the consortium (where relevant);

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

Type of action	Excellence	Impact	Quality and efficiency of the implementation
	Soundness of the concept, including trans-disciplinary considerations, where relevant; Extent that proposed work is ambitious, has innovation potential, and is beyond the state of the art; Mobilisation of the necessary expertise to achieve the objectives of the topic, ensure engagement of all relevant key stakeholders.	Enhancing innovation capacity and integration of new knowledge; Strengthening the competitiveness and industrial leadership and/or addressing specific societal challenges; Improving European citizens' health and wellbeing and contribute to the IMI2 objectives;[17] Any other environmental and socially important impacts; Effectiveness of the proposed measures to exploit and disseminate the project results (including management of IPR), to communicate the project, and to manage research data where relevant.	Clearly defined contribution to the project plan of the industrial partners (where relevant); Appropriateness of the management structures and procedures, including manageability of the consortium, risk and innovation management and sustainability plan.

The scheme above is applicable to a proposal in a two-stage submission procedure under IMI2 JU Call 17. 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 17, for the evaluation of first-stage proposals, the threshold for each one of the two first criteria (‘excellence’ and ‘impact’) will be 3. There is no overall threshold. For the evaluation of second-stage proposals under a two-stage submission procedure; the threshold for individual criteria will be 3. The overall threshold, applying to the sum of the three individual scores, will be 10.

The Award criteria, scores and threshold for IMI2 JU Call 18 and 19 are 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
 	
IMI2 JU Call 18
	▪ 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** **IMI2 JU Call 18,** **Single stage Evaluation** **IMI2 JU Call 19**	▪ 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 under IMI2 JU Call 18, as well as in a single-stage submission procedure under IMI2 JU Call 19. 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 the IMI2 JU Call 18, 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.

Under IMI2 JU Call 19, for the evaluation of proposals under a single-stage submission procedure:

- the threshold for individual criteria will be 4;
- the overall threshold, applying to the sum of the three individual scores, will be 12.

For all IMI2 JU Calls launched under this Annual Work Plan:

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.[18]

Where appropriate and duly justified, IMI2 JU Calls for proposals may follow a two-stage process.

Under the single-stage evaluation process, evaluated proposals will be ranked in one single list. The best-ranked proposals, in the framework of the available budget, will be invited to prepare a Grant Agreement.

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[19] 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. The 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 the 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, the IMI2 JU may organise hearings with the applicants to:
- clarify the proposals and help the panel establish their final assessment and scores, or
- improve the experts' understanding of the proposal.

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

[19] 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

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

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
Single-stage	Maximum 5 months from the submission deadline at the single stage.	N/A	Maximum 8 months from the submission deadline.
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 Work Plan.

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 Work Plan.

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 Work Plan.

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: http://www.imi.europa.eu/apply-funding/call-documents/imi2-call-documents#imi2-call-documents-collapsible-1.

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. [20]

In order to ensure excellence in data and knowledge management consortia will be requested to Disseminate scientific publications on the basis of open access[21] (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.

Single-stage proposals and 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[22] (e.g. IMI2 JU model Grant Agreement).

[20] Article 19 of Horizon 2020 Framework Programme and Articles 13 and 14 of the Horizon 2020 Rules for Participation.
[21] 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
[22] http://www.imi.europa.eu/apply-funding/call-documents/imi2-call-documents

2.4 Support to Operations

2.4.1 Communication and events

Communication objectives

IMI2 JU has set up a communications strategy aiming to pursue five main strategic goals:

- promote IMI2 JU and raise awareness levels and perception of IMI2 JU among all target groups focusing on results and impact;
- attract the best researchers from relevant target groups to apply for funding under IMI2 Calls for proposals;
- increase the engagement of patients in IMI2 JU's activities;
- increase the engagement of SMEs in IMI2 JU's activities;
- gain support for IMI2 JU among key groups of policymakers and opinion leaders.

The year 2019 will be dedicated to consolidating the communication of IMI project results, building on the 10th anniversary communication campaign launched in 2018. The main objective in the area of communication will be to demonstrate the EU-added value of IMI2 JU: to what extent IMI2 JU is delivering results in the field of health that are tangible and translate into concrete benefits for European citizens.

As a follow up of the 2018 Stakeholder Forum, the Communications team will also focus its activities on the current and future cross-sectoral collaboration in IMI projects.

Communication support to IMI2 JU stakeholder strategies: patients and SMEs

As the IMI2 JU patient strategy keeps evolving with patients and carers reaching new ways of meaningful involvement in IMI projects, the Communications team will continue to support awareness-raising activities and to encourage patients to get involved in both IMI's projects and its broader activities.

In line with Horizon 2020, IMI2 JU will be expected to ensure 20% of its budget goes to SMEs. Yet the JU is competing with other funding programmes to attract SME participation, some of them SME tailored. The Communications team will continue to focus on a comprehensive outreach and support strategy by (i) improving communication on IMI2 JU through SRGs/regional contact points/clusters, (ii) by participating in partnering events and investor conferences and (iii) by providing specific resources for SMEs such as dedicated webinars or new content for the dedicated SME webpage in the JU website.

Further develop IMI success stories

IMI2 JU now holds close-out meetings with the representatives of projects that have finished. These meetings are providing IMI2 JU with a wealth of success stories that can be adapted for different audiences and channels and back up IMI2 JU's key messages. IMI2 JU will also continue to maintain close contacts with ongoing projects to gather and promote their latest news and results.

In order to amplify the reach of project success stories and results, IMI2 JU will continue to work in close collaboration with the communication unit of the European Commission's Directorate-General for Research and Innovation, responsible for services such as the Horizon Magazine and the webpage for EU research success stories.

Media outreach

The coverage of IMI2 JU in both the general and specialist press tends to be either neutral or positive in tone. In 2019, IMI2 JU will work to ensure that this trend continues by building and maintaining links with journalists, issuing regular press releases, organising press interviews, and inviting journalists to IMI2 JU events.

At the same time, IMI2 JU will remain alert to issues that could damage IMI2 JU's reputation and respond accordingly, for example by preparing briefings or sets of questions and answers.

Communication channels

IMI2 JU will continue to develop the following channels:

- events (both IMI2 JU and external);
- website;
- newsletter;
- social media (LinkedIn, Twitter);
- multipliers (e.g. European Commission & EFPIA, States Representatives Group (SRG), SC, National Contact Points, relevant scientific associations, patient organisations, etc.);
- media (general and specialist, mainly in Europe but also elsewhere);
- direct mailings;
- publications;
- videos;
- direct contacts with opinion leaders.

Social media

Building on the success of the IMI 10th anniversary campaign in 2018, in 2019 IMI2 JU will continue to develop its brand on social media, especially Twitter. This will include developing engaging content with strong visuals and using promoted / sponsored tweets at key moments of the year.

Key events in 2019

Event	Timeline
Promote IMI2 JU projects	Throughout year
IMI2 JU presence in the European Parliament	Throughout year
IMI2 JU presence at relevant external events, e.g. BIO, BIO-Europe, EAPM, BioFIT	Throughout year
Promote IMI2 JU Calls for proposals (webinars, info days, website, etc.)	Q2, Q4
IMI2 JU Stakeholder Forum 2019	Q2
Organise a coordination meeting with IMI project partners responsible for communications	Q1/Q2

2.4.2 Procurement and contracts

In order to reach its objectives and adequately support its operations and infrastructures, IMI2 JU will allocate funds to procure the necessary services and supplies. To make tender and contract management as effective and efficient as possible, IMI2 JU resorts extensively to multi-annual framework contracts and EU inter-institutional tenders. Most essential framework contracts are already in place and will be renewed beyond 2019.

In 2019, the IMI2 JU also intends to launch and conclude the following procurement procedures:

Subject	Indicative/ max. amount	Type of procedure & contract	Indicative schedule
Optimising exploitation of regulatory relevant IMI results	250 000 EUR	Open call for tender & framework service contract	Contract conclusion Q3 2019

2.4.3 IT and logistics

IMI2 JU information technologies (IT) strategic objective is to deliver value to the business and to be a key enabler of new business initiatives with the goal of supporting and shaping the present and future of the JU. Operations and administration information systems and infrastructure aim at making all IMI2 JU processes simpler and more efficient.

In order to achieve the afore-mentioned goal, the IMI2 JU IT team will focus its 2019 activities on three areas:

- business operations information systems;
- collaboration, communication and administration management information systems and;
- infrastructure, security and office automation support.

2.4.3.1 Business operations information systems

In 2017, IMI2 JU's business operations started utilising the full suite of Horizon 2020 IT tools for the management of IMI2 JU calls, applications, evaluations and grants. In 2018, all projects under IMI2 JU started reporting under those tools. The IT team will monitor satisfactory functioning for all end-users, in close liaison with the European Commission services.

To provide reliable reporting and statistics for the benefit of all stakeholders, the IMI2 JU Programme Office is working on a new data warehouse project, combining various data sources (eGrants/CORDA, Submission OF Information Application - SOFIA), and other reference data). The first release (planned for the beginning of 2019) will include entirely new business intelligence environment based on QlikSense, which will gradually replace existing Qlikview reports and dashboards. It will also automatically feed the JU website with projects and participants' data and provide a possibility for embedding dashboards on the Intranet.

Since IMI1 projects go on until at least 2020 and some of the IMI2 JU specific requirements (e.g. EFPIA and Associated Partners annual reporting of in-kind contributions) are not available in eGrants, we will continue the maintenance and development of the in-house SOFIA.

2.4.3.2 Collaboration, communication and administration management information systems

IMI2 JU Programme Office has well established collaborative platforms to provide support to the governance bodies, namely the Governing Board, the SC, the SRG and the SGGs. These platforms will be maintained and updated both from a content and operations point of view.

The planned implementation of the European Commission document management and human resources systems (Hermes-Ares-NomCom HAN and SYSPER2) will lead to the phaseout of relevant in-house Liferay applications.

In order to facilitate internal communication, we foresee a complete revamp of the Intranet with improved structure and usability.

2.4.3.3 Infrastructure, security and office automation support

IMI2 JU shares IT infrastructure, related IT operations and office automation support with other JUs that are also located in the same premises. In the context of the common infrastructure, the following activities are foreseen for 2019 and are expected to provide efficiency gains in the operation of the organisation:

- monitoring and maintenance of the common infrastructure and end-user office-automation support covering incidents, service requests and improvements (Q1 – Q4 2019);
- implementation of the new common framework contract for the provision of IT services.

2.4.4 Human Resources

The 2019 objective for HR shall be: recruit, train, assess, motivate and retain highly qualified staff with a view to ensure effective and efficient operation of the JU, as well as equal opportunities. This objective will be implemented through the following four main themes.

Staffing

The staffing needs of IMI2 JU will be the same as in 2018. The total number of staff remains at 54 temporary and contract agents (of which 39 temporary agents and 15 contract agents), as well as two additional seconded national experts.

In accordance with the Staff Regulations, technical adaptations have been made to the Staff Establishment Plan in order to create a margin for reclassification (promotions) of staff. Those adaptations do not affect the total number of staff.

Organisation development

The human resources team will advise management on means and actions to enhance operational efficiency and effectiveness. The main action shall be the oversight of duties and responsibilities assigned to staff in order to achieve the fulfilment of IMI2 JU objectives and tasks.

HR management

Human resources will deal with core functions such as: day-to-day management of administrative workflows and processes; performance management and assessment; safety and wellbeing at work; salary, compensation and benefits; employee motivation, communication, and training. It is expected that during 2019 IMI2 JU will start working in the European Commission human-resource IT system, SYSPER II, which will help in the personnel administration.

Inter-JU cooperation

The efficiency and cost-effective management of IMI2 JU resources is also based on a close collaboration with other Joint Undertakings through arrangements and mechanisms of pooling expertise for specific time-bound tasks. In 2019, the JUs will continue to share the human-resource IT tools where necessary, common Calls for tender, as well as a common approach to implementing rules of the EU staff regulations.

2.4.5 Administrative budget and finance

Budget 2019

The budget forecast 2019 for staff (Title 1) and administrative activities (Title 2) has been defined in line with the planning of the year. The increase of 6.86% in 2019 compared to 2018, is mainly due to staff management as well as increasing meetings costs related to experts and close out projects. A comparison table of the financial years 2018 and 2019 is set out below.

	Heading Title 1	Financial year 2018	Financial year 2019	Evolution	Comments
Chapter		Budget EUR	Budget EUR	%	
11	Staff in active employment	5,425,000	5,740,000	5.8	3.5% standard annual promotion and indexation set out in the EU Financial Regulation. 2 positions of Seconded National Experts
12	Staff recruitments - miscellaneous expenditure	20,000	20,000	0.0	
13	Missions and duty travels	190,000	190,000	0.0	
14	Socio-medical structure	360,000	360,000	0.0	
17	Entertainment and representation	20,000	20,000	0.0	
	Title 1 - Total	**6,015,000**	**6,330,000**	**5.24**	
	Heading Title 2	Financial year 2018	Financial year 2019	Evolution	Comments
Chapter		Budget EUR	Budget EUR	%	
20	Office building and associated costs	729,000	756,000	3.7	Additional costs with newly rented space and cleaning.
21	Information technology purchases	712,000	779,000	9.4	Additional recurrent license, maintenance of paperless system and new Intranet.
22	Office equipment (movable property and associated costs)	153,000	153,000	0.0	
23	Current administrative expenditure	123,000	123,000	0.0	
24	Telecommunication and postal expenses	68,000	78,000	14.7	Increase due to higher number of teleconferences
25	Expenditure on formal meetings	158,000	158,000	0.0	
26	Administrative costs in connection with operational activities	300,000	388,154	29.4	Increase in the activities such as SGG, projects close out meetings.
27	External communication, information and publicity	625,000	625,000	0.0	
28	Service contracts	730,000	730,000	0.0	
29	Expert contracts and cost of evaluations	700,000	900,000	28.6	Increase in number of Calls' topics.
	Title 2 - Total	**4,298,000**	**4,690,154**	**9.12**	
	Total Administrative Costs	**10,313,000**	**11,020,154**	**6.86**	

The operational budget is covered under section 2.2.2. Scientific priorities for 2019. For an overview of the Budget Plan 2019 – see Chapter 3.

Financial Management

During 2019, the Programme Office will implement the updated IMI2 JU Financial Rules in line with the 2018 revised Regulation (EU, Euratom) 2018/1046 on the financial rules applicable to the general budget of the Union, repealing Regulation (EU, Euratom) No 966/2012 (2012 Financial Regulation).

In addition, the finance team will continue with its day-to-day activities of initiation, verification and payments of invoices and cost claims, creation of commitments, recovery orders, and analysis of periodic reports and negotiations of financial and administrative parts of projects. These activities will be conducted in a timely manner that will be monitored through corporate KPIs, in particular payment times and budget execution.

Best practice and highest quality standards will be ensured through the Financial Circuits Manual and a set of standard operating procedures and workflows. In addition, knowledge dissemination will be further developed through the development of further guidance and the tenure of several financial workshops, in particular targeting beneficiaries, with the aim to reduce errors in financial reporting.

2.4.6 Data protection

The IMI2 JU will continue its efforts undertaken in the wake of the entry into effect of the General Data Protection Regulation, following the adoption of the successor regulation to 'Regulation (EC) No 45/2001 of the European Parliament and of the Council of 18 December 2000 on the protection of individuals with regard to the processing of personal data by the Community institutions and bodies and on the free movement of such data'.

The IMI2 JU, with the active involvement of its Data Protection Officer, will continue to implement the changes brought about by the overhaul of the EU data protection regime. This will include finalising the update of the JU's internal data protection rules, guidelines and practices, raising awareness among IMI2 JU staff and stakeholders, and contributing to the activities of the inter-institutional data protection networks and working groups in which the JU participates.

2.4.7 Access to documents

IMI2 JU will continue to address requests for access to IMI2 JU documents according to Regulation (EC) No 1049/2001, in a spirit of openness and transparency in order to bring its activities and outputs closer to the public. In this context, the Programme Office will further develop a transparency policy on activities of its governance bodies in accordance with the Council Regulation setting up IMI2 JU. In particular, IMI2 JU will continue the implementation of the standard operating procedure (SOP) on Access to documents and the training of the staff on access to documents issues.

Furthermore, the objectives of actions in this field will continue, as a means to keep a high-level of public confidence in IMI2 JU by giving the opportunity to the public to monitor its work. In addition, this will bring additional benefits such as:

- improving public awareness of IMI2 JU activities and processes;
- stimulating the interaction on key issues.

2.5 Governance

Key objectives

- Further develop an IMI2 JU strategic orientation and related objectives.
- Ensure that activities are in line with and support IMI2 JU strategic orientation.
- Further improve the efficiency and effectiveness of the IMI2 JU's governance activities.
- Promote and maintain a positive reputation among stakeholders and partners as a key facilitator of healthcare research.

Planned activities

- Support to the Governing Board, the SC, the SRG and management.
- Align planning activities (strategy, annual work plans and related budget) and the associated monitoring and reporting activities.
- Improve responsibilities and accountability.
- Enhance communication and transparency.

IMI2 JU will continue to provide support to the Governing Board, the SC, the SRG, and the Stakeholder Forum and their working groups.

The **Governing Board** gathers representatives of IMI2 JU members. It has the responsibility for overseeing the operations of the IMI2 JU and the implementation of its activities. It will meet at least twice.

The **Scientific Committee** (SC) will continue in its advisory role to the IMI2 JU and will notably be consulted on the scientific priorities to be addressed in Annual Work Plans and on the scientific achievements to be described in the Annual Activity Report. Three meetings of the SC are planned for 2019. The Chair will participate in the Governing Board meetings as an observer. Information can be found at: http://www.imi.europa.eu/about-imi/governance/scientific-committee

The **States Representatives Group** (SRG) will be consulted on the Annual Work Plan (and subsequent amendment(s)) and will receive information on Calls outcomes and evaluation process. At least two meetings of the SRG are planned for 2019. The Chair will participate in Governing Board meetings as an observer. Information can be found at: http://www.imi.europa.eu/about-imi/governance/states-representatives-group

In addition, a joint meeting between the SC and the SRG is planned in order to support the activities initiated to strengthen the synergies between the two advisory bodies and exchange on topics of common interest.

In order to cover all areas of life science research and innovation of public health interest and to further support the IMI2 JU objectives, the JU will pursue its action to attract a wide range of stakeholders from various sectors, notably by promoting the possibility to become **Associated Partners** at programme or topic level and supporting such an involvement. Practical information can be found at: http://www.imi.europa.eu/get-involved.

The SGGs continue to ensure the coordination of IMI2 JU's work in seven strategic areas and work to make the development of new topics more transparent and effective. The SGGs are made up of representatives from companies active or interested in the area covered by the scope of the SGG as well as representatives from the European Commission, the IMI2 JU Programme Office and the SC. Currently, the seven established SGGs focus on the following areas: immunology; diabetes / metabolic disorders; neurodegeneration; translational safety; infections control; oncology; and digital health and patient-centric evidence generation (which replaced the data and knowledge management in 2018).

In 2019 the SGGs will continue to develop comprehensive strategies for future projects for their specific areas.

Each SGG will meet at least 2 to 3 times a year to discuss their portfolio of projects and ensure synergies with ongoing projects, both projects within IMI2 JU and those outside. They may engage with external parties to consult on topic development or key challenges in specific areas as required. Efforts will be made to enhance communication with these bodies as well as seek feedback on any significant IMI2 JU activities and developments.

In 2019, facilitation of better cross-SGGs coordination will continue, notably through the dedicated IT platform set up in 2017, as well as a series of dedicated cross-SGGs meetings. These improved efficiency mechanisms will facilitate the increased flow of information not only within a given SGG, but also with IMI2 JU governance bodies (Governing Board, SC, SRG). Therefore, the SGG meeting agendas, publishable minutes and attendance lists will be more readily available. In addition, they will be called upon to advise on how best to exploit IMI2 JU projects' outputs, enhance cross-projects' collaboration, as well as explore synergies with similar or complementary activities at national and global level.

In line with article 13.3 (b) of IMI2 JU Regulation, costs of activities related to allowing the SGGs perform these tasks and achieve their objectives are considered as eligible in-kind contributions under the conditions set out in the SGG charter.[23]

Expected results

- Streamlined governance activities

Actions:

- Preparation of plans, reports, briefings, decisions
- Organisation of consultations and assessment of the input
- Organisation of meetings and presentations
- Implementation of decisions and recommendations
- Coordinate information across governance structures.

[23] http://www.imi.europa.eu/sites/default/files/uploads/documents/reference-documents/IMI2_GB_DEC_2016_21_Decision_on_new_SGGs_Charter_SIGNED_30SEP2016.pdf

2.6 Internal Control framework

In 2019, the IMI2 JU will continue working on the improvement of its internal operational and financial processes and procedures. In particular, the new Internal Control Framework (ICF) – aligned with the revised control framework adopted by the European Commission – will be fully implemented based on the characteristics, indicators and targets developed during 2018 and adapted to the specific IMI2 JU environment.

In parallel, the Programme Office will: ensure the alignment with and implementation of the Horizon 2020 legal framework and programme management tools; develop guidance materials; and keep its financial procedures effective and up to date.

Another relevant element of the control strategy operated by IMI2 JU will be the revision – in line with the European Commission and DG RTD – of its Antifraud Strategy with the appropriate communication and training measures to staff and beneficiaries.

The specific target set by the IMI2 JU on internal control is to sustain the IMI2 JU operational and financial performance[24] in order to ensure the achievement of its objectives.

2.6.1 Ex-ante and ex-post controls

Ex-ante controls

During 2019, the IMI2 JU Programme Office will continue to work effectively in its day-to-day activities of initiation, verification and payments of invoices and cost claims, creation of commitments, recovery orders, validation of financial and technical reports and following-up on other financial and administrative aspects of the projects.

These activities will be conducted in a timely and efficient manner according to the principle of sound financial management. All activities will be monitored through the defined set KPIs, in particular, the time to pay and the budget and work plan execution. Best practice and highest quality standards will be ensured through the availability of the newly adopted Horizon 2020 Vademecum on Grant Agreement Preparation (GAP, the Vademecum on monitoring and reporting and the Vademecum on Amendments). These procedures will complement the existing set of financial manuals, SOPs and workflows.

Specific attention will be placed on:

- implementation of the joint guidance on Horizon 2020 ex-ante controls for interim and final payments;
- increased financial checks during the GAP phase;
- raising the awareness of beneficiaries on financial and administrative aspects of Horizon 2020 rules and how to avoid errors in cost reporting.

Ex-post controls

For projects running under the IMI1 programme, the Programme Office will carry on with the implementation of its ex-post audits strategy as a means to ensure the legality and regularity of operational expenditure. This strategy complements ex-ante controls embedded in IMI's management processes and includes the correction of any amounts found to have been paid in excess. Errors of a systematic nature will also continue to be extended to cover unaudited financial statements ('Form C') of the same participants.

[24] Effectiveness, efficiency and economy of operations; reliability of reporting; safeguarding of assets and information; prevention, detection, correction and follow-up of fraud and irregularities; and adequate management of the risks relating to the legality and regularity of the underlying transactions, taking into account the multiannual character of programmes as well as the nature of the payments (IMI2 JU Financial Rules, Art 12.2).

Representative and, if necessary, risk-based audits of beneficiaries will be launched during the year to cover new cost claims received and validated by IMI2 JU since the last audited period. Systematic risk-based audits of accepted declarations of in-kind contributions by EFPIA companies will not be continued in 2019, as the programme is reaching its end and the planned, near totality of the companies' contributions will have been covered by audits. Risk-based audits may nevertheless be initiated should a specific need arise.

As regards the IMI2 JU programme, the JU's ex-ante and ex-post controls of grants are both aligned with the harmonised strategies adopted for the entire Horizon 2020 Programme. The IMI2 JU Programme Office will carry out the ex-ante checks as prescribed in the Horizon 2020 Control strategy. As for ex-post controls, the Commission Common Audit Service (CAS) will carry out the Horizon 2020 audits in accordance with the common Horizon 2020 audit strategy. IMI2 JU contributes to the implementation of the audit strategy in close cooperation with the CAS. The harmonised legal framework will enable IMI2 JU to draw an additional element of assurance from extension of audit results on shared beneficiaries across the Horizon 2020 programme as well as from audits sampled by CAS in line with the overall programme objectives.

In line with the IMI2 JU Regulation, controls of in-kind contributions by EFPIA companies will be based essentially on review of audit certificates provided annually by independent auditors.

2.6.2 Internal and External audits

The audit environment is an assurance and accountability pillar within the IMI2 JU internal control framework since it provides reasonable assurance about the state of effectiveness of risk management and control processes and serves as a building block for the annual Declaration of Assurance of the Executive Director.

The Audit Manager will coordinate audits carried out by IMI2 JU's internal and external auditors and will follow up and asses the implementation of the Internal Audit Service (IAS) of the European Commission and the European Court of Auditors (ECA) audit recommendations with the objective to confirm the effective implementation.

Internal audits are carried out by the IAS in liaison with the Audit Manager.

In 2019, the focus will be put on:

- coordination of the new risk assessment to be carried out by the IAS in view of the strategic internal audit plan for 2019 – 2021 and the approval of the new multiannual audit plan by the Governing Board.

External audits are carried out by ECA. ECA will audit and issue opinions on the legality and regularity of the underlying transactions, revenue, and reliability of accounts. In accordance with the IMI2 JU Financial rules, IMI2 JU's 2018 annual accounts will be audited by an external audit company while the Court will draw an opinion on the basis of their work.

In view of the overall corporate objective of receiving an unqualified ('clean') ECA audit opinion and positive statement of assurance, the key activities will focus on:

- liaising and supporting ECA auditors throughout the audit on 2018 and 2019 accounts and a possible performance audit;
- liaising with an independent financial audit firm (contracted in 2018 under the EC (DG BUDG) framework contract) throughout the audit of accounts for financial year 2018 and 2019.

3 Budget 2019

An overview of the 2019 budget per chapters is set out below.

STATEMENT OF REVENUE								
	Heading Revenue	**Budget 2019.0**		**Budget 2019 Amendment 1**		**Amended Budget 2019.1**		**Comments**
Chapter		Commitment Appropriation (CA)	Payment Appropriation (PA)	Commitment Appropriation (CA)	Payment Appropriation (PA)	Commitment Appropriation (CA)	Payment Appropriation (PA)	
10	European Union financial contribution (including EFTA contribution/Draft Budget 2019)	267,722,662	190,575,842	-139,100,891		128,621,771	190,575,842	Commitment appropriations include EUR 5,510,077 for administrative costs and EUR 123,111,694 for operational costs. Payment appropriations include administrative costs of EUR 5,510,077 and operational costs of EUR 185,065,765.
C2	Appropriations carried over	114,341,000		12,599,206	30,943,429	126,940,206	30,943,429	The amount carried over from previous year. Administrative expenditure - payment appropriation. Operational expenditure - commitment and payment appropriation.
	Title 1 - Total	**382,063,662**	**190,575,842**	**-126,501,685**	**30,943,429**	**255,561,977**	**221,519,271**	
20	EFPIA contribution	5,510,077	5,510,077			5,510,077	5,510,077	EFPIA contribution to IMI JU administrative costs.
21	Subsidy from other Members other than the Union and the Associated Partners, or their constituent entities or their affiliated entities		1,000,000				1,000,000	Four EFPIA companies contribution to operational payment appropriations
	Title 2 - Total	**5,510,077**	**6,510,077**			**5,510,077**	**6,510,077**	

STATEMENT OF REVENUE								
Chapter	**Heading Revenue**	**Budget 2019.0**		**Budget 2019 Amendment 1**		**Amended Budget 2019.1**		**Comments**
		Commitment Appropriation (CA)	Payment Appropriation (PA)	Commitment Appropriation (CA)	Payment Appropriation (PA)	Commitment Appropriation (CA)	Payment Appropriation (PA)	
30	Associated Partners contributions		845,000				845,000	Bill and Melinda Gates Foundation contribution to operational payment appropriations
	Title 3 - Total		**845,000**				**845,000**	
	Total contributions	**400,172,945**	**228,874,348**	**-126,501,685**	**30,943,429**	**261,072,054**	**228,874,348**	

STATEMENT OF EXPENDITURE

	Heading Title 1	Budget 2019.0		Budget 2019 Amendment 1		Amended Budget 2019.1		Comments
Chapter		Commitment Appropriation (CA)	Payment Appropriation (PA)	Commitment Appropriation (CA)	Payment Appropriation (PA)	Commitment Appropriation (CA)	Payment Appropriation (PA)	
11	Staff in active employment	5,740,000	5,740,000			5,740,000	5,740,000	Salaries
12	Staff recruitments - miscellaneous expenditure	20,000	20,000		923	20,000	20,923	Miscellaneous expenditure on staff recruitment: travel expenses, etc.
13	Missions and duty travels	190,000	190,000		12,400	190,000	202,400	Mission expenses
14	Socio-medical structure	360,000	360,000		35,136	360,000	395,136	Other staff costs: training, language classes, medical service, interim staff
17	Representation	20,000	20,000		5,560	20,000	25,560	Representation, receptions and internal meetings
	Title 1 - Total	**6,330,000**	**6,330,000**		**54,019**	**6,330,000**	**6,384,019**	

	Heading Title 2	Financial year 2019		Budget 2019 Amendment 1		Amended Budget 2019.1		Comment
Chapter		Commitment Appropriation (CA)	Payment Appropriation (PA)	Commitment Appropriation (CA)	Payment Appropriation (PA)	Commitment Appropriation (CA)	Payment Appropriation (PA)	
20	Office building and associated costs	756,000	756,000		31,876	756,000	787,876	Rent, works, common/IMI charges and parking. Additional costs: indexation, insurance, water/gas, electricity, heating, maintenance + repairs, security and surveillance.
21	Information technology purchases	779,000	779,000		382,190	779,000	1,161,189	IT purchases, software licences, software development, IMI website.
22	Office equipment (movable property and associated costs)	153,000	153,000			153,000	153,000	Purchases and rental of office equipment, maintenance and repair.
23	Current administrative expenditure	123,000	123,000		36,000	123,000	159,000	Office supply. Literature, subscriptions, translation services, bank charges and miscellaneous office expenditure.
24	Telecommunication and postal expenses	78,000	78,000		24,689	78,000	102,689	Data communication such as telephone, video conferences and postal services.
25	Expenditure on formal meetings	158,000	158,000		39,711	158,000	197,711	Official meetings such as SRG, Scientific committee, Governing Board and working groups created by the Governing Board.
26	Administrative costs in connection with operational activities	388,154	388,154		64,086	388,154	452,240	Expenditure in connection with research activities and objectives of IMI (workshops, meetings and events targeting IMI projects).

	Heading Title 2	Financial year 2019		Budget 2019 Amendment 1		Amended Budget 2019.1		Comment
27	External communication, information and publicity	625,000	625,000		67,876	625,000	692,876	External communication and events such as Info Days, stakeholder forums.
28	Service contracts	730,000	730,000		401,143	730,000	1,131,143	Studies, audits.
29	Expert contracts and cost of evaluations	900,000	900,000		12,040	900,000	912,040	Costs linked to evaluations, expert contracts.
	Title 2 - Total	**4,690,154**	**4,690,154**		**1,059,611**	**4,690,154**	5,749,765	
	Total administrative costs Title 1 + Title 2	***11,020,154***	***11,020,154***		**1,113,630**	***11,020,154***	**12,133,784**	

	Heading Title 3	Financial year 2019		Budget 2019 Amendment 1		Amended Budget 2019.1		Comments
Chapter		Commitment Appropriation (CA)	Payment Appropriation (PA)	Commitment Appropriation (CA)	Payment Appropriation (PA)	Commitment Appropriation (CA)	Payment Appropriation (PA)	
30	Implementing the research agenda of IMI2 JU	262,212,585	186,910,765	-126,560,585		135,652,000	186,910,765	Grant agreements – Payments and Commitments
C2	Appropriations carried over from 2018	114,341,000		58,900	29,829,799	114,399,900	29,829,799	The amount carried over from 2018
	Total operational costs Title 3	***376,553,585***	***186,910,765***	-126,501,685	**29,829,799**	**250,051,900**	**216,740,564**	
	Total contributions	**387,573,739**	**197,930,919**	-126,501,685	**30,943,429**	**261,072,054**	**228,874,348**	

An overview of the 2019 budget and structure per budget lines is set out in the table below:

Expense budget line	Description	Commitment appropriations	Payment appropriations	C2 – Payment Appropriation (PA)
A01100	Staff in active employment and costs linked to employment	3,959,000	3,959,000	
A01101	Family Allowances	374,000	374,000	
A01102	Transfer and expatriation allowance	405,000	405,000	
A01110	Contract Agents	636,000	636,000	
A01111	Seconded National Experts	0	0	
A01130	Insurance against sickness	98,000	98,000	
A01131	Insurance against accidents and occupational diseases	15,000	15,000	
A01132	Unemployment insurance for temporary staff	39,000	39,000	
A01133	Pension	0	0	
A01140	Birth and death allowance	10,000	10,000	
A01141	Annual travel costs from the place of employment to place of origins	59,000	59,000	
A01144	Fixed local travel allowances	3,000	3,000	
A01149	Other allowances	0	0	
A01172	Cost of organising traineeships within IMI2 JU	32,000	32,000	
A01175	Translation and typing services and work to be contracted	0	0	
A01177	Other services rendered	5,000	5,000	
A01178	PMO fees	45,000	45,000	
A01180	Sundry recruitment expenses	0	0	
A01181	Travelling expenses (taking up duty)	5,000	5,000	
A01182	Installation allowance	43,000	43,000	
A01183	Moving expenses	0	0	
A01184	Temporary daily allowance	10,000	10,000	
A01190	Weightings (correction coefficient)	2,000	2,000	
A01191	Salaries adaptation	0	0	
11	**Staff in active employment**	**5,740,000**	**5,740,000**	
A01200	Miscellaneous expenditure on staff recruitment	20,000	20,000	923
12	**Staff recruitments - miscellaneous expenditure**	**20,000**	**20,000**	**923**
A01300	Mission expenses	190,000	190,000	12,400

Expense budget line	Description	Commitment appropriations	Payment appropriations	C2 – Payment Appropriation (PA)
13	**Missions and duty travels**	**190,000**	**190,000**	**12,400**
A01401	Socio-medical structure, EU school	80,000	80,000	
A01410	Other trainings	110,000	110,000	1,329
A01430	Medical service	5,000	5,000	229
A01440	Trainings covered by the SLA	6,000	6,000	10,211
A01490	Other interventions	159,000	159,000	23,367
14	**Socio-medical structure**	**360,000**	**360,000**	**35,136**
A01700	Representation expenses	20,000	20,000	5,560
17	**Representation**	**20,000**	**20,000**	**5,560**
	Title 1 - Total	**6,330,000**	**6,330,000**	**54,019**
A02000	Rentals	586,000	586,000	1,800
A02001	Guarantees	0	0	
A02002	Contributions	0	0	
A02010	Insurance	0	0	
A02020	Water gas electricity and charges	131,000	131,000	
A02030	Cleaning and maintenance	10.000	10.000	
A02040	Furnishing of premises (works)	10,000	10,000	4,925
A02050	Security and surveillance	19,000	19,000	25,151
A02090	Other expenditure on buildings	0	0	
20	**Office building and associated costs**	**756,000**	**756,000**	**31,876**
A02101	Hardware, infrastructure and related services	255,000	255,000	231,999
A02102	Software development, licenses and related services	524,000	524,000	150,191
A02103	Other expenses maintenance and repair	0	0	
21	**Information technology purchases**	**779,000**	**779,000**	**382,190**
A02200	Purchase	123,000	123,000	
A02201	Rentals	10,000	10,000	
A02202	Maintenance utilisation and repair	20,000	20,000	
A02203	Other office equipment	0	0	
22	**Office equipment (movable property and associated costs)**	**153,000**	**153,000**	**-**

Expense budget line	Description	Commitment appropriations	Payment appropriations	C2 – Payment Appropriation (PA)
A02300	Stationery and office supply	40,000	40,000	2,800
A02320	Bank charges	0	0	
A02321	Exchange rate losses	0	0	
A02329	Other financial charges	0	0	
A02330	Legal expenses	0	0	
A02350	Other operating expenditure	13,000	13,000	33,200
A02351	Petty expenses	0	0	
A02360	Library stocks purchase of books and subscriptions	44,000	44,000	
A02370	Translation interpretation	26,000	26,000	
23	**Current administrative expenditure**	**123,000**	**123,000**	**36,000**
A02400	Correspondence and communication expenses	78,000	78,000	24,689
24	**Telecommunication and postal expenses**	**78,000**	**78,000**	**24,689**
A02500	Formal meetings	158,000	158,000	39,711
25	**Expenditure on formal meetings**	**158,000**	**158,000**	**39,711**
A02600	Administrative costs in connection with operational activities	47,154	47.154	10,263
A02601	Events	10.000	10.000	
A02602	Workshops	325,000	325,000	49,823
A02603	Knowledge Management	6,000	6,000	4,000
26	**Administrative costs in connection with operational activities**	**388,154**	**388.154**	**64,086**
A02700	External communication	225,000	225,000	64,876
A02701	Events	300,000	300,000	
A02702	Material	100,000	100,000	3,000
27	**External communication, information and publicity**	**625,000**	**625,000**	**67,876**
A02800	Ex-post Audits	536,000	536,000	263,257
A02801	Studies, consultancy	114,000	114,000	81,686
A02802	Audit services	80,000	80,000	56,200
28	**Service contracts**	**730,000**	**730,000**	**401,143**
A02900	Evaluation Experts meetings	750,000	750,000	10,403
A02901	Evaluation Facilities	150,000	150,000	1,637
A02902	Evaluations ENSO	0	0	
29	**Expert contracts and cost of evaluations**	**900,000**	**900,000**	**12,040**
	Title 2 - Total	**4,690,154**	**4,690,154**	**1,059,611**

Expense budget line	Description	Commitment appropriations	Payment appropriations	C2 – Payment Appropriation (PA)
B03000	Implementing the research agenda of IMI1 JU	0	0	
B03001	Call 1	0	0	
B03002	Call 2	0	700,000	
B03003	Call 3	0	1,000,000	
B03004	Call 4	0	1,495,000	
B03005	Call 5	0	7,000,000	
B03006	Call 6	0	6,350,000	
B03007	Call 7	0	500,000	
B03008	Call 8	0	7,000,000	
B03009	Call 9	0	3,000,000	
B03010	Call 10	0	800,000	
B03011	Call 11	0	14,000,000	
B03012	ENSO 2012	0	0	
B03013	ENSO 2013	0	0	
B03020	Implementing the research agenda of IMI2 JU	0	0	
B03021	IMI2 Call 1	0	1,000,000	
B03022	IMI2 Call 2	0	17,000,000	
B03023	IMI2 Call 3	0	4,000,000	
B03024	IMI2 Call 4	0	0	
B03025	IMI2 Call 5	0	5,000,000	
B03026	IMI2 Call 6	0	6,000,000	
B03027	IMI2 Call 7	0	4,000,000	
B03028	IMI2 Call 8	0	3,000,000	
B03029	IMI2 Call 9	0	3,700,000	
B03030	IMI2 Call 10	0	6,000,000	
B03031	IMI2 Call 11	0	300,000	
B03032	IMI2 Call 12	0	0	
B03033	IMI2 Call 13	0	30,065,765	
B03034	IMI2 Call 14	0	15,000,000	
B03035	IMI2 Call 15	0	35,000,000	
B03036	IMI2 Call 16	0	15,000,000	
B03037	IMI2 Call 17	40,786,000	0	
B03038	IMI2 Call 18	62,325,694	0	
B03039	IMI2 Call 19	20,000,000	0	
B03999	Recovery Ex-post audit	0	0	
30-C1	**Implementing the research agenda of IMI2 JU**	**123,111,694**	**186,910,765**	
B03033 - C2	IMI2 Call 13	114,341,000		

Expense budget line	Description	Commitment appropriations	Payment appropriations	C2 – Payment Appropriation (PA)
B03020-C2	Implementing the research agenda of IMI2 JU	12,540,306		**29,773,961**
B03020-C2	Implementing the research agenda of IMI2 JU	3,062*		
B03000-C2	Implementing the research agenda of IMI1 (FP7) projects	55,838**		55,838
	Title 3 - Total	**250,051,900**	**186,910,765**	**29,829,799**
	Total expenditures	**261,072,054**	**228,874,348**	

*amount de-committed from IMI2 (H2020) project that can be used in case late interest payments need to be paid.
** amounts recovered from IMI1 (FP7) projects' beneficiaries during 2018 and carried over to 2019.

3.1 Staff Establishment Plan 2019

Grade	Establishment Plan 2018			Year 2019											
				Posts evolution						Organisational evolution			Establishment Plan 2019		
				Promotion / Career advancement			Turn-over (departures/arrivals)			New posts (per grade)			Requested (Budget)		
	PERM	TEMP	TOTAL	Officials	TA - LT	TA - ST	Officials	TA - LT	TA - ST	Perm	TA - LT	TA - ST	PERM	TA	TOTAL
AD16															
AD15															
AD14		1	1											1	1
AD13															
AD12		2	2											2	2
AD11		2	2											2	2
AD10															
AD9		5	5		+ 1									6	6
AD8		7	7		- 1 + 1									7	7
AD7		4	4		- 1									3	3
AD6		2	2		+ 2									4	4
AD5		10	10		- 2									8	8
Total AD		**33**	**33**											**33**	**33**
AST11															
AST10															
AST9															
AST8		1	1											1	1
AST7															
AST6															
AST5															
AST4		2	2		+ 2									4	4
AST3		2	2		- 2									0	0
AST2															
AST1		1	1											1	1
Total AST		**6**	**6**											**6**	**6**
SC6															
SC5															
SC4															
SC3															
SC2															
SC1															
Total SC		**0**	**0**											**0**	**0**
Overall Total		**39**	**39**											**39**	**39**

Contract Agents Grade	2018	2019
FG IV	2	2
FG III	12	12
FG II	1	1
FG I	0	0
Total CA	**15**	**15**

Seconded National Experts	2018	2019
	2	**2**

Annex I - IMI2 Call 17 topics text

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[25] 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[26].

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[27], 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)[28] is the main reference for the implementation of research priorities for IMI2 JU. The scientific priorities for 2018 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.

[25] 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.
[26] http://www.who.int/medicines/areas/priority_medicines/en/
[27] 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.
[28] http://www.imi.europa.eu/sites/default/files/uploads/documents/About-IMI/research-agenda/IMI2_SRA_March2014.pdf

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

Applicant consortia shall ensure that where relevant their proposals are in compliance with the General Data Protection Regulation (EU) 2016/679[29] and Clinical Trial Regulation (EU) 536/2014[30] (and/or Directive 2001/20/EC[31)] and any relevant legislation[32].

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[33], 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).

[29] 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.

[30] 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.

[31] 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.

32 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.

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

Topic 1: Optimising future obesity treatment

Topic details

Topic code	IMI2-2019-17-01
Action type	Research and innovation action (RIA)
Submission and evaluation process	2 stages

Specific challenges to be addressed

The prevalence of obesity is increasing and affects more than 650 million people of all ages to become one of the foremost global health threats [3]. Obesity is complex. We only have a crude understanding of its underlying causes and biology, how to best describe and define it. Defining obesity as a disease has been debated over the past years and it is still not recognised as such in many countries. However, obesity is included in the WHO classification system ICD10 under 'Endocrine, nutritional and metabolic diseases' [2][3]. Obesity can be preventable, but once it has occurred it is considered a chronic disease for which treatments/interventions are often inadequate. Currently we have no way of predicting who will respond to or benefit from what kind of treatment or intervention [4][34].

Obesity can seriously impair health through a broad range of complications such as cardiovascular disease, type 1 and 2 diabetes (T1D and T2D), cancer, musculoskeletal disorders, psychosocial imbalances, and reduced quality of life, and impacts the treatment of other conditions [5]. Weight reduction has been shown to have a positive effect on these co-morbidities and may increase the effectiveness of treatments specific for other co-morbidities. Lifestyle modification is an integral part of the weight management journey, but is often insufficient on its own, and can be complimented by pharmacological and surgical add-on treatments to achieve greater and more sustainable weight loss, as appropriate. It is likely that there are subgroups of patients that are more suited to certain types of treatment and results risk dilution of perceived efficacy unless these groups are identified and treatment is personalised. People with T1D have traditionally been thought to have low body mass index (BMI), but current research has shown otherwise [6]. The obesity prevalence in T1D is increasing faster than in the general population [7].

This topic focuses on multifaceted profiling of patients with obesity in order to define clinically meaningful and relevant subgroups as a premise for optimising future prevention and treatment of obesity and its complications. Stakeholders are expected to pool pre-existing observational and/or clinical data to establish a database with enough phenotypic granularity for a data-driven stratification of obesity into subgroups based on a set of operational parameters including subject characteristics, biomarkers[35] and questionnaires. The outcome of this proposal should work towards a common understanding and an aligned vocabulary among stakeholders to facilitate scientific, medical, economic, and political acknowledgement of obesity as a disease and the importance of weight loss and weight maintenance.

Need and opportunity for public-private collaborative research

This initiative, based on a public-private partnership, provides a unique scientific opportunity to address the challenges of maximising the efficacy of preventing and treating obesity. The major advantages of using the IMI platform are the ability to address these challenges in an independent effort, to engage with multiple stakeholders that otherwise might not interact in this context such as academia, patient organisations, clinical researchers, pharmaceutical industry, food, diagnostic companies including small and medium-sized enterprises (SMEs) with knowledge and interest in obesity and its complications. Recognised academics in this field and a range of companies with expertise in obesity and its complications approaching this topic from each their own individual angle would be needed to optimally analyse and interpret the large pool of data and impact the obesity landscape. The industry partners contribute with the necessary expertise to ensure that the scope

[34] In the context of this topic, treatment refers in a broad sense to a variety of different interventions for patients with obesity including lifestyle advice on appropriate diet and exercise alone or in combination with drugs or obesity surgery.

[35] Biomarkers should be understood in a wide sense, i.e. any measure that can be used for clinically meaningful and operational sub-classification of obesity, e.g. including the microbiome, should such data exist.

of the analysis is fit for the purpose of developing innovative treatment paradigms and medicines. The participation of patient organisations will ensure the relevance for patients and they should be actively consulted as a source of unique knowledge. Therefore, to ensure success of the action, it is important to engage with a broad range of stakeholders including patients, clinicians and decision makers.

Scope

The scope of the topic is to identify pathophysiologically and clinically meaningful subgroups of obesity that will allow for optimisation of prevention and treatment of obesity and its complications. Establishing (or revisiting) a robust sub-classification may include the current use of body mass index as the best anthropometric measure, or alternatively waist circumference or waist-to-hip ratio; it may include a direct or indirect measure for the duration of disease (e.g. acknowledging the difference between paediatric onset obesity and decades of metabolic insult); genetics, phenotypes, markers of fatty liver disease, characteristics of the gut microbiota, and epigenetics, to name a few.

More specifically the objectives of the topic are to:

- establish a federated database by pooling of the baseline data from pre-existing cohorts from observational or interventional studies to achieve as broad and detailed information on patients with obesity as possible, including sufficient clinical phenotyping and multi-omics data;
- perform data-driven analysis of the federated database to identify and characterise patient subgroups and potential biomarkers for diagnosis, prediction of the development of complications, and potentially inform on appropriate type of and response to treatment as well as identifying markers for effective weight management;
- fill the gaps of information regarding selected biomarkers by reanalysing pre-existing biobank samples. Such biomarkers should be affordable and operational in the context of real-world clinical practise and clinical development of innovative medicines and other treatments;
- address specifically type 1 diabetes (T1D) and type 2 diabetes (T2D) as examples of conditions in which both clinical phenotype and treatment is influenced by obesity in an intricate manner, including public education about obesity in T1D. While there is a lot of data available on obesity in relation to T2D, there is little on T1D and obesity, therefore one focus will be on generating new knowledge on T1D[36]. As part of this, data sets from the T1D Exchange programme will be available;
- collect and integrate patient perspectives in relation to diagnosis and treatment of obesity to understand the need, perceived barriers and value of determining medical treatment for patients with obesity;
- conduct a shared value analysis among key stakeholders reflecting values and challenges within the obesity landscape for optimising treatment and prevention. Engagement of external stakeholders is encouraged to generate educational material to support a common understanding of obesity. The content could include determinants and consequences of obesity including weight management.
- establish a Patient Advisory Board including representatives from patient organisations in order to ensure that patient-driven research and insights relevant for the project are identified and considered within and across the different work packages.

Expected key deliverables

The ambition is that the proposed topic should lead to:

- a federated database of pre-existing phenotypic characterisation that can be used for the funded action and sustained for future analysis (see below on estimate on size of database);
- a set of operational variables that can be used for stratification of obesity into clinically meaningful patient subgroups, i.e. subgroups that may require different or respond differently to treatment of obesity and its complications;
- a detailed description of the clinical characteristics and manifestations of the identified patients subgroups, and wherever possible any existing or expected differences in treatment preference, effect, size, and sustainability of the effect and safety;

[36] Corrigendum: applicants should note that the text under this bullet point has been updated to clarify the objective.

- an algorithm based on the set of operational variables that can be used to identify subjects that require and respond differently to prevention and/or treatment of obesity in clinical practice;
- description of the impact of obesity on T1D and T2D in terms of patient characteristics, clinical manifestation, treatment and outcomes, whether similar or different from non-obese patients with T1D or T2D. Use of corresponding data from the federated database is expected to be very useful to contrast or balance these findings;
- documentation of patient preferences regarding diagnosis and treatment of obesity;
- a shared value analysis among key stakeholders and the establishment of a common understanding and vocabulary about obesity as a disease.

Expected impact

Paving the way for an optimised and more personalised future obesity treatment, the identified patient subgroups should, where data are available, be analysed for treatment results, including weight loss and weight maintenance, and prevention and/or development of complications. Importantly, novel ways of defining and diagnosing obesity may also develop and detail the classification of obesity, and contribute to improving prevention, personalising health and lifestyle interventions, and weight management as well as the precision of evidence-based medicine and development of novel treatments. Deciphering the heterogeneity of obesity and the potentially differential effect of weight loss and weight maintenance should lead to:

- novel ways of describing and defining the obesity disease;
- potential for novel and innovative diagnostics for classification and evaluation of the obesity disease;
- increased understanding and respect for obesity as a chronic disease entity;
- increased potential to contribute to the development of more targeted prevention and lifestyle interventions;
- increased potential to develop targeted delivery of safe and effective treatments to clinically meaningful subgroups of patients with obesity;
- reducing the barrier of entry for innovative translational research and medicines development;
- improved clinical trial design;
- increased precision of evidence-based obesity medicine;
- better understanding of how to design effective measures to prevent and treat obesity based on its stratification into patient subgroups;
- increased understanding of the effect or lack of effect of weight loss on a broad range of obesity related complications;
- increased understanding of how obesity impacts other diseases as exemplified by impact on incidence, characteristics, treatment, costs, and outcomes of e.g. T1D.

Applicants should also demonstrate how their proposal will impact the competitiveness and industrial leadership of the European Union by, for example, engaging suitable SMEs.

Potential synergies with existing consortia

Applicants should take into consideration, while preparing their short proposal, relevant national, European (both research projects as well as research infrastructure initiatives), and non-European initiatives. Synergies and complementarities should be considered in order to incorporate past achievements, available data and lessons learnt where possible, thus avoiding unnecessary overlap, duplication of efforts and funding.

The action generated by this topic should consider initiatives such as previous IMI projects and other projects, consortia that have addressed the compilation of cohorts from legal/ethical and technical/analytical perspectives e.g:

EMIF (European Medical Information Framework) http://www.emif.eu/,

DIRECT (Diabetes Research on patient stratification) https://www.direct-diabetes.org/

RHAPSODY (for precision therapy and prevention of diabetes) https://imi-rhapsody.eu/

MetaCardis (the role of gut microbes in cardiometabolic diseases) http://www.metacardis.net/

Diogenes (Diet, Obesity and Genes)

http://www.diogenes-eu.org/; https://cordis.europa.eu/result/rcn/51783_en.html

Joint Programming Initiative Healthy Diet for Healthy Life (https://www.healthydietforhealthylife.eu/) with European Nutritional Phenotype Assessment and Data Sharing Initiative (http://www.enpadasi.eu/index.html and the two projects: Confronting Obesity: Co-creating policy with youth: https://cordis.europa.eu/project/rcn/216413_en.html and Science and Technology in childhood Obesity Policy: https://cordis.europa.eu/project/rcn/214762_en.html

Data from these projects within the obesity and diabetes areas could also be of importance for the current topic.

In order to have the same federated database platform, the applicants should also consider interacting with the project **EHDEN** resulting from the topic European Health Data Network IMI2 – Call 12[37], which will deliver an operational, federated network in order to have direct access to RWD for developing new or incremental services in healthcare area.
Likewise, IMI2 **PREFER** project should be considered regarding patient preference for preventive measures and treatment https://www.imi-prefer.eu/**.**

Industry consortium

The industry consortium is composed of the following EFPIA partners:

- Novo Nordisk A/S (lead)
- Boehringer Ingelheim
- Sanofi

In addition, the industry consortium includes the following IMI2 Associated Partners:

- Juvenile Diabetes Research Foundation (JDRF)
- Obesity Action Coalition (OAC)
- T1D Exchange

The industry partners will bring in-depth knowledge in the fields of clinical pharmacology and translational medicine, clinical data management, bioinformatics analysis, and of obesity. The industry partners will also provide know-how and means to support the establishment of the federated database including legal advice, setting up the database, and making analysis feasible, accessible and sustainable over time.

Limited supplementary funding could be made available for supporting further analysis of biobanked samples and development of digital tools to assist physicians in subgrouping of patients based on the outcome of the analysis (to be discussed by the full consortium).

The industry consortium will provide access to the following observational cohorts:

Gutenberg Health Study (Univ. Med. Center Mainz, Germany)

The Gutenberg Health Study (http://www.gutenberg-gesundheitsstudie.de/ghs/willkommen.html) [8] is a population-based, prospective, single-center cohort study including more than 15 000 subjects with 5-(completed) and 10 year (planned) follow-up that started in 2007 at the University Medical Center Mainz and is supported by Boehringer Ingelheim. Approximately 3 500 subjects with a BMI >30 kg/m^2 at baseline have been included. The study focuses on cardiovascular diseases, cancer, eye diseases, metabolic diseases, diseases of the immune system and mental diseases. The study aims at improving the individual risk prediction for diseases, and includes a comprehensive data set comprising anthropomorphic characteristics, general health status, disease status, and clinical chemistry parameters. In addition, DNA, citrate/EDTA plasma samples, serum and urine samples have been banked and are available for -omics analyses. Access is granted to the Gutenberg Health data after review of specific research studies proposed by the selected

[37] http://www.imi.europa.eu/sites/default/files/uploads/documents/IMI2Call12/IMI2_Call12_CallText.pdf

consortium and release by the GH Steering Committee. Support for data analysis of the Gutenberg Health Study, as well as further biomarker research/validation by omics methods analysis of bio-banked samples, will be provided by Boehringer Ingelheim.

The T1D Exchange database

The T1D Exchange clinical registry comprises data from about 35 000 children and adults with T1D in the U.S.; about 2/3 of adults and close to half of youth being overweight or obese. There is prospective 5-year-follow-up data and biosamples are available for a subset of the subjects [9][10]. The registry's aim is to characterise the population of adults and children with T1D in the U.S. with respect to diabetes history and medical history. The registry includes a comprehensive data set of anthropomorphic characteristics, general health status, disease and treatment status, and clinical chemistry parameters.

Anonymised data from clinical trial cohorts from industry partners can be made available supplementing the academic cohorts, e.g. for validation of findings or addressing specific research questions.

Indicative duration of the action

The indicative duration of the action is 60 months.

Indicative budget

The indicative in-kind and financial contribution from EFPIA partners and IMI2 JU Associated Partners is EUR 8 301 139.

This contribution comprises an indicative EFPIA in-kind contribution of EUR 7 100 000 and an indicative IMI2 JU Associated Partners in-kind contribution of EUR 1 201 139. The latter includes EUR 1 000 000 financial contribution provided by JDRF whose allocation will be decided by the full consortium at stage 2 when preparing the full proposal.

The financial contribution from IMI2 JU is a maximum of EUR 8 301 000.

Applicant consortium

The applicant consortium will be selected on the basis of the submitted short proposals. The applicant consortium is expected to address all the research objectives and make key contributions to the defined deliverables in synergy with the industry consortium, which will join the selected applicant consortium in preparation of the full proposal for stage 2. This may require mobilising, as appropriate, the following:

- existing research activities either within public health or clinical services in the field of obesity treatment with interests in better defining phenotypes of obesity and their responses to treatment, and;
- expertise in e.g. anthropology, epidemiology, public health, health economics, data management and harmonisation, bioinformatics, systems medicine or multi-omics analysis, lifestyle treatment, public relations; healthcare professionals skilled in obesity care and/or research;
- access to general databases of obesity including both obese with or without T1D and T2D. In addition, since T1D is often juvenile onset and T2D is now becoming more frequent in adolescents, special attention should be paid to including childhood obesity cohorts;
- access to pre-existing clinical cohorts (expected total number from public and private data sets n=50 000) with as broad and detailed relevant phenotyping as possible and access to biobanked specimens for selected biomarker analysis wherever available (including documented informed consent), ideally including both childhood and adult cohorts across different ranges of obesity and when relevant different treatment approaches

The involvement of patient organisations is imperative to making findings relevant. They should be involved at least as advisors to the analysis and interpretation, and as advocates for the community outreach. In addition, the results from the project should be discussed in a dialogue with regulators.

Relevant SMEs with proven expertise are encouraged to participate in the applicant consortium. SMEs can be of great benefit to IMI projects and, inter-alia strengthen the competitiveness and industrial leadership of the European Union. Their involvement might offer a complementary perspective to industry and academia, and

strengthen the long-term impact of the project. For these reasons, applicants should consider engaging SMEs throughout the proposal. Under this topic, the contribution of SMEs could be considered in providing expertise and activities such as data and knowledge management; project management with expertise and experience relevant to IMI2 JU/H2020 projects.

Suggested architecture of the full proposal

The applicant consortium should submit a short proposal which includes their suggestions for creating a full proposal architecture, taking into consideration the industry contributions and expertise provided below.

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.

The below architecture for the full proposal is a suggestion. The architecture of the full proposal should be designed to fulfil the objectives and key deliverables within the scope of this proposal. However, there are already from the participating partners some cohorts and data available that the applicants may want to consider how to include and analyse. A plan for aspects related to sustainability, facilitating continuation beyond the duration of the action should also be proposed.

In addition to being an active contributor to the key deliverables of the relevant work packages, the participating patient organisations will support communication internally and help disseminate information externally. The Patient Advisory Board is expected to meet with work package leads four times a year, either in person or via a teleconference. Both industry and academic partners are expected to contribute to Patient Advisory Board activities, and thus funds should be reserved for this purpose.

Work package 1 – Project management

The goal of this work package is the overall project coordination including:

- financial management and monitoring of deliverables and milestones;
- legal and contractual management;
- ethics management.

Work package 2 – Data federation and database management

The goals of this work package are as follows:

- provision of pre-existing observational and/or clinical data from obese and obesity-risk cohorts;
- provision of multi-omics data, where possible;
- converting data from different cohorts into a standard format;
- perform a quality control of biobanked cohort samples, before these are analysed for additional biomarkers (i.e. ensure standardised quality and fitness-for-purpose of the samples);
- harmonisation of anonymised and converted data into a common structure to be able to be pooled;
- making data accessible to database for analysis;
- construction of a federated database and establishment of suitable database analysis tools;
- database management and administration of users, permissions and security;
- ensure legal issues including data sharing agreements;

- develop plan for sustainability of database and ways to ensure creation of value from the project results beyond the project period.

Work package 3 – Systems biology and data analysis

The goals of this work package are as follows:

- setup of a web portal and tools enabling analysis and visualisation of data, including an Application Programming Interface (API) for programmatic access for data analysis;
- perform integrative analysis across data sets and cohorts to identify the patient sub-groups;
- comparison of patient cohorts and identifying relevant gaps and biosamples for analysis;
- perform additional biomarker analysis in bio-banked samples for relevant gaps identified;
- identify and/or establish assays for analysis of biosamples.

Work package 4 – Analysis of T1D, T2D and obesity

The goals of this work package are as follows:

- epidemiology: determine prevalence of overweight/obesity among people with T1D, T2D and obesity in general population, by demographic group (age, income, ethnicity), by lifestyle (diet, exercise frequency, etc.);
- characterisation of the obese phenotype in T1D, T2D and obesity;
- determine how obesity and its converse, weight loss, affect T1D, T2D and obesity disease characteristics, treatment effectiveness, clinical outcomes;
- identify mechanisms underlying the effect of obesity on T1D, T2D and obesity metabolism and outcomes toward the goal of developing improved treatments in the future;
- assess the effects of long-term obesity in people with T1D, T2D and obesity, and 'metabolic memory' phenotypes conferred by obesity that may persist even after weight loss;
- assess whether any of the above is distinct for T1D due to the autoimmune milieu and whether specific therapeutic strategies should be targeted or not;
- weight management in T1D, T2D and obesity: determination of effective therapeutic and lifestyle interventions for obesity prevention and weight loss in people with T1D, T2D and obesity;
- communication of findings to the public to educate all customers about T1D, T2D and obesity and to increase citizen and patient involvement in identifying relevant approaches and optimising study design.

Work package 5 – Patient preferences

The goals of this work package are as follows:

- collection and generation of information on patient preferences in relation to the need, value and assessment of obesity treatment, taking the social, cultural and other environment of the patient into account;
- apply an analytic mindset and tools to synthesise a patient perspective to ensure the relevance and value to patients across the project. Liaise and collaborate with patients and key stakeholders to facilitate outcomes and learnings including educational material with relevant patient organisations.

Work package 6 – Shared value analysis and communication

The goals of this work package are as follows:

- establish a network consisting of key internal and external stakeholders to engage in collaboration around obesity from public health and payers' perspective;
- conduct a shared value analysis to extract common values and challenges. Based on this analysis, generate a shared value package/communication to reflect current thinking among stakeholders;

- engage across work packages to shape communication and deliverables as relevant to address public health perspectives and support knowledge about obesity, prevention and treatment opportunities.

Industry contribution

In summary, the industry consortium will provide the following to the project:

- access and support for analysis of the Gutenberg Health Study;
- access to the T1D Exchange data;
- anonymised data from clinical trial cohorts from industry partners supplementing the academic cohorts;
- in-depth knowledge in the fields of clinical pharmacology and translational medicine, clinical data management, bioinformatics analysis, and of obesity;
- know-how and means to support the establishment of the federated database including legal advice, setting up the database, and making analysis feasible, accessible and sustainable over time;
- limited supplementary funding for supporting further analysis of biobanked samples;
- limited supplementary funding of development of digital tools to assist physicians in subgrouping of patients based on the outcome of the analysis;
- management of the consortium including the Patient Advocacy Board.

Expected Applicant consortium contribution:

In summary, the applicant consortium is expected to provide the following:

- pre-existing cohort data from patients with obesity and data from comparative non-obese patients;
- biobanked samples for analysis;
- data-driven analysis tools and expertise;
- follow-up analysis of data and definition of further biomarker analysis needs;
- generation of a subgrouping tool, e.g. an application based on a diagnosis algorithm including a measure of the confidence level of the suggested subgroup;
- bioinformatic expertise;
- public-health and public relations skills;
- capability of omics analysis;
- access to validated platforms for analysis of bio-samples;
- assay development;
  - data reformatting and harmonisation.

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Topic 2: Open access chemogenomics library and chemical probes for the druggable genome

Topic details

Topic code	IMI2-2019-17-02
Action type	Research and innovation action (RIA)
Submission and evaluation process	2 stages

Background and specific challenges to be addressed

In biomedicine, discoveries arising from novel enabling technologies and reagents have garnered a quarter of the Nobel Prizes for chemistry and medicine in this century. Among the myriad of these transformative techniques and reagents, bibliometric evidence shows that pharmacological modulators (chemical and biological probes) have both the greatest scientific citation impact, the greatest sway on exploratory biomedical research, and provide the best mechanism to understand the relevance of a protein as a potential drug target [1][1]. Indeed, the field of drug discovery and the development of new molecular entities are predicated on the availability of sound mechanistic principles. Unfortunately, our understanding of human disease remains inadequate, and as a result clinical success rates for novel mechanisms remain low. Currently only one out of ten clinical drug candidates reaches the Open Access Chemogenomics Library and Chemical Probes for the Druggable Genome market after an average of 10 years and at a cost of at least EUR 2 billion in R&D expenses per drug.

Ultimately, the most effective method of dramatically improving the efficiency of R&D is to initiate studies on the ‘right’ target, and this is possible only if we dramatically increase our understanding of disease mechanisms. Experts agree that genetics and big data are promising approaches to select the right target, the appropriate biomarkers and the patients that are most likely to respond to any given treatment. However, this promise is a long way from reality in most cases; experience has shown there still remains a difficult path from prioritising a candidate gene with human genetics through to a successful R&D project [1][2].

We urgently need to close the gap between establishing a genetic link and the underlying disease mechanism for potential drug targets, and, to this end, we believe that there is an immediate need to design a set of open access (*i.e.* unencumbered and free of intellectual property restrictions) chemical compounds for the entire druggable genome. The set, which would comprise an openly accessible chemogenomics library and selected high-quality chemical probes will provide scientists across the world with the tools to interrogate and validate independently new candidate genes identified by modern genetic studies and bioinformatics in a variety of informative biological systems [1][3][1][4][1][5][1][6][1][7] among which advanced, patient-derived assays will be the most relevant.

Need and opportunity for public-private collaborative research

The creation of an open access set of tools with which to interrogate the entire druggable genome is a challenge of scale and breadth that cannot be solved by a single institution. Moreover, a partnership between EFPIA members, mid-sized companies, Associated Partner organisations, academia and SMEs will be essential to achieve this goal, as these institutions have complementary resources and expertise necessary for success. For example, industry has extensive medicinal chemistry and screening facilities, but these capabilities must be used in the context of biological validation, most commonly performed in academia. Access to patient samples that are genotyped and accompanied by their clinical histories must be accessed by involving physician scientists in academic institutions. New technological and experimental approaches will also be needed to speed up the process of creating new tool compounds. We also believe that impact is dependent on open science because a pre-competitive, shared risk investment model will allow the partnership to provide the wider community access to the generated reagents quickly and with no strings attached, thus amplifying its impact. Moreover, open science also better assures adherence to high standards of quality and the reproducibility of results (a major issue in biological research), with concomitant increases in productivity and innovation. Finally, through a public-private partnership, both funding and expertise will be highly leveraged.

Scope

Currently, the druggable human genome is estimated to consist of at least 3 000 genes. This topic aims to generate potent, well-characterised, functional, small-molecule modulators for a significant number of these and, at the same time, lay the foundation for identifying a set of openly accessible (i.e. unencumbered from restrictions on use) tool compounds for the entire druggable human genome. With this set of chemical tools available, scientists will be poised to interrogate the latest findings emerging from big data approaches and human genetic studies, thus compressing time from gene discovery to target prioritisation, and ultimately to patient benefits. Importantly, although we imagine the consortium can make great progress by assembling and characterising pre-existing compounds into an initial chemogenomics set, this is not enough. It is imperative to fill the significant gaps by discovering and developing novel chemical tools/probes against under-studied proteins (or protein families) that may be involved in the initiation and progression of disease.

The overall aim of this topic will be as follows:

- establish a framework to assemble an open-access chemogenomics library for the druggable genome – namely a physical library supported by compound meta-data;
- further enrich the open access library by inventing new, deeply characterised chemical probes to selected specific protein families;
- develop open-access assays from well characterised human disease tissue with a special emphasis on immunology, oncology (including immune-oncology) and neuroscience to profile the chemical tools and chemical probes;
- establish sustainable infrastructure, with high priority on accessible platforms and appropriate governance, for prolonged discovery and dissemination of tool compounds, assays, and associated data, beyond the lifetime of this project;
- develop a communication plan to facilitate the dissemination of the compound sets and to ensure their appropriate use.

N.B. A chemogenomics library describes the use of target family-directed chemical libraries in target or cell-based assays as a means of accessing new areas of biology and accelerating drug discovery research based on the assumption that similar receptors bind similar ligands. Such sets, although containing compounds that individually do not fulfill the stringent criteria of a chemical probe, can still be used to interrogate multiple members of protein families to help prioritise the most therapeutically relevant ones that could then form the basis of a chemical probe project. In contrast, a chemical probe is a small molecule that modulates the function of a protein in a specific and selective way. The compound must exhibit a defined *in vitro* potency for a single target and possess a minimum 30-fold selectivity relative to other sequence-related proteins of the same family. Furthermore, the probe must be profiled against a standard selection of other unrelated, pharmacologically relevant targets and large protein families of relevance to drug discovery (specificity), and, finally, have demonstrated on-target effects in cells (cellular activity).

Expected key deliverables

The consortium will generate an open access chemogenomics library consisting of about 5 000 compounds that cover roughly 1 000 protein targets (i.e. one third of the current druggable genome). Here, the term open access includes not only the right to publish findings using these tools, but also includes the unencumbered and pre-publication dissemination of the results, the tools themselves, the assay protocols, and all the associated data packages. This open access chemogenomics set will serve as a substantial head start on generating a library covering the entire druggable genome. In addition, the consortium will develop chemical probes for two to three jointly agreed target families with an initial focus on E3 ligases and solute carriers (SLCs), which may be carried out in partnership with existing IMI consortia, such as ReSolute. For this component, up to 100 novel, well characterised, high-quality chemical probes, as defined by leaders in chemical biology [1][5][1][6][1][7][1][8] are intended to be generated. To achieve this goal, the consortium will generate recombinant proteins, solve crystal structures, and establish all biochemical and cellular assays needed to ensure that the probes meet the established stringent quality criteria, including target engagement in cells [1][9]. Finally, the consortium will develop scientific and sociological mechanisms to extract biological and disease information from the chemogenomics libraries and chemical probes – and their targets. Given the technical issues that plague interpretation of data from established cell lines, we strongly believe that this will depend on accessing more relevant assays through which to profile the compounds. These assays must be shown to be reproducible, to be derived from genotyped and deeply phenotyped patient-derived tissue and the results to be made available broadly, so that biological data from all the assays can be combined and mined [1][10]. The partnership is

expected to develop around 20 novel human tissue-derived assays in three major therapeutic areas of immunology, oncology (including immune-oncology) and neuroscience and test tool molecules and chemical probes in these assays.

Project success will require the partnership to establish enabling infrastructure to generate the probes. This includes cell and biochemical assay panels for characterisation of the compounds, including off-target analysis, a complementary database and a modern, scalable compound store and compound logistics. In addition, the partnership must explore new technologies in the field of fragment-based screening and high-throughput proteomics to accelerate the process of tool compound generation and characterisation. Finally, the consortium will set up platforms that permit broader access to these technologies both from within and outside the consortium – so the community can participate and help achieve, or exceed, the projects goals.

With this proposal, it is planned to lay the foundation on which to build and organise a worldwide network of laboratories to generate chemical tools for the entire druggable genome. Outstanding scientific leadership will be required in order to achieve this vision. It is also envisaged that this endeavor will help identify new scientific opportunities, identify and build strategic partnerships with other projects (e.g. patient groups, international consortia, other IMI projects), and promote truly openly accessible science.

The chemogenomics library, the chemical probes, and the accompanying metadata (potency, selectivity, activity in cell-based assays) are intended to be open access, i.e. use of the compounds will be made available unencumbered, in a pre-publication state and free from restrictions on use. After quality control, assays and data generated by the consortium will also be made publicly available without restrictions. In addition, technologies developed throughout the project must be likewise non-exclusive, platform-oriented, ready for application, openly and freely available for use, dissemination, and commercialisation during and following the completion of the project. Finally, as part of a sustainability concept, the partnership will provide non-exclusive access to the synthetic routes of these compounds to large and/or mid-size vendors that are willing to distribute the chemogenomics library and/or chemical probes and their controls worldwide.

Expected impact

This project will provide the wider academic community with unencumbered access to the highest quality tool compounds for a large number of novel targets, and the expected impact should therefore be transformative. Presently, many companies and organisations are already in the process of setting up their own chemogenomics libraries. Although these have the potential to be phenomenal resources for the companies, their utility is also limited: they are not widely available to academia, they are likely to overlap, and each compound set is not as deeply characterised as could be managed within a larger, more focused, more resourced and more transparent project. By making a high-quality, broader compound set available, the consortium will seed a massive community target prioritisation and target deconvolution effort [1][2]. Moreover, in providing chemical tools without restriction, the consortium will also make available tools to invent new assays and unencumbered starting points for probe development or drug discovery. The consortium's centralised, cell-based and biochemical assay panels will serve as a resource for the entire chemical biology community. The ability to access these capabilities will provide significant incentives for external scientists to contribute innovative compounds to the network, thus expanding the impact with donated resources. The cell and tissue platform with the high-quality, patient-derived cell assays will provide the opportunity for clinical scientists to undertake translational medical research and biomarker discovery, and will provide the roadmap for other clinical centers to access the libraries and make important translatable discoveries.

The availability of chemical probes to unprecedented targets will also open up exciting new research avenues. As an example, open access, novel E3 ligase binders will provide much needed starting points for the development of new protein-targeting chimeras (PROTAC). In addition, the research strategies undertaken in this topic may serve as a template for the technology development to expand the project to include tool generation for areas of the genome currently not considered as druggable.

The management and data infrastructure and the assembled global collaborative network will lay the foundation for unparalleled progress in providing high-quality, open-access tool compounds as a basis for reproducible research. Indeed, this topic has the potential to cause a fundamental shift towards a more open and pre-competitive approach to the costly field of target prioritisation and discovery without compromising the proprietary research models required in industry. Finally, the significant amount of freely accessible, high-quality data generated within this consortium will be a rich source for future analyses by data scientists. Artificial intelligence and machine learning applications using high-quality data on highly diverse compounds

across many pharmacological mechanisms will spur research in new fields of biology and generate a source of targets for proprietary projects in various therapeutic areas.

Open access – additional dissemination obligation

Considering the specific nature of this topic, it foresees application of an additional dissemination obligation (IMI2 JU MGA art. 29.1). All results of this project will be made available to the scientific community by open access (i.e. unencumbered, pre-publication, and free from restriction on use). Open access parameters include not only the right to publish findings using these tools, but also the right to disseminate the tools, results, assay protocols, and all the associated data packages, including cell-based assays.

Potential synergies with existing Consortia

Applicants should take into consideration, while preparing their short proposal, relevant national, European (both research projects as well as research infrastructure initiatives), and non-European initiatives. Synergies and complementarities should be considered in order to incorporate past achievements, available data and lessons learnt where possible, thus avoiding unnecessary overlap and duplication of efforts.

Therefore, the synergies with the following past and ongoing IMI1 & IMI2 projects could be considered by the applicants:

- Unrestricted Leveraging of Targets for Research Advancement and Drug Discovery (ULTRA-DD): https://www.imi.europa.eu/projects-results/project-factsheets/ultra-dd
- Research Empowerment on Solute carriers (ReSOLUTE): https://re-solute.eu/
- Open PHACTS (terminated): https://www.imi.europa.eu/projects-results/project-factsheets/open-phacts

Please note that during the project implementation phase the applicants could also consider other potential knowledge generated by the forthcoming projects under IMI2 JU:

- European Screening Centre: unique library for attractive biology (ESCulab): https://www.imi.europa.eu/sites/default/files/uploads/documents/apply-for-funding/open-calls/IMI2_Call12_CallText.pdf
- Development of a platform for federated and privacy-preserving machine learning in support of drug discovery: https://www.imi.europa.eu/sites/default/files/uploads/documents/apply-for-funding/call-documents/imi2/IMI2%20CALL%2014%20TOPICS%20TEXT_EN.PDF

Synergies with the following European and international initiatives could also be highly relevant:

- Structural Genomics Consortium (SGC, https://www.thesgc.org/) that has in depth expertise concerning all aspects of this proposal;
- US National Institutes of Health initiative, Illuminating the Druggable Genome (https://ncats.nih.gov/idg), which will provide the bioinformatics tools to help improve the understanding of the properties and functions of proteins that are currently not well studied within commonly drug-targeted protein families;
- European Bioinformatics Institute (EMBL-EBI, https://www.ebi.ac.uk/) for data handling and analyses;
- Open Targets (https://www.opentargets.org/) for target identification;
- H2020 iNEXT consortium (https://cordis.europa.eu/project/rcn/194892_fr.html) for fragment screening;
- H2020 OpenRiskNet (https://cordis.europa.eu/project/rcn/206759_fr.html) for compound design;
- ERIC EU-OPENSCREEN (www.eu-openscreen.eu) for screening;
- ESFRI-consortium ELIXIR (www.elixir-europe.org) for sustainable infrastructure for biological information;
- ERIC INSTRUCT (www.instruct-eric.eu) for structural biology infrastructure.

Industry consortium

The industry consortium is composed of the following EFPIA companies:

- Bayer (project co-lead)
- Boehringer Ingelheim (project co-lead)
- Pfizer
- Servier
- Takeda

As part of this endeavour, each pharmaceutical industry partner is willing to contribute at least 10 high-quality chemical probe compounds from their current or previously terminated R&D projects; at least 50 chemogenomics tool compounds from their own compound collections; and support the development of a minimum of 5 chemical probes by in-kind (especially chemistry).

In addition, the industry consortium includes the following IMI2 Associated Partners:

- Diamond Light Source (UK)
- Ontario Institute for Cancer Research (Canada)
- The Montreal Neurological Institute at McGill University (Canada)
- The Royal Institute of Technology (Sweden)

Indicative duration of the action

The indicative duration of the action is 60 months.

Indicative budget

The indicative in-kind and financial contribution from EFPIA partners and IMI2 JU Associated Partners is EUR 30 257 000.

This contribution comprises an indicative EFPIA in-kind contribution of EUR 23 800 000, of which EUR 9 930 000 financial contribution to the beneficiaries receiving JU funding in the selected action and an indicative IMI2 JU Associated Partners in-kind contribution of EUR 6 457 000.

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.

The financial contribution from IMI2 JU is a maximum of EUR 27 935 000.

Applicant consortium

The applicant consortium (academic groups and SMEs) is expected to demonstrate expertise, leadership and a proven track record in all scientific areas addressed in the topic, including:

- adherence to open-access principles, and expertise in developing and managing open-access projects, which are essential to provide unencumbered and pre-publication access to the chemogenomics tools, chemical probes, patient-derived assays, and associated data packages to the scientific community free of any restrictions on use;
- expression, characterisation and structure determination of soluble proteins, integral membrane proteins, and protein complexes in an integrated project at large scale;
- assay development across a large number of different proteins and protein classes, including cell-based target engagement assays;
- screening compound libraries at scale, using a variety of approaches including high-throughput, focused, computational, fragment and DNA-encoded libraries;

- ‘hit-to-probe’ capabilities, including using structure-guided methods to improve efficiency and systematic characterisation in relevant biophysical, biochemical, and especially cellular/phenotypic assays;
- strategies to systematically map the knowledge space of protein families, including developing computational approaches and physical reagents to facilitate cross-screening;
- generation, characterisation and dissemination of chemogenomics libraries, including systematic compound characterisation *in vitro* and in cells;
- establish quality-control metrics and both demonstrate and record their use in practice, including mechanisms to solicit independent input into quality;
- development of innovative technologies to speed up the generation of tool compounds, and innovative approaches to accelerate their wider adoption in academia and industry;
- development of strategies to ensure that chemical probes are appropriately used by the community in biological assays;
- track record of scientific success in partnerships with clinical centres, and success in managing contracts and ethical issues;
- track-record of obtaining project-specific ethical approvals for clinical research collaborations;
- using patient-derived samples to advance drug discovery in close cooperation with industrial partners, including the development of novel assays.

SMEs can be of great benefit to IMI2 JU actions and can strengthen the competitiveness and industrial leadership of the European Union. Their involvement in the action might offer a complementary perspective to industry and the academia, and help deliver the long-term impact of the funded action. For these reasons, applicants should consider engaging SMEs throughout the proposal. For example, under this topic, the contribution of SMEs would be considered beneficial for broad profiling of chemogenomics compounds and chemical probes.

Members of the applicant consortium are also expected to demonstrate excellence and a proven record of accomplishment (evidenced by collaborative publications) in establishing networks of recognised thought leaders in all relevant sectors indicated in the topic, including:

- a global network that spans medicinal chemistry, biological assays, human biology, experimental medicine and clinical research;
- proven track record of achieving high-value/high-impact outcomes catalysing research in pioneer target areas of drug discovery;
- ability and history of leveraging additional funds with diverse and international organisations, including patient groups, foundations, philanthropy and SMEs;
- history of making research output widely available and evidenced commitment to open science principles;
- mechanism in place to efficiently and effectively disseminate chemical and biological research materials (e.g. chemical probes, protein constructs, antibodies).

Members of the applicant consortium are expected to have successfully collaborated with a network of scientific researchers especially with industry and should demonstrate:

- previous impact on launching or adding value to internal drug discovery projects in the pharmaceutical industry;
- previous impact on providing the foundation for experimental medicine studies in the public sector;
- previous success in collaborations among networks of academics and SMEs – as evidenced through shared projects and co-authored publications;
- previous success in governing and managing large projects, including e.g. finance, intellectual property and inter-institutional contracts;

- a track record of consistently achieving (or even exceeding) milestones and deliverables on time and within budget;
- a track record of making new technologies widely available, for example as generally accessible platforms or commercial products;
- experience in managing varying interests of multiple stakeholders.

Suggested architecture of the full proposal

The applicant consortium should submit a short proposal that includes their suggestions for creating the full proposal architecture, taking into consideration the industry contributions and expertise provided below.

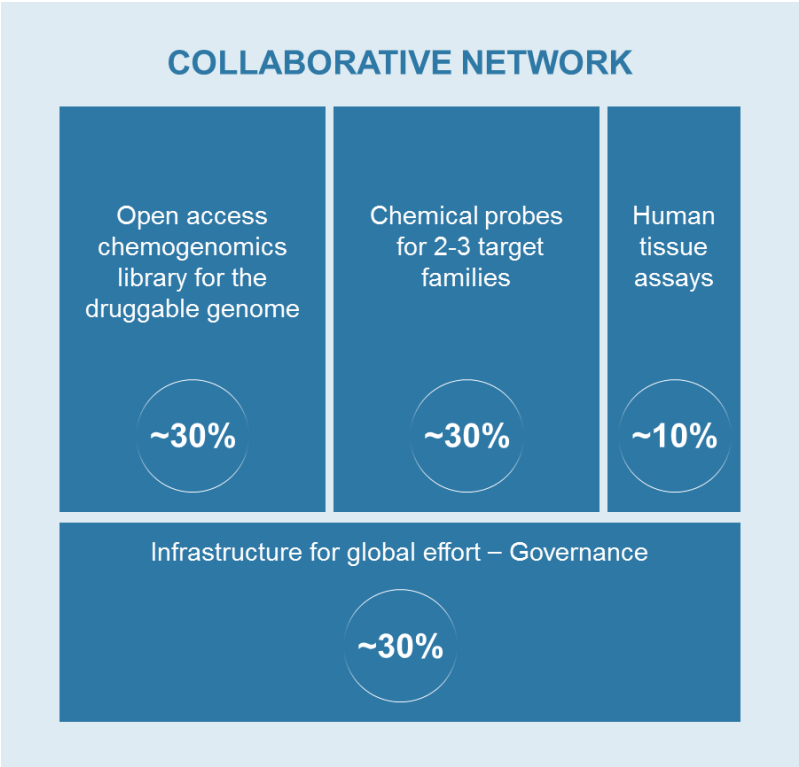
In the spirit of the partnership, and to reflect how IMI2 JU call topics are built on identified scientific priorities agreed together with EFPIA beneficiaries/large industrial beneficiaries, these beneficiaries intend to significantly contribute to the programme and project leadership as well as project 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.

The full consortium will define project aspects such as governance, guiding principles and project plan. The architecture below for the full proposal is a suggestion.

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

The planned endeavour consists of four parallel pillars that include an underlying sustainable network infrastructure. The expected resource distribution to the four pillars is indicated below (% of overall resources):



Pillar 1 – Open-access chemogenomics library for the druggable genome

In the first pillar, it is planned to establish a chemogenomics library consisting of compounds meeting predefined target-specific criteria (biochemical activity, selectivity, physico-chemical profile sufficient for cell-based assays, evidence of cellular target engagement and no general cytotoxicity). To ensure transparency and quality, acceptance of compounds into this library will be governed by an arm's length committee of independent experts from academia. The acceptance criteria for Pillar 1 compounds (e.g. selectivity, potency) will not be as stringent as for chemical probes (Pillar 2 compounds), but because of the extensive annotation, Pillar 1 compounds will be very valuable for target prioritisation, target deconvolution, and as starting point for chemical probes. They will also enable a fast-track approach to develop drug leads for exciting new targets.

The following work packages are planned to achieve Pillar 1 goals:

Work package 1 – Collection of available compounds from academia and industry

Deliverables: 30-100 mg of pure material for ~2 000 compounds identified and collected from the following sources meeting predefined criteria:

- compounds (1 000-2 000 compounds covering a variety of targets) identified and collected from known literature compounds;
- inclusion of openly available chemogenomics compound sets that fulfil stringent quality criteria;
- acquisition of compounds provided by participating pharmaceutical companies (at least 50 per participating EFPIA partner);
- compounds for selected target families generated within this IMI2 project (see Pillar 2);
- establish an independent review mechanism to assess the quality of the compound to be included in the set.

Work package 2 – Annotation of library compounds

Deliverables:

- data packages necessary to enable use of the compounds in pre-clinical studies by scientists globally;
- making data available to the scientific community via a publicly accessible database (see Pillar 4, work package 10), either generated within the consortium, or in collaboration with an existing public partnership.

Work package 3 – New methods for chemogenomics compound generation and profiling

Deliverables:

- protocols for novel and broadly applicable assay principles for biochemical, biophysical and cell-based assays to speed up generation of chemogenomics compounds and their characterisation;
- broadly applicable, novel technological and experimental approaches with the potential to speed up the hit-to-probe process by more than 6 months;
- generation of the remaining 2 000 to 3 000 compounds needed to cover one third of the druggable genome (assumption: 5 000 compounds needed to cover 1 000 targets, i.e. 1/3 of the druggable genome);
- establishing the strongest possible chemogenomics open source network of collaborations, allowing efficient sourcing of externally generated high-quality chemogenomics compounds and sets.

Industry and Associated Partner contribution to Pillar 1:

- provide at least 50 chemogenomics compounds per EFPIA partner from proprietary compound collections as open access chemogenomics compounds; solid material for testing;
- compound profiling in established assay panels that are available within the companies;
- access (free of charge) to the Diamond Light Source (Associated Partner) platforms for external groups contributing to the project deliverables;
- membership in scientific and decision-making committees (e.g. definition of target family-specific criteria and assessment of candidate compounds).

Expected applicant consortium contribution to Pillar 1:

- develop tools to identify chemogenomics compounds from patents, scientific publications and other sources;
- synthesis to provide solid material of chemogenomics compounds for testing;
- provide compound profiling to confirm that they meet the agreed upon criteria;
- experience in high-throughput, fragment-based screening;
- experience in covalent-ligand chemoproteomics approaches;
- assemble the remaining 2 000 to 3 000 chemogenomics compounds to cover one third of the druggable genome via internal activities or through collaborations and/or crowdsourcing;
- characterise selected compounds by determining three-dimensional protein-small molecule complex structures to high resolution and accuracy;
- membership in scientific and decision-making committees (definition of target family specific criteria; assessment of candidate compounds);
- manage independent peer-review mechanism to assess suitability of compounds for inclusion in the set.

Pillar 2 – Chemical probes for 2 – 3 emerging target families

For the second pillar, the aim will be to generate chemical probes for proteins within a minimum of 2-3 priority target families of high therapeutic interest. The initial priority will be on E3 ligases and solute carriers (SLCs), although we will not limit the scope to these target families. E3 ligases and SLCs were selected as initial priority families due to their high therapeutic importance, coupled with their relative intractability. This combination makes them ideally suited for a consortium-based approach for developing high-quality chemical tools. The inclusion of other target families will be agreed jointly by the consortium.

The number of chemical probes generated per family will depend on a number of considerations, including the strength of the genetic links to disease, experimental feasibility, therapeutic potential, as well as the number of members of the target family class. While working on probe projects, the consortium will also generate compounds that may not meet the stringent probe criteria but will be valuable as chemogenomics compounds thereby enriching the collection described in Pillar 1.

The following work packages are planned to achieve Pillar 2 goals:

Work package 4 – Protein production

Deliverables:

Validated protein expression clones, protein purification protocols, recombinant proteins for assay development and for 3D-structure determination; recombinant antibodies to facilitate assay development.

Work package 5 – Assay development for target engagement

Deliverables:

- protocols for target-specific biophysical, biochemical and cell-based assays and use of those assays for probe generation and confirming target engagement;
- genetically-engineered cell lines (such as knockout cells) to inform on target selectivity.

Work package 6 – Structure determination and chemical starting matter

Deliverables:

Generation of protein structures necessary to support probe generation. Depending on the target families selected, protein structures for both soluble and membrane proteins will be required. All protein structures generated in this project will be deposited in the Protein Data Bank (https://www.wwpdb.org/). In addition, fragment screens will be conducted to identify starting points for probe generation.

Work package 7 – Generation of chemical probes

Deliverable:

At least 100 well-characterised chemical probes, meeting stringent criteria for potency, selectivity and with demonstrated on-target effects in cells. This WP includes medicinal chemistry capabilities.

Work package 8 – Technology development

Deliverables:

Development of transferrable technologies for broadly applicable methods to speed up probe development and characterisation along the whole value chain from target selection to probe characterisation. This will include (but not exclusively) automation approaches, cloud-computing platforms, algorithms, parallelisation, reagents, devices, protocols and documentation.

Industry and Associated Partner contribution to Pillar 2:

- design and access to fragment or other bespoke libraries;
- access to larger compound screening collections;
- high-throughput screening (HTS) or focused screens to identify hits;
- crystal-based fragment screening at Diamond Light Source (Associated Partner);
- access (free of charge) to the Diamond platforms for external groups contributing to the project deliverables;
- expertise in triage and validation of screening hits;
- design and synthesis of research chemical probes;
- medicinal chemistry to optimise hits;
- protein expression and purification for selected priority targets;
- assays (e.g. selectivity screening panels) and structure determination to support probe development;
- establish quantitative chemical probe criteria, in conjunction with the applicant consortium.

Expected applicant consortium contribution to Pillar 2:

- ability to access chemical libraries from leading academic chemists and chemical biologists;

- small- and medium-scale screening of EFPIA partner chemical libraries;
- secondary biochemical screens to validate and prioritise hits;
- off-target biochemical and cell-based screens;
- crystallographic fragment screening and protein-ligand structure determination to support probe development;
- design and synthesis of chemical probes;
- medicinal chemistry to optimise hits;
- assays (e.g. selectivity screening panels) and 3D-structure determination to support probe development;
- high-throughput cloning, expression, purification, and novel 3D structure solution (if necessary);
- established quantitative chemical probe criteria, in conjunction with industry;
- technology development to improve quality and speed up the development and dissemination of chemogenomics compounds and of chemical probes.

Pillar 3 – Human tissue assays

All chemical probes and selected chemical tools will be subjected to unbiased phenotypic screening in patient-cell-derived assays for target validation in the human disease context. Specific assays will be in new and emerging areas of immunology (e.g. inflammatory bowel disease, scleroderma, interstitial lung disease, lupus, arthritis, and fibrosis in different organs), oncology (including immuno-oncology) or neurological areas (e.g. neuroinflammation and neurodegeneration). Assays developed previously in the Ultra-DD and other IMI programs might be leveraged and expanded to include new and emerging areas of research.

The following work packages are planned to achieve Pillar 3 goals:

Work package 9 – Human tissue assays

Deliverables:

- develop at least 20 novel human tissue-derived assays in three major therapeutic areas of immunology, oncology (including immune-oncology) and neuroscience. Selected established high-quality translational assays will be optimised and miniaturised and others (such as more complex co-culture systems) will be developed within the project;
- validate these assays by using tool molecules and test chemical probes, including gold-standard positive and negative controls. The cell-based assays will be derived from human material, such as blood and tissue biopsies;
- when possible and if scientifically appropriate, the consortium will convert primary cells into a renewable resource, such as human stem cells and spheroids as well as organoids;
- both primary and stem-cell derived cells will be deeply characterised phenotypically, and to the extent possible within the funding frame, also characterised by deep -omics technologies.

Industry and Associated Partner contribution to Pillar 3:

- contribute high-quality compounds for screening in these biological assays;
- provide scientific expertise and advice to support setup and develop the human tissue assays (including details on protocols, throughput formats and patient-genetic stratification for sample collection as needed);
- access to patient-derived assays for neurodegeneration;
- profile the compounds emerging from Pillars 1 and 2 above into assays and generate target validation data packages collaboratively with the consortium partners.

Expected applicant consortium contribution to Pillar 3:

- network of target and disease experts to profile each probe in disease-relevant assays (e.g. immunology, cancer and neurology);
- access to patient-derived human material (fluids, blood, tissue, other);
- ethical and legal frameworks to engage in such collaborations;
- strategies to include genotyping and deep phenotyping of patient-derived cells and tissue;
- mechanism to characterise probes in other consortia with panels of cell-based assays, e.g.
  Sanger Institute (https://www.sanger.ac.uk/)
  NCI panel (https://dtp.cancer.gov/discovery_development/nci-60/cell_list.htm)
  BTCure (https://www.imi.europa.eu/projects-results/project-factsheets/btcure)
  STEMBANCC (https://www.imi.europa.eu/projects-results/project-factsheets/stembancc);
- engage additional collaborators who are leading the field in functional cell assays and disease models for particular targets;
- mechanism to access additional, relevant phenotypic assay panels in priority areas.

Pillar 4 – Infrastructure and governance to lay the foundation for a global effort on the whole druggable genome

To establish an efficient and coordinated effort within this project, an additional goal of the fourth pillar is to align this project with similar projects or individual efforts globally, in order to reduce duplication of effort and to leverage the IMI investment. The consortium will work with global efforts to adopt such standards, and to this end, will establish or implement standardised, broad cell-based and biochemical assay panels to characterise chemogenomics compounds and chemical probes. The consortium will also establish a database for all data generated, as well as a central compound store and compound logistics (e.g. via a contract service organisation). The intention is for the chemogenomics library and the corresponding sustainable infrastructure to form the nucleus of a coordinated, worldwide, open-access effort to put together a reference compound library covering the entire druggable genome. Consequently, an important aspect of this project will be to provide leadership and a governance structure for the network, which will include investigators not only within the IMI consortium but also from complementary projects around the world. Although many members of the network will be working independently, and with independent funding, the aim is for all partners within the network to follow a jointly agreed masterplan to maximise synergies. In addition to the network, the consortium will find innovative ways to add compounds to the library, including e.g. setting up competitions for young scientists via crowdsourcing to add to the project deliverables. In summary, it is essential for the consortium to develop an international partnership comprising screening centres and chemical biologists around the world. We plan to encourage open-access publication of the results of the research in open-access scientific journals, help create platforms to share results, and work with commercial vendors to make the physical samples of tool compounds available for years to come to the biomedical community.

The following work packages are planned to achieve Pillar 4 goals:

Work package 10 – Infrastructure and platforms

Deliverables:

- compound logistics to handle distribution of all chemogenomics compounds and probes as well as compound exchange between partners;
- more than 500 assays established/accessible to annotate chemogenomics compounds and probes generated within this project with a potential to test compounds from network;
- easily accessible database containing all data generated within this project with a potential to hold data from related endeavours; format suitable for chemists and biologists; these data will be generated and made accessible according to FAIR (findable, accessible, interoperable, reusable) principles;

- long-lived platforms and transferrable infrastructure (e.g. open source code, commercially available services, cloud-hosted servers) to make the new technologies available to a wide audience beyond the consortium;
- open access and dissemination framework established.

Work Package 11 – Global framework

Deliverables:

- the framework for a global network with partners around the world that work on related goals, established with a governance structure that supports efficient collaboration and sustainability;
- partnership agreements with major European and international efforts in screening assay development; patient-derived cell assays, chemical screening, chemical probe generation and compound profiling;
- a process for recruitment and rigorous triage of external activity and contributions.

Work package 12 – Project management

Deliverables:

A management and governance structure which ensures that the project completes all deliverables in a timely and efficient manner.

Industry and Associated Partner contribution to Pillar 4:

- director or senior scientist/manager to represent company on joint steering committee;
- experts in drug discovery to manage collaborations in specific scientific areas or on specific targets/target families;
- contributions to collaborative scientific meetings, management of internal versus external activities;
- advice, involvement or secondment on infrastructure development, e.g. compound management, database, platform technologies, partnering opportunities and governance framework.

Expected Applicant consortium contribution to Pillar 4:

- experienced managers to ensure that the key consortium deliverables are completed;
- senior scientists to manage project deliverables, to disseminate the project outputs and to engage in collaborations to maximise impact;
- database, loader and visualisation tools to enable open access use of all data generated in this project and within related initiatives; partnering with public databases (e.g. ChEMBL) if possible;
- development of compound logistics for this project and for related initiatives to enable easy access to the chemogenomics compounds and the chemical probes, e.g. in collaboration with established SMEs;
- management of finance, valuation of deliverables, communication etc;
- create international alliance of screening, probe generation and compound profiling initiatives and align toward consortium objectives;
- dissemination of results in the form of publications, meeting presentations, and via the consortium's website;
- screening assays for broad profiling, e.g. broad panels for kinases, G-protein-coupled receptors (GPCRs); assays for cell permeability and unspecific toxicity;
- plan for sustainability of infrastructure after the end of this project, e.g. via partnering with contract research organisations (CROs), national facilities and vendors.

Sustainability

Sustainability measures beyond the duration of the proposed action should be considered based on the expected results generated by the action. At stage 2 the full consortium would have to propose a sustainability plan to be implemented during the project duration and including relevant resources and budget. Sustainability is of utmost importance for this project.

- The chemogenomics library and the chemical probes, and the existing and new data from their use, should be easily accessible on a continuous basis. The applicant consortium should have a convincing plan how to achieve this, e.g. via non-exclusive access to the synthetic routes of these compounds to vendors be they large, mid-size or even start-ups, that are willing to distribute the chemogenomics library and/or chemical probes and their controls.
- A significant investment in hardware, software and expertise for compound logistics, database and assay panels will be needed to make this project a success. To make best use of the investment, the applicant consortium should already have an initial plan for sustainability.
- This project is planned as part of a global initiative for creating an open-access chemogenomics library for the entire druggable genome. This ambitious goal, which is beyond the scope of this particular call, will not be achieved within the timeframe of this IMI project, thus, sustainability of the infrastructure and platforms is of utmost importance for the overall mission.

The applicant consortium should already have an initial plan for sustainability, e.g. via CROs that are interested to continue operations as part of their business or via letters of intent from universities or other research organisations concerning the continued use of the research tools and the infrastructure. A detailed plan will be developed and implemented within the project.

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Topic 3: Intelligent prediction and identification of environmental risks posed by human medicinal products

Topic details

Topic code	IMI2-2019-17-03
Action type	Research and innovation action (RIA)
Submission and evaluation process	2 stages

Specific challenges to be addressed

Pharmaceuticals are present in the environment as a consequence of patient use, manufacture, and improper disposal. They predominantly enter the aquatic environment via patient use and are typically found in concentrations from sub-ng/l to a few µg/l [1].

In the European Union (EU) an environmental risk assessment (ERA) is required as part of the marketing application and approval for new drugs [2]. Currently the ERA is conducted late in drug development and often parallel to Phase III clinical trials and after significant investment. An ERA is triggered if the predicted environmental concentration (PEC) exceeds 0.01 µg/l. More focused, exposure-independent environmental assessments are also required if (i) the drug is highly lipophilic (logD ≥4.5) and could fulfil the criteria for a persistent, bioaccumulative and toxic (PBT) chemical, and/or (ii) the drug is a potential endocrine disruptor that acts on the reproductive axis requiring tailored assessment. Chronic sub-lethal ecotoxicity testing has only been required since 2006 in the EU [2].

The growing regulatory and scientific concerns regarding pharmaceuticals in the environment have reached the point where some stakeholders are advocating:

- the inclusion of environmental hazard and risk within the patient-benefit evaluation that underpins the marketing authorisation of a drug;
- a catch-up scheme for medicines authorised for use prior to 2006 that lack comprehensive environmental assessments;
- increased transparency of environmental data;
- increased consideration of environmental properties in drug development (i.e. greener drug design).

The inclusion of environmental hazard and risks in the patient-benefit analysis challenges the current drug development paradigm where environmental testing is conducted parallel to Phase III clinical trials. Without validated tools to predict environmental risk earlier in drug development this could impact the availability of life-changing medicines to patients within Europe and impact the competitiveness of the industry. These tools can also be used to prioritise established pharmaceuticals for testing and tailor specific test requirements to conclude on environmental risk in an effective and efficient manner. Many of these concerns are captured within the current European Commission (EC) strategic review of pharmaceuticals in the environment (PiE) [3] and they form the foundation for this IMI2 JU topic.

Burns et al. (2018) [4] have already demonstrated that prioritisation approaches need to consider consumption, environmental exposure potential (generic and spatially explicit exposure), lipophilicity, mode of action, pharmacological potency, target conservation and read-across, in order to identify drugs of potential environmental concern and ensure that the right species are chosen for a tailored environmental assessment. The availability of tools and models to assist with the prioritisation of approximately 1500 legacy drugs that lack any environmental data for tailored ERAs has the potential to deliver significant animal welfare benefits and cost savings without compromising environmental protection. It is also important that a database of environmental information on active pharmaceutical ingredients (APIs) is maintained, developed and populated within iPiE-25 in a manner that maximises the transparency of ERA data to all external stakeholders, in order to help inform ongoing environmental monitoring campaigns and other scientific and regulatory activities. The availability of these data in the public domain would also reduce unnecessary duplication of testing, including some vertebrate testing on fish, and reduce the number of conflicting

environmental risk assessments that exist for some compounds. Additionally, the same tools and models used for prioritisation could be used to predict the risk of human metabolites of APIs.

Need and opportunity for public-private collaborative research

A public-private collaborative research partnership is required to identify and manage the environmental risks of human medicinal products across the whole of their product life cycle as no single stakeholder can proactively manage and mitigate these risks alone. The holistic environmental stewardship of human medicines requires consensus across many stakeholders and technical experts, potentially including:

- regulatory agencies (i.e., European Medicines Agency (EMA), U.S. Food and Drug Administration (FDA), national environment agencies, European Commission's Directorate-General for Environment) may contribute publicly available information on registered APIs;
- EMA and the EC as key stakeholders can contribute to appropriate assessment designs to address the issue of PiE and deliver elements of the PiE strategy;
- inter-governmental organisations with responsibility for environmental health policy such as environmentally persistent pharmaceutical pollutants (e.g. United Nations Environmental Programme and the Strategic Approach to International Chemicals Management (SAICM), the Organisation for Economic Co-operation and Development (OECD));
- medicinal chemists and structural biologists to support ambitions for exploring the feasibility of greener drug design;
- specialised subject matter experts may identify and extract public data and populate a species diverse ecotoxicological database;
- academia may contribute by elaborating theoretical and hypothesis-driven experimental testing programmes to validate hazard or risk predictions, and define prioritisation parameters;
- experts in artificial intelligence and machine-learning specialists to support the identification of relationships at a systems-wide level that can act as predictors of environmental hazard and risk;
- environmental engineers including scientists from the waste water industry;
- social scientist community and socio-economists to determine the relative value society and patients place on safety, efficacy and environmental considerations versus access to medicines;
- patient-oriented organisations;
- physicians and pharmacists who have interests in the environmental impact of pharmaceuticals and association professional development training;
- independent consultants that may support the development of *in vivo*, *in vitro* and *in silico* tools for ecotox hazard identification, prioritisation and risk assessment;
- industry may provide input with reference to their large product portfolio, in particular test materials, pre-clinical and clinical data, unpublished ecological information, and contribute to experimental validation programmes.

Scope

The overall objective of this project is to ensure the environmental safety of human medicinal products through patient use by providing innovative and predictive tools to:

- identify environmental hazards and risks associated with candidates in drug development;
- screen and prioritise established, 'legacy' pharmaceuticals for a tailored environmental assessment;
- make environmental data for human medicinal products more transparent to all stakeholders through the development of a publicly available database.

This project aims to validate approaches to prioritise the risks of human medicinal products. A recent review of prioritisation approaches is described in Burns et al. (2018; [4]) that could form the basis for strategies employed in this project. It is important that the predictive *in silico*, *in vitro* and *in vivo* tools and models:

- are extended to include other targets and endpoints in a wider range of taxa and environmental compartments;
- have their predictive capability maximised at a systems level through the application of innovative machine learning approaches and artificial intelligence innovation;
- are validated to understand their predictive capability and applicability domain;
- are assessed for their feasibility to be integrated earlier into drug development to flag environmental concerns sooner than within the current industry model; and
- are applied to established APIs that lack comprehensive datasets to address and prioritise concerns about the environmental risks associated with legacy medicinal products.

Thus, the focus of this project will be on developing methods and guidance for targeting predictions and screening assays on the various types of compound classes represented in the area of human pharmaceuticals. Whilst this project is primarily focused on environmental exposure pathways and associated risks for human medicinal products, some of the project outputs could have potential use in the prioritisation of veterinary medicines. The tools and models developed could also be used to help screen or set safe discharge targets for API manufacturing sites. To deliver these objectives the following issues or themes fall within the scope of the project:

- to work across a broad group of stakeholders including the pharmaceutical industry to define what constitutes a greener API;
- to weigh the feasibility of designing greener APIs with the priorities of patient efficacy and safety;
- to drive innovative approaches to assess environmental risks. Such innovative approaches should include: (i) improving the predictability and applicability of the fish plasma model, (ii) providing three-dimensional *in vitro* cell culture approaches to assess API uptake, metabolism, elimination and toxicity in fish as a key priority for the pharmaceutical industry given the high level of drug target conservation in fish, and (iii) applying artificial intelligence and machine learning approaches to improve comparative toxicological predictions between preclinical and environmental safety assessments. The tools being developed must have the potential to be applied much earlier within drug development than existing environmental assessments and possibly be aligned with ongoing preclinical drug, safety and metabolism assessments;
- to consider environmental impacts in other environmental taxa and for other environmental compartments beyond surface waters, e.g. groundwater, secondary poisoning etc.;
- to address concerns with off-target effects and the environmental relevance of these effects;
- to assess and determine the validity of the tools and models for underrepresented mechanisms-of-action (MOA) classes of APIs and define the applicability domain for the each of the tools and models according to OECD standards;
- to apply and validate the tools, models and methodologies developed with an ambition to assess at least 25 legacy APIs, including key metabolites, selected in agreement with key external stakeholders. It is expected that any ERA data for priority APIs identified, generated and validated in this project will be made publicly available outside the iPiE-25 programme;
- to maximise the knowledge generation potential of a pharmaceutical ecotoxicology/environmental database including the integration of predictive capabilities and maximisation of data accessibility and transparency to all stakeholders;
- to enable the pharmaceutical ecotoxicology/environmental database to capture spatially refined exposure assessments and measured environmental concentrations for prioritised compounds and the integration of tools and models to provide probabilistic or semi-probabilistic approaches to ERA;
- to develop a database as a central resource for the collation of ERA supporting data with the support of the EMA and national competent authorities, in order to minimise duplicate testing, particularly on vertebrates, and remove any requirement for inefficient monograph type approaches.

APIs that are potential sex steroid receptor agonists and antagonists have a categorical inclusion, and require a tailored ERA, hence these fall outside the remit of this topic call. Also given that antibiotics have a mode of

action largely restricted to prokaryotic organisms and only require limited testing to conclude on environmental risk they don't require further consideration within this topic call. Finally, due to complexity of investigating environmentally relevant mixtures of APIs and other chemicals models should be developed and validated based on exposure to single compound exposures. However, it should be recognised that many of the tools and models being developed and validated in this project could be applied to mixture assessments.

Expected key deliverables

The expected deliverables should be achieved during the 5-year duration of the funded project.

- Establish a clear definition of what constitutes a greener API and how feasible this ambition is relative to the priorities for patient efficacy and safety.
- Agreement on future ERA and risk prioritisation strategy with our key stakeholders (i.e. the EC and EMA) together with an associated socioeconomic impact assessment for the implementation of this strategy.
- Delivery of validated predictive models/tools together with supporting documentation and guidance that can (i) be integrated earlier within drug development and (ii) prioritise established or legacy APIs for a tailored ERA. The validated tools and models should be made publicly available and consider including:
    - clearly defined validity domain for each tool and model developed within the project and consideration of underrepresented classes of APIs within their validation;
    - the scientific basis for false negative and false positive predictions needs to be considered as do the different regulatory and industry tolerances for false predictions against regulatory decision making and its consequences for drug development;
    - tailored and definitive ERA data for approximately 25 APIs, including some key metabolites, that have been used to test, validate and refine the prioritisation framework and supporting guidance.
- An updated knowledge-driven ecotoxicology and ERA database with integrated software to support semi-probabilistic and probabilistic risk assessments. The fully transparent, long-term hosted and sustainable software should integrate mode of action/read across grouping with associated structural alerts, a wider coverage of APIs together with recommendations for an EU-wide Pharmaceutical Ecotoxicology Database supported by industry and the European Commission. These data are expected to be available in the public domain.

Expected impact

The overall aim of this project is to apply innovative approaches to ensure the environmental safety of human medicinal products such that both (i) environmental concerns do not become a barrier to patient access to medicines, and (ii) the intended use of medicines does not pose an unacceptable risk to the environment.

This project aims to determine the extent to which human medicinal products pose a risk to the environment and to provide innovative tools and models to assess environmental properties earlier within drug development. Current empirical approaches to identify environmental hazard and risk are not suitable for integration earlier within drug development; they are long in duration and require significant test material, hence bespoke models trained and validated on actual pharmaceuticals may offer a genuine alternative.

The current European guidelines for environment risk assessment came into force in 2006 [2]. Therefore, human medicinal products authorised before this date have incomplete environmental datasets and often lack long-term chronic ecotoxicology data. It is estimated that approximately 1500 active pharmaceutical ingredients lack sufficient environmental data to conclude on the risks that they pose to the environment. Within the recommendations made by Deloitte [3] as part of the European Commission strategic review on pharmaceuticals in the environment, an ERA catch-up procedure was advocated for (all) legacy pharmaceuticals that lack data. To conduct a full Phase II Tier A ERA on all medicines authorised before 2006 equates to about EUR 1 billion worth of ERA testing, a significant amount of vertebrate testing, and would saturate the environmental CRO capacity to conduct such studies, in addition to testing for new APIs, for decades. Therefore, an intelligent approach to prioritisation and testing is required. The validation and implementation of such an approach through iPiE-25 could save the pharmaceutical industry more than EUR 500 million without compromising environmental protection. This is serious money and a resource that can be invested in developing innovative medicines for patients, in particular where there is an unmet patient need.

This project aims to refine, extend, validate and implement these prioritisation approaches to ensure the environmental safety of established medicinal products.

The transparency and accessibility of environmental data for human medicinal products remains a concern to many stakeholders [3] and the current lack of visibility is resulting in duplicated regulation testing by the pharmaceutical industry within marketing applications. To maximise the transparency of environmental data to all stakeholders this project aims to develop an EU-wide pharmaceutical ecotoxicology database. The availability of environmental data (e.g. ecotoxicological endpoints) in the public domain will (i) help all stakeholders better understand the risks posed to the environment by human medicinal products, (ii) allow environmental chemists to present their monitoring work in the context of risk, and (iii) reduce duplication of environmental testing across the industry. The database will also enable the environmental risks of a human medicinal product to be actively managed across its product life cycle and help facilitate the industry extended environmental risk assessment (eERA) model.

Applicants should also indicate how their proposal will impact the competitiveness and industrial leadership of the European Union by, for example, engaging suitable small and medium-sized enterprises (SMEs).

Potential synergies with existing consortia

Applicants should take into consideration, while preparing their short proposal, relevant national, European (both research projects as well as research infrastructure initiatives), and non-European initiatives. Synergies and complementarities should be considered to incorporate past achievements, available data and lessons learnt where possible, thus avoiding unnecessary overlap and duplication of efforts and funding.

Possible synergies and collaborations could exist with:

- the IMI iPiE Project (http://i-pie.org/) and the iPiE-SUM database (https://ipiesum.eu/)
- the EcoDrug database (http://www.ecodrug.org)
- the IMI eTox project (http://www.etoxproject.eu/)
- the United Kingdom Water Industry Research (UKWIR) Chemicals Investigation Programme
- the NERC-Defra Chemicals in the Environment directed research programme
- the NORMAN Network (https://www.norman-network.net/)
- ChemPop Project funded in the UK which will consider correlations and possibly causations of historical aquatic and terrestrial faunistic and floristic data with historical micro-/macropollutant presence
- US FDA Environmental AssessmentsEuropean Medicines Agency and environmental data within European public assessment reports (EPAR)
- regulatory agencies developing the Japanese and Canadian ERA schemes
- Global Chemical Outlook of the UNEP (United Nations Environment Programme): https://www.unenvironment.org/
- EU Technology Plattform SusChem Europe: http://www.suschem.org/
- Start – Strategien zum Umgang mit Arzneimittelwirkstoffen im Trinkwasser: https://www.researchgate.net/project/start-Strategien-zum-Umgang-mit-Arzneimittelwirkstoffen-im-Trinkwasser

Industry consortium

The industry consortium is composed of the following EFPIA companies:

- AstraZeneca (lead)
- Bayer
- BMS
- Eli Lilly

- GSK
- Novartis
- Roche
- Sanofi
- Servier

The industry consortium will contribute the following:

- expertise and experience in leading and managing large scale public-private partnerships;
- provide physico-chemical, ecotoxicology and environmental fate data that are regulatory compliant (provision of existing data by the industry partners does not count as in-kind support);
- drug discovery and development expertise;
- computational chemistry expertise;
- support for test compound selection and experimental design;
- synthesis of test materials (e.g. 14C API or metabolites) for validation work where existing material is not available;
- design and execution of environmental risk assessments that comply with EMA and FDA regulations;
- identification of appropriate assays to support tailored environmental assessments;
- techniques and statistical methodology development;
- expertise in regulatory sciences and in strategic approaches to collaborate with environmental authorities to introduce innovative environmental methodologies;
- legal expertise related to intellectual properties management and complex partnership co-development structures.

Specific industry contributions are listed under the relevant work packages (WPs) and need to be taken into account by the applicant consortia.

Indicative duration of the action

The indicative duration of the action is 60 months.

Indicative budget

The indicative in-kind and financial contribution from EFPIA partners is EUR 4 550 000.

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

The financial contribution from IMI2 JU is a maximum of EUR 4 550 000.

Applicant consortium

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

The applicant consortium is expected to address all the research objectives and make key contributions to the defined deliverables in partnership with the industry consortium which will join the selected applicant consortium in preparation of the full proposal for stage 2. Applicant consortia could consist of members from academia, SMEs and subject matter experts in environmental fate, toxicity, modelling and risk assessment. SMEs could include contract research organisations (CROs) providing regulatory compliant studies to support the validation work; alternatively, they could provide tools, assays, models or database development to help deliver the topic objectives. Scientists from regulatory agencies are also actively encouraged within the consortium and wider regulatory engagement will be invited via the formation of a scientific advisory board for iPiE-25.

This requires mobilising, as appropriate:

- experience in leading, managing and measuring impact of public-private partnership consortia;
- expertise in programme management and professional provision of project management services, administration, governance and compliance;
- communication expertise, preferably for stakeholder management of large-scale consortia;
- expertise in ecotoxicology, environmental exposure assessment and environmental risk assessment;
- expertise in environmental exposure modelling and approaches for semi-probabilistic and probabilistic environmental risk assessment;
- proven ability to generate regulatory compliant environmental risk assessment studies;
- expertise in mode-of-action-driven ecotoxicology;
- expertise in data management and curation, database development, data visualisation;
- expertise in the development and implementation of evidence-based decision software;
- social science experience to support engagement with stakeholders across the product life cycle;
- expertise in analytical and environmental chemistry to support environmental assessments and environmental monitoring;
- statistics and statistical modelling expertise relevant for the design and analysis of ecotoxicology and environmental monitoring studies;
- expertise in artificial intelligence and machine learning approaches to big data analysis;
- expertise in drug discovery and drug development;
- proven ability to impact environmental policy and regulation;
- expertise in assessing and judging the quality and relevance of ERAs and supporting studies.

Suggested architecture of the full proposal

The applicant consortium should submit a short proposal which includes their suggestions for creating a full proposal architecture, taking into consideration the industry contributions and expertise provided below.

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.

The below architecture for the full proposal is a suggestion. The architecture of the full proposal should be designed to fulfil the objectives and key deliverables within the scope of this proposal.

Work package 1 – Determining the feasibility of greener drug design (year 1 and 2)

One of the options identified within the European Commission strategic review of pharmaceuticals in the environment recommended an EU/industry co-funded initiative to promote the design of APIs that pose lower risks to the environment (Option 3; [3]), so-called ‘green drugs’. The overall aim of this work package is to determine the feasibility of greener drug design.

The goals of this work package may include:

- Consulting with stakeholders across the product life cycle of a human medicinal product to identify what range of properties may constitute a greener drug and its relative importance versus patient efficacy and safety, of which latter must be fundamental for human medicines. This consultation should include medicinal chemists, drug discovery biologists, drug safety and metabolism experts, environmental risk assessors (regulatory and industrial), pharmacists, physicians and patient groups. The focus should be based on risk rather than hazard alone and should consider looking beyond the final active pharmaceutical ingredient to consider environmental impacts across the product life cycle. We anticipate a stakeholder workshop to disseminate, discuss and refine the findings of this review.
- Identifying the specific challenges of integrating environmental considerations earlier within the drug discovery and development cycle. Specific consideration should be given to current innovation and best practice in drug stabilisation and drug delivery strategies, particularly for oral therapy, versus what may constitute a 'green drug'.
- Reviewing and quantifying the anticipated impact that innovations in personalised medicines, nano-based therapies and biologically-based pharmaceuticals may bring to the environment [5].
- Identifying a series of potential 'green' interventions and an associated roadmap for implementation where environmental considerations could be integrated across the product life cycle to proactively manage environmental risks of human medicinal products together with a health and socioeconomic impact assessment. This should be illustrated with potential case studies where possible.

Industry members of the project will bring their knowledge of drug discovery and development, together with relevant strategies to improve drug stability and delivery to help determine the feasibility of greener drug design. Industry will also describe the financial risks, levels of attrition and the criteria for model/ toolbox integration earlier within the development life cycle. Industry will also contribute its environmental knowledge into the activities to define a greener medicinal product and actively participate in stakeholder events and workshops.

Work package 2 – Development of an EU-wide Pharmaceutical Ecotoxicology Database (years 1–5)

To maximise the transparency of environmental data to all stakeholders this work package aims to develop an EU-wide pharmaceutical ecotoxicology and environmental fate database that captures (i) robust and reliable environmentally relevant toxicity thresholds for pharmaceuticals in a standardised format, and (ii) environmental risk assessments at an active substance rather than a product level to provide a view of environmental risk irrespective of product use.

The database should be knowledge-based and curated to ensure that the reliability and relevance of data is sufficient for regulatory decision-making. The database should also include decision-based reasoning and arguments for the inclusion/exclusion of data that can be open to scrutiny.

To help support a 'reality check' of predicted environmental concentration-based risk assessments, the database and associated software should support semi-probabilistic and probabilistic risk assessments that also include measured environmental concentrations and predictions from spatially explicit exposure modelling.

The fully transparent, long-term hosted and sustainable software should also integrate (i) mode of action/read across grouping with associated structural alerts, (ii) a wider coverage of pharmaceutical actives and (iii) recommendations for how it can be migrated to a sustainable EU-wide Pharmaceutical Ecotoxicology Database supported by industry and the European Commission.

Industry members of the project will provide environment data to support the development of the database. They will also contribute to the design of the database and help identify the types of visualisation tools and outputs that can be built into the functionality of the database and associated software. Industry will also work with the European Commission and the European Medicines Agency to ensure the wider sustainability of the EU-wide Pharmaceutical Ecotoxicology Database.

Work package 3 – Tool-box development and refinement (years 1–4)

This work package is focused on driving innovative approaches to (i) assess and identify environmental risk earlier within drug development and (ii) screen and prioritise the risks of established APIs that lack environmental data. It is expected that appropriate tools and models, such as the fish plasma model, will be extended to consider active pharmaceutical ingredients with a wider range of chemical properties and mechanisms of action. Such innovative approaches may include:

- improving the predictability and applicability of the fish plasma model through experimental validation accounting for plasma protein binding and availability [6];
- providing three-dimensional *in vitro* cell culture approaches or 'organs on a chip' to assess API uptake [7][8], metabolism [9], elimination and toxicity in fish as a key priority [10][11], given the high level of drug target conservation in fish [12];
- modelling internal API concentrations in wildlife species other than fish;
- applying artificial intelligence and machine learning approaches to improve comparative toxicological predictions between preclinical and environmental safety assessments [13][14]. Chronic ecotoxicity predictions integrating MOA would be particularly welcome. The tools being developed must have the potential to be applied much earlier within drug development than existing environmental assessment and possibly be aligned with ongoing preclinical drug, safety and metabolism assessments [15][16];
- considering environmental impacts in other MOA relevant environmental taxa and for other environmental compartments beyond surface waters, e.g. terrestrial risk assessment, irrigation and groundwater-related risks [17][18][19], secondary poisoning etc;
- addressing concerns with off-target effects and the environmental relevance of these effects;
- providing guidance how these tools can be integrated within a framework to prioritise established human medicinal products for a tailored environmental risk assessment.

Industry members of the project will partner across all aspects of the work package and provide appropriate expertise and generate test materials and where required new data to support model development. Industry will also help inform how the guidance can be pragmatically included within our existing business models.

Work package 4 – Validation of the prioritisation approach (years 1–5)

This work package should validate the prioritisation approaches advocated by work package 3. It is important that the predictive tools and models are validated such that they can be integrated with confidence earlier within drug development and used to effectively prioritise established or legacy APIs for a definitive or tailored ERA. The validated tools and models should include:

- tailored and definitive ERA data for approximately 25 APIs, including some key metabolites, that have been used to test, validate the toolbox and refine the prioritisation framework and supporting guidance;
- supporting documentation and guidance;
- clearly defined validity domain for each tool and model developed within the project and consideration of underrepresented classes of APIs within their validation;
- integrating the new experimental data into this project database, thereby strengthening its power and coverage;
- a consideration of the scientific basis for false negative and false positive predictions and the different regulatory and industry tolerances for false predictions and the consequences for regulatory decision-making and drug development.

Industry members of the project will contribute across all aspects of this work package. This may also include the generation of new tailored ERA data specifically designed to support the validation approach.

Work package 5 – Toolbox integration and guidance (year 2–5)

Once the prioritisation approach has been validated the toolbox needs to be integrated where appropriate within the drug discovery and drug development pipeline, and within a formal framework to prioritise established human medicinal products. This work package will engage with relevant stakeholders across the product life cycle to implement this guidance.

Industry members of the project will contribute across all aspects of this work package.

Work package 6 – Dissemination (possibly in conjunction with WP 7, year 1–5)

Dissemination of the project structure as a whole, of the descriptions of work for all work packages, of intermediate results and of the final tools that will be developed within this project, by means of:

- a regularly updated project website, reporting on progress of the project;
- collation of publications;
- congress posters and presentations by members of the different work packages;
- at least one final conference where the overall results and produced tools from iPiE-25 will be presented to both subject matter experts and the interested public at large.

Industry members of the project will contribute across all aspects of this work package.

Work package 7 – Coordination and management (year 1–5)

Appropriate coordination and management activities are key components for rounding up the work plan. Scientific coordination will deal with strategic direction by gathering and reacting to new scientific ideas, optimising the use made of the project committees, and supervising work package leaders as they execute their role. It will also comprise the definition of quality policies and continuing assessment of the project's degree of success. Management will put all the contractual, administrative and financial mechanisms in place to ensure a smooth workflow during the project lifetime.

Industry members of the project will be embedded in partnership throughout the coordination and management of the project, its work packages and agreed milestones and deliverables; it is anticipated that an industry partner will co-lead each work package. Industry will also work with key stakeholders in the EC and the wider pharmaceutical industry to ensure the long-term sustainability of the database.

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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 17 should read this topics text, the https://www.imi.europa.eu/sites/default/files/uploads/documents/apply-for-funding/call-documents/imi2/IMI2_ManualForSubmission_v1.7_November2018.pdf and other relevant documents (e.g. IMI2 JU Model Grant Agreement).

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Indicative Budget	
From EFPIA companies and IMI2 JU Associated Partners	EUR 43 108 139
From the IMI2 JU	EUR 40 786 000

Call Topics

IMI2-2019-17-01 **Optimising future obesity treatment**	The indicative contribution from EFPIA companies is EUR 7 100 000 The indicative IMI2 JU Associated Partners contribution is EUR 1 201 139 The financial contribution from IMI2 JU is a maximum of EUR 8 301 000	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.
IMI2-2019-17-02 **Open access chemogenomics library and chemical probes for the druggable genome**	The indicative contribution from EFPIA companies is EUR 23 800 000 The indicative IMI2 JU Associated Partners contribution is EUR 6 457 000 The financial contribution from IMI2 JU is a maximum of EUR 27 935 000	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.
IMI2-2019-17-03 **Intelligent prediction and identification of environmental risks posed by human medicinal products**	The indicative contribution from EFPIA companies is EUR 4 550 000 The financial contribution from IMI2 JU is a maximum of EUR 4 550 000	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.

Annex II - IMI2 Call 18 topics text

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[38] 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[39].

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[40], 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)[41] is the main reference for the implementation of research priorities for IMI2 JU. The scientific priorities for 2019 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.

[38] 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.
[39] http://www.who.int/medicines/areas/priority_medicines/en/
[40] 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.
[41] 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[42] and Clinical Trial Regulation (EU) 536/2014[43] (and/or Directive 2001/20/EC[44)] and any relevant legislation[45].

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[46], 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).

[42] 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.

[43] 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.

[44] 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.

45 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.

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

Topic 1: Central repository of digital pathology slides to support the development of artificial intelligence tools

Topic details

Topic code	IMI2-2019-18-01
Action type	Research and Innovation Action (RIA)
Submission and evaluation process	2 stages

Specific challenges to be addressed

Although pathology is the cornerstone of the workup of many diseases such as cancer, autoimmune diseases, and transplant rejection, it still relies heavily on the subjective interpretation of a histology sample by a qualified pathologist who captures observations and conclusions in a report. Once the observations are captured, the slides are archived and only the pathologist's report and diagnoses (considered as raw data in good laboratory practice (GLP) nonclinical studies) remain accessible. Therefore, significant information from the histology slides is no longer easily available. This hinders the discovery of new clinico-pathological entities that are relevant to patients' prognosis and treatment.

The recent developments of high-throughput slide scanners offer a possibility for making the entire information contained in the millions of glass slides produced every year, available for search. Ensuring storage and access to digital slides will overcome the current limitations to accessing and sharing pathology material together with the associated metadata. It will facilitate case consultation, help identify sub-types of diseases, assess the translatability of nonclinical safety observations and animal models, and thereby rationalise the design of clinical trials and the use of animal models.

The rise of deep learning and its unexpected ease at interpreting images offer unprecedented opportunities to develop tools for automated detection, classification and quantification of abnormalities in tissues. Hence, many initiatives are already looking at utilising histopathology slides in a digital format as a source of data for biomedical research. Current research focuses on a relatively reduced set of diseases and/or are fragmented and geographically limited, which may hinder their ability to deliver outside of much-targeted applications.

This is mostly because, although clinically relevant and efficient, disease-centric models cannot be easily expanded towards more general purposes.

However, the full transformative potential of deep learning applied to histopathology goes far beyond what is presently undertaken. In the future, it will provide the pathologist with smart suggestions regarding diagnoses and mechanistic or therapeutic hypotheses (predict patient's outcomes and responses to treatment), significantly improving overall patient safety and diagnosis. To achieve this ambitious goal, a much larger series of slides offering a broader coverage of tissues and lesions is required. Whereas such coverage may be difficult to achieve solely with clinical material, nonclinical toxicology studies provide an incredibly valuable and abundant source of histopathology slides, comprising all the normal tissues from multiple species, and a large diversity of lesions. As these lesions are similar to those seen in clinical practice, but in a more pure form, and at stages rarely encountered in humans, they will be a great help for the community developing artificial intelligence (AI). They will also likely offer an opportunity to expedite the development of assisted diagnosis tools applicable to nonclinical safety studies and clinical practice.

Need and opportunity for public-private collaborative research

The refinement of the pharmaco-therapeutic armamentarium requires the improvement of disease classification and of diagnostic and prognostic criteria. This is an ongoing effort in several areas of medicine. However, for many diseases, it is hampered by limited access to large histopathology series and the absence of reliable quantitative methods. To overcome these obstacles, it is necessary to make large sets of histopathology slides accessible to the medico-scientific community in a digital form.

The current efforts in the field of machine learning and histopathology focus on the development of disease-specific models. Although their potential clinical utility is compelling, such models are limited to a particular tissue. The development of holistic models is necessary to support improvements in disease classification and translational research, which will in turn accelerate the discovery of new clinico-pathological entities and provide assisted diagnostics tools.

The magnitude of the challenges addressed by the Call topic is such that they cannot be addressed solely by the academic or industry sectors.

Firstly, it requires the collection of sufficiently large sets of histology data along with associated clinical information. The pharmaceutical industry will provide high-quality slides from nonclinical species obtained during toxicology testing. Public partners such as hospitals and pathology laboratories are an invaluable source of clinical slides and associated data, from clinical trials, observational studies and archives.

Secondly, the infrastructure to host such collections can only be the result of the combined efforts by public and private sectors. Moreover, the interactions between academic, pharmaceutical industry and small and medium-sized enterprise (SME) partners will constitute a significant factor of success for the development of innovative software tools and efficient end-user applications. Lastly, the involvement of representatives of health and regulatory authorities will allow frameworks for policies or roadmaps pertaining to the validation and qualification of digital slides and their use for peer review, primary read and adjudication of nonclinical studies and clinical cases.

Scope

The overall scope of the Call topic is to collect, host and sustain virtual slides along with associated data and to support the collaborative development of artificial intelligence in pathology.

The funded action will also address the regulatory, legal and ethical challenges associated with the collection, sharing and mining of the virtual slides.

Objective 1: Sustainable infrastructure

To deliver the infrastructure hosting several petabytes of digital slides and making the data accessible for research. It represents the hardware layer of the funded action and could take the form of a data centre, either centralised or decentralised. The key factors of success for this objective are the storage capacity and the possibility to exchange rapidly large amounts of data.

The achievement of this objective is also critical for sustainability and the long-term impact of the funded action. The ambition is that after the end of the funded action, the repository will be maintained and developed, following a model similar to public repositories for genomics (e.g. National Center for Biotechnology Information (NCBI) /Gene Expression Omnibus (GEO) — https://www.ncbi.nlm.nih.gov/geo/) and that it becomes the central place for hosting raw digital slides associated with scientific and medical publications. The planned infrastructure is expected to allow pathologists to concomitantly review difficult cases and to consolidate large case series including histopathology and clinical information in order to establish diagnostic criteria. The sustainability beyond the end of the funded action will take the form of a business model that leaves open access free of charge for non-profit purposes. This will represent a major advantage compared to the current approach of smaller databases.

Objective 2: Data

To compile digital histopathology slides from nonclinical safety studies, as well as from clinical series needed to populate the initial version of the repository, and contribute to developing tools and artificial intelligence models. The key factor of success is the diversity of lesions, tissues, and species while providing sufficient sample sizes. In addition, the slides will be made publicly available for the development of artificial intelligence in pathology in line with the sustainability model described in objective 1.

Objective 3: Tools

To deliver a mechanism of an honest broker (see ‘Expected key deliverables’ and ’Suggested architecture of the full proposal’ sections) by developing a software ensuring the optimal and secure contribution of clinical and nonclinical material. Efforts will also be undertaken to propose a unified open digital slide format and tools

to search, access, upload, register, download, view and homogeneously annotate information. In addition, AI models and tools, such as assistance to general diagnosis, screening for slides for lesions, and content-based image retrieval will be developed at a later stage of the funded action.

Objective 4: Regulatory framework

To advance the regulatory framework around the utilisation of digital pathology slides for nonclinical safety testing, evaluation of clinical trials and dissemination/discussion of difficult clinical cases. This will accelerate the adoption of roadmaps for the qualification of the usage of digital slides for peer-review or primary slide reading, as well for the development of artificial intelligence based tools for pre-screening and assisted diagnosis. This objective should be achieved by building on already existing and ongoing interactions and efforts between health and regulatory authorities, and professional societies.

Expected key deliverables

Based on these objectives, a number of key deliverables have been identified:

- mechanisms for adequate management of confidential information possibly associated with digital slides, through the establishment of a specific entity (further referred to as the honest broker);
- sustainable infrastructure to host a large series of digital slides (approximately three million during the lifetime of the project) ensuring confidentiality and privacy through the application of an honest broker concept. Meta-data and annotations will be provided in compliance with existing standards[47];
- nonclinical slide collection: approximately two million slides covering all tissues from several species and with the broadest spectrum of lesions should be collected. This material, obtained from toxicology studies, prospectively whenever possible, will represent a uniquely valuable asset for the fast development of models. Lesions elicited during toxicity testing are progressive and often in relatively pure form which is useful for developing models that recognise elementary lesions. Furthermore, such models developed initially on animal tissues can with little additional effort be expanded to clinical tissues and more complex lesions. It is required that the slides meet high standards of quality (e.g. orientation of samples, section thickness, staining) in order to optimally contribute to the development of AI models;
- clinical slide collection compliant with the quality and ethical standards: approximately one million digital slides should be provided from the archives and/or prospectively collected in the routine clinical practice over the project lifetime. They should be in a form of documented clinical series covering all the diseases areas such as (but not limited to):
    - oncology (e.g. breast, prostate and colon carcinoma, non-small cell and small cell carcinoma of the lung, hepatocellular carcinoma, or renal cell carcinoma, etc.);
    - dermatology (e.g. lupus, atopic dermatitis, melanocytic lesions, drug-induced skin reactions);
    - hepatology (e.g. autoimmune hepatitis, alcoholic and non-alcoholic steatohepatitis, drug-induced hepatitis, allograft rejection, tumours);
    - nephrology (e.g. glomerulonephritides, tubulointerstitial nephritides, drug-induced kidney injury, allograft rejection);
    - pneumology (e.g. idiopathic pulmonary fibrosis/usual interstitial pneumonia, nonspecific interstitial pneumonia).
- the established open-source data format for digital slides;
- developed open-source, cross-platform software tools to:
    - upload, search and access slides and associated metadata;
    - visualise and annotate the slides;
    - download slide for data mining and model development.
- AI models for:
    - identification of tissues and lesions;
    - generation of morphological and molecular signatures from slides.
- engagement with regulatory authorities for adapting guidelines to the new field of digital pathology;
- a sustainability plan for the maintenance and future development of the repository towards a central place gathering virtual slides from clinical cases series and raw data associated with publications. The plan should explore and propose a business model making the use of digital slides for commercial developments subjected to fees, while open access for research purposes should remain free of

[47] For example: International Harmonization of Nomenclature and Diagnostic Criteria (INHAND — https://www.toxpath.org/inhand.asp), Standardization for Exchange of Nonclinical Data (SEND — https://www.toxpath.org/send.asp) or International Classification of Diseases (ICD — https://www.who.int/classifications/icd/en/)

charge. Besides funding the storage of a massive amount of slides, the plan should also include the activities related to the control of the high quality of slides and validation of new slides while enriching future collection.

Expected impact

Applicants should describe how the outputs of the project would contribute to the following impacts and include baseline, targets and metrics to measure impact:

- catalyse research in digital pathology by providing a unique combination of animal and human histopathology. By offering the first complete coverage of tissues and elementary lesions, this repository will offer an unprecedented opportunity to build holistic models and allow generic mining of histopathology, irrespective of a particular tissue or indication;
- enable the development of artificial intelligence tools for rare diseases and uncommon conditions, which currently are left out of the models because of the paucity of cases;
- help identify sub-types in common diseases, possibly unveiling new clinico-pathological entities amenable to specific therapeutic interventions. It could also contribute to assessing the translatability of animal models for disease modelling, safety and efficacy studies, and thereby rationalise the design of clinical trials and the use of animal models. Ultimately, it should accelerate and improve patient treatment and management, thereby enhancing patient health along with the more efficient use of healthcare resources;
- clear the way for the use of digital slides in nonclinical safety and clinical consultation, and facilitate the approval of AI-based tools for slide screening and assisted diagnosis;
- in the long term, the repository delivered by the consortium will be maintained through sustainability mechanisms defined by the consortium and will provide the community with an infrastructure to host additional digital slides (e.g. associated with the publication of case reports, cases series for disease stratification and clinical trials).

Applicants should indicate how their proposal will impact the competitiveness and industrial leadership of Europe by, for example engaging suitable SMEs.

Potential synergies with existing Consortia

Applicants should take into consideration, while preparing their short proposal, relevant national, European (both research projects as well as research infrastructure initiatives), and non-European initiatives. Synergies and complementarities should be considered in order to incorporate past achievements, available data and lessons learnt where possible, thus avoiding unnecessary overlap and duplication of efforts.

Therefore, the applicants should explore possibilities of synergies with a similar past and ongoing IMI1 and IMI2 as well as upcoming IMI2 projects.

Industry consortium

The industry consortium is composed of the following EFPIA companies:

- Novartis (Lead)
- Janssen (Co-lead)
- Bayer
- Boehringer Ingelheim
- Novo Nordisk
- Pfizer
- Roche
- Sanofi
- Servier
- UCB

The industry consortium will contribute the following expertise and assets:

- the major part of the contribution will consist approximately in two million digital slides, mostly prospectively collected from high-quality nonclinical safety studies. These activities will be crucial to gather sufficient critical mass of high-quality slides needed for achieving the planned objectives;

- digital slides from clinical trials will be brought in. However, the vast majority of the clinical collection will be provided by the applicant consortium (see work package 3 ‘expected applicant consortium contribution’);
- experience and guidance for the harmonisation of metadata associated with digital slides;
- experience and guidance for the interaction with health authorities with respect to the qualification of digital and computational pathology in drug development.

Indicative duration of the action

The indicative duration of the action is 72 months.

Indicative budget

The indicative in-kind and financial contribution from EFPIA partners is EUR 37 771 260.

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.

The financial contribution from IMI2 JU is a maximum of EUR 32 320 000.

Applicant consortium

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

This may require mobilising, as appropriate the following expertise and capabilities:

- proven expertise in the management of digital slides in various formats including mastering of tools/mechanisms to collect/extract digital slides from various places (e.g. sponsors, contract research organisations (CROs)), transferring them securely to a central repository, and ensuring derived data can be returned to the contributor on demand;
- expertise in developing large databases for digital slides and related metadata, and tools to interact with them. Metadata correspond to various modalities associated with digital slides accessible for example via clinical registries, electronic health records, e.g. tabulated summaries of elementary lesions for non-clinical toxicology studies, summaries of information on the diagnosis, clinical presentation, genetic abnormalities and/or biomarker values for clinical samples;
- expertise in developing end-user applications for the visualisation, annotation, and analysis of digital slides;
- expertise in managing large clinical databases and large amounts of data;
- proven mastering of methodologies in creating tools for editing labels, anonymising/coding digital slides, encrypting individual files, and other methodologies required to set up the mechanism of the honest broker;
- the expertise of developing and training large-scale deep learning models for histopathology, such as convolutional neural networks, and evaluating the performance thereof;
- expertise in generating, annotating and sharing digital slides;
- solid scientific, medical, and clinical (including pathologist) expertise and knowledge in the research areas targeted by the topic text;
- legal, ethical and regulatory expertise related to patient privacy, informed consent, data anonymisation, and electronic submission of trial/safety data;
- professional project data management and communication capabilities with previous experience in large European public-private partnership settings.

In their proposal, applicants should demonstrate access to the following resources:

- proven access to large and well clinically documented collections of digital slides from clinical and diagnostic cases (e.g. from well-established pathology department(s)) relevant to disease areas enumerated under ’Key deliverables’, organised in series with appropriate informed consent and preferred molecular biomarker annotation (e.g. next generation sequencing (NGS) oncogene panels or whole exome sequencing);
- adequate infrastructure and computing power to train deep-learning models, host and make accessible large amounts of data (approximately 3 peta-bytes for three million digital slides);

- infrastructure to scan a large number of slides (approximately one million).

Suitable SMEs can, for instance, be considered for the following activities: infrastructure management, honest broker mechanism, end-user interfaces and slide scanning.

The suggested architecture of the full proposal

The applicant consortium should submit a short proposal which includes their suggestions for creating a full proposal architecture, taking into consideration the industry participation including their contributions and expertise provided below.

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.

The proposal should be articulated around the following phases, which may overlap as needed to allow the optimal utilisation of resources and production of deliverables:

Phase 1: Establish an honest broker and infrastructure.

Phase 2: Data collection, tools for access and visualisation.

Phase 3: Artificial intelligence models and tools for morphological data mining and assisted diagnosis.

The architecture outlined below for the full proposal is a suggestion. The architecture of the full proposal should be designed to fulfil the objectives and key deliverables within the scope of this topic.

Work package 1 – Project management, coordination, and sustainability

This work package will address the strategy and implementation of project management. This will encourage regular meetings and interaction between sub-groups and teams to coordinate and follow up on the work effort. The applicant consortium with input from industry partners will develop the sustainability plan. Its objective should be to provide an infrastructure to host additional digital slides contributed by authors of case reports, clinical series or clinical trials, with the same level of annotation, anonymisation and accessibility for model development, as during the research phase. The plan should comprise financial, legal, ethical and structural aspects as well as scalability of the storage/access capacity.

Industry contribution:

Assurance of the coherence of consortium activity, and involvement in project management including planning, budgeting, follow-up and tracking of the work packages' progress, and consolidation of the reports. Project risk management and comprehensive communication and dissemination of the project's progress and its milestones will also be provided.

Expected applicant consortium contribution:

Providing detailed follow-up and tracking, via regular work package reports, early reports of any unexpected organisational or structural issues or delays with respect to the project deployment and intermediate objectives.

Work package 2 – Infrastructure and database hosting

This work package consists of the development of the infrastructure that will host approximately three million digital slides shared during the course of this project, and ensure that they are easily accessible to other project participants through available internet servers. The applicant consortium will ensure that the proposed

infrastructure is amenable to expansion and is coordinated with the sustainability plans. The choice of the infrastructure will be coordinated with the industry partners and other consortium partners to ensure compatibility with the tools.

Industry contribution:

Advice for the harmonisation of metadata associated with the digital slides provided.

Expected applicant consortium contribution:

Building an infrastructure (data centre) to host three million digital slides and implement a database to register the corresponding files and associated metadata.

Work package 3 – Data collection & management

To support the other work packages, a data management system/database, able to register the digital slides contributed to by the industry partners and the applicant consortium, is needed. It will ensure the encoding of the data and compliance with patient privacy legislation and the confidentiality agreements established with the industry partners through an honest broker mechanism. The data management should also ensure that contributed digital slides, stripped from all proprietary information, are coded while retaining links with associated metadata (e.g. species, staining, tissue), and possibly complementary data such as clinical pathology, biomarkers, omics profiles, when shared by the contributor. Metadata will use controlled terms from the International Harmonization of Nomenclature and Diagnostic Criteria (INHAND) or International Classification of Diseases (ICD) classifications. This work package also comprises the handling, shipping and scanning of cases contributed as glass slides.

Slide scanners currently deliver the file in a proprietary format, which has limited compatibility outside the product family. In addition to data management, this work package will deliver a common, unique file format for virtual slides that are compatible with open-source visualisation software, where images associated with the virtual slide such as the label or the overview can be edited in order to remove confidential information.

Industry contribution:

Approximately two million glass or digital slides from nonclinical toxicology studies, animal models of diseases, or clinical trials, along with metadata, compliant with INHAND/ICD nomenclature, whenever possible, and structured under the standardisation for exchange of nonclinical data (SEND) format.

Expected applicant consortium contribution:

- honest broker mechanism: to allow all participants to share data comfortably in a secure environment, the applicant consortium should include an organisation with a proven track record of acting as an independent honest data broker from a legal and historical perspective. The mechanism and expected contribution should consist of:
    - setting up the database, encoding mechanisms and registering digital slides accordingly;
    - ensuring that digital slides contributed by members of the consortium are stripped from any information that could link them back to a specific study or patient when made available for the project (including elements of the digital slides themselves such as pictures of the original label);
    - ensuring information security and managing access rights between members of the consortium and the public, at the level of the individual digital slides through encryption;
    - keeping the possibility for a contributor to link scientific results (e.g. model predictions) to the contributed slide, if requested at the time of the submission of the digital slide;
    - if glass slides are submitted, organising their physical transfer to scanning facility, registration in the repository and return to the contributor.
- digital or glass slides from clinical series and archives: the clinical partners of the applicant consortium will provide approximately one million digital or glass slides from clinical case series obtained from the archives and/or prospectively collected from routine clinical practice in pathology laboratories, with accompanying diagnostic and clinical data using a controlled vocabulary (e.g. ICD);
- scanning of glass slides.

Work package 4 – Tools for accessing, annotating and mining digital slides

This work package intends to develop the following tools:

- tools for accessing slides: software tools to interact with the database will be developed to enable access to the virtual slides and the related metadata through search functionalities;
- tools for visualisation and annotation: the annotation of virtual slides refers to the delineation of regions of interest representing particular tissues, features, structures or lesions. Currently, available tools offer some of the required functionalities, which are usually insufficient to perform complex annotation tasks required for the training of deep-learning based models. Cross-platform, open-source tools will be developed to visualise and navigate fluently virtual slides of various file formats hosted in the database, including possible original formats developed in this project. The software tool will offer annotation functionalities for the optimal annotation of slides by pathologists and histologists.

Industry contribution:

- defining the functionalities required;
- guiding the development of tools to ensure implementation according to required functionalities;
- testing tools and providing feedback.

Expected applicant consortium contribution:

- providing tools to interact with said databases and managing metadata along with the digital slides;
- setting up end-user applications for the visualisation, annotation, and analysis of digital slides;
- providing large-scale deep learning models for histopathology, such as convolutional neural networks.

Work package 5 – Regulatory framework for digital slides and AI-based methods

The consortium is expected to have a strategy for the translation of the relevant project outputs such as policies or frameworks for the qualification of the use of digital pathology slides for peer-review and primary reading in nonclinical safety assessment and evaluation of clinical efficacy. It will explore the optimal utilisation of the digital slides from patients to develop AI in pathology in compliance with the General Data Protection Regulation (GDPR). It will also envisage the roadmap for the qualification of AI-based tools for the pre-screening of normal tissues in nonclinical safety and possibly selected domains of clinical practice. A plan for interactions with regulatory agencies/health technology assessment bodies with relevant milestones and allocated resources should be proposed to ensure that at least qualification advice or opinions are provided on the proposed methods during the course of the funded action.

Use of digital slides: the project will provide a platform to exchange and publish virtual slides from nonclinical and clinical studies. Although professional associations and some regulatory bodies have already developed guidance or opinions regarding the use of digital pathology techniques for regulated laboratory work, their applicability is still limited. This project will ideally accelerate the dialogue and create an interface between health authorities, regulatory bodies, clinicians and the pharmaceutical industry regarding the use of digital slides for the primary assessment of nonclinical safety studies, clinical trials and diagnosis.

AI-based methods: the ambition of the project generated from this topic is to catalyse the development of artificial intelligence in pathology by facilitating access to digital slides, a critical resource for training deep-learning based models. These models could serve as prediction engines for assisted diagnostics tools. This project should provide a platform for interaction between the scientific experts and health authorities aiming towards defining a framework for the qualification of these complex tools for clinical and regulatory use, e.g. the project's central repository could be used as a clinical reference or external quality assessment tool for pathologists.

Industry contribution:

Guidance for the interaction with health authorities with respect to the qualification of digital and computational pathology in drug development.

Expected applicant consortium contribution:

- engaging with health authorities representatives to get input to be discussed in the different governance structures of the funded action;
- organising and leading discussions for the adoption of frameworks or roadmaps for the qualification of the usage of digital slides and AI tools as described in the topic text, the use of clinical slides from archives and for the sharing of rare cases or published cases series. Therefore, the overall contribution should consist of:
    - contribute to the evolution of the use of digital slides as a surrogate of glass slides in nonclinical safety assessment (peer-review, primary read);
    - establishing a framework for or a roadmap towards the validation/qualification of artificial intelligence tools for nonclinical safety applications such as screening, lesion detection and grading, and for routine clinical use such as support for lesion detection, qualification/quantification of events, clinical decision-making support tools;
    - contribute to the evolution of the regulatory framework around the use of clinical slides from archives and AI tools in clinical trials;
    - defining the regulatory context for the sharing of rare cases or published cases series.

Topic 2: Health Outcomes Observatories – empower patients with tools to measure their outcomes in a standardised manner creating transparency of health outcomes

Topic details

Topic code	IMI2-2019-18-02
Action type	Research and Innovation Action (RIA)
Submission and evaluation process	2 stages

Specific challenges to be addressed

Patient outcomes and their experience of healthcare, and thus their overall care, could be improved through systematic capture of the patient voice and perspective.

There is general agreement on the need for increased patient centricity in healthcare provision. Current conceptualisations and measures of disease and clinically relevant disease outcomes have generally been developed from the perspective of the clinician and often fail to completely capture the totality of the disability, the symptoms of the disease and the impact on a patient's health-related quality of life (HRQOL) and a patient's experience of their healthcare from the patient's perspective. Important patient-to-patient variations in disease presentation and symptomology may also be lost in the effort to develop a generalisable framework for the disease.

It is important to complement existing clinical outcome measurements with patient-generated measures of disease and HRQOL to ensure that the patient perspective of disease and the impact of healthcare interventions are more completely captured and that disease heterogeneity is better understood. Patient-reported outcomes (PROs) are significant indicators for quality of life and quality of treatment. Their medical and psychological impact has been described for a broad range of diseases. A fine balance must be struck between maintaining authenticity and faithfully capturing the voice of the patient and making the data collected interpretable and generalisable.

In order to achieve this, it is essential to provide patients with tools that have the ability to better capture the entirety of the impact of a disease and treatments (e.g. signs, symptoms, tolerability), allowing them to document their disease more completely and in a structured manner. To be effective, these tools should be built on the basis of accepted standards, developed in partnership with all relevant stakeholders and accepted and integrated into the existing healthcare ecosystem.

A reward system that truly focuses on value requires measurement and transparency of patient outcomes.

Healthcare systems that have the goal of rewarding innovators and service providers on the basis of the value they create for patients need to collect transparent and reliable data on outcomes. Disease registries have already been established in a wide range of diseases. However, these registries tend to measure a non-standardised set of outcomes, are rarely interoperable, focus on clinical measurements, and have varying terms and conditions for access to the data captured. As a result, they often fall short of providing sufficient transparency of patient outcomes in specific diseases to inform scientific and policy decisions.

At the level of the individual patient, the data generated, once structured and subjected to a degree of standardisation, will enable patients to have more productive interactions with their healthcare provider. At the level of the healthcare system, this data will allow a systematic measurement of health outcomes and the possibility to set up a reward system based on value – which can be defined as the level of health outcomes achieved for a given cost.

There is a lack of models for capturing and managing patient-reported health data in an ethical and sustainable way.

Structured health data is invaluable for all stakeholders, from the individual patient, healthcare professionals (HCPs), the life science industry, and policy makers to the patient advocacy groups. There have been a few successful examples of approaches to integrate patient-reported health data into clinical care. In an era of greater focus on the patient, it is thus critical for a society that patient-reported health and experience data is captured and managed in an ethical manner ensuring broad and appropriate access while safeguarding patients' privacy and building high levels of trust.

Need and opportunity for public-private collaborative research

Despite rapid advances in medical science and a revolution in health technology, the lack of standardisation and integration of data remains an obstacle to fully realising the promised benefits of the digital revolution[48]. Measurement methodologies and outcome standards need to be endorsed by those both generating the data and those using the data, and be part of the broader healthcare ecosystem in order to be trusted and accepted. The complexity of the challenges is such that it requires action that is collective, innovative and nurtured in an environment where sensitive information can be shared securely.

- patient associations need to engage actively to develop tools and approaches, and to build trust and patient engagement.;
- regulatory authorities need to be part of the dialogue regarding novel endpoints, data requirements, and acceptability of evidence from patient-generated data;
- privacy and legal experts need to set up the appropriate governance models, consent forms and access terms in order to allow data sharing, ensure trust and, therefore, support sustainability;
- life sciences companies are critical, not only for bringing in expertise, commitment to long-term research, innovation and evidence generation in the disease areas, but also for providing funding and ensuring that the model can be made sustainable over the long term;
- small and medium-sized enterprises (SMEs) and other innovators such as digital companies need to be involved to develop the appropriate tools and technologies;
- public sector experts including medical experts, ethicists, social scientists, biostatisticians and researchers are required to identify or develop the appropriate measurements and the right methodologies for capturing and analysing the data;
- data custodians and data management experts are also essential.

Scope

The goals of this topic are as follows:

1. identify appropriate standards for capturing the patient perspective when measuring health outcomes and patients' experience of healthcare, and obtain support for these standards among relevant stakeholders. Where appropriate the partners will give preference to standards already being developed (e.g. International Consortium for Health Outcomes Measurement - ICHOM) and will follow the Observational Medical Outcomes Partnership Common Data Model (OMOP CDM) developed through Observational Health Data Sciences and Informatics (OHDSI);
2. implement appropriate technology solutions (including adopting existing technology where appropriate) that would allow individual patients to record and measure their outcomes according to these standards and use the information for a more structured dialogue with their HCPs. The technical solution developed will make extensive use of smartphones and/or other commercially available wearable devices to collect both patient outcome measures and objective measures of patient function;
3. establish the appropriate platform to collect, process and manage data in the best interest of patients, patient organisations, health authorities, healthcare professionals, the research community and health care payers, and in compliance with General Data Protection Regulation (GDPR) and other relevant rules and regulations;
4. create a sustainable, socially acceptable and ethical model for the continuous collection of data and an appropriate model for providing access to the identifiable or anonymised or aggregated data to researchers with a legitimate interest in analysing them.

[48] As acknowledged by the OECD in their paper: Fujisawa, R. and N. Klazinga (2017), "Measuring patient experiences (PREMS): Progress made by the OECD and its member countries between 2006 and 2016", OECD Health Working Papers, No. 102, OECD Publishing, Paris, https://doi.org/10.1787/893a07d2-en

These goals can be achieved through the creation of a consortium whose mission will be to establish health outcomes observatories in three selected disease areas, collecting health data in (at least) three different European countries[49] for each disease area. It would be desirable for the three countries selected to reflect variability across Europe in order to provide experience and guidance for scaling the initiative more effectively to other countries in the future.

The observatories should be designed according to the following principles:

- full integration within the respective countries' healthcare systems;
- consistency in design across observatories to allow for comparability of patient outcomes across countries;
- a sustainable model for the observatories;
- robust patient consent and engagement;
- standardisation and interoperability across countries.

The disease areas selected are:

- diabetes type 1 and type 2;
- inflammatory bowel disease (IBD);
- cancer (side effects of chemotherapy and immuno-oncology).

Criteria considered for this selection were: (a) their prevalence in the European population; (b) their chronic and progressive nature; (c) their significant impact on patients' quality of life; (d) their compatibility with patients' digital literacy; (e) the patients have sufficient autonomy and motivation to become engaged in self-management of their disease; and (f) the investment in novel medicines and disease management tools for these diseases by EFPIA members and IMI Associated Partners. The disease areas will focus on adult patients.

Expected key deliverables

The overall aim is the creation and operation of observatories in (at least) the three disease areas identified collecting health data in (at least) three different European countries. The deliverables from the project funded under this topic would all be made public and a key objective is to set up the observatories on a sustainable basis.

To achieve this, the applicants will have to focus on the following deliverables:

- an appropriate, societally accepted, governance and sustainability model for the observatories in three different European countries that allows inclusion in the respective national health ecosystem, and develops revenue streams to fund the continued operation of the observatories beyond the life of the initial project term;
- all legal and ethical analysis required to ensure appropriate consents for data collection, data management and access terms and conditions;
- the legal set up and operation of the observatories, sustainable beyond the life of the initial project term;
- the design and set-up of the appropriate infrastructure leveraging where possible existing technological solutions that would allow the collection of patient-generated data using an accepted common data model (e.g. OMOP CDM);
- the design of a methodology for identifying the appropriate measurements of outcomes for respective diseases taking into consideration the need to also ensure broad stakeholder acceptability and comparability of these measurements;
- the identification of the appropriate measurements of outcomes for the focus diseases of this project and the creation of an adequate digital tool leveraging as much as possible existing solutions;
- the launch of the respective digital tools;
- the publication of annual reports after the third year comparing health outcomes in the three European countries and identifying lessons learned and opportunities for improvement.

For the three specific disease areas, the work will focus on the following deliverables:

- identification and validation of key outcome measures to inform health economic evaluations in the disease area;

[49] European Union and H2020 Associated countries

- analysis of patient outcome data in combination with electronic health records by means of advanced methodologies for patient stratification to determine ideal levels of care;
- a digital decision-making system based on the stratification above to allow personalised treatment.

Expected impact

Applicants should describe how the outputs of the project will contribute to the following impacts and include baseline, targets and metrics to measure impact:

- enable **individual patients** to:
  - receive close to real-time information on their disease status;
  - hold more informed discussions with healthcare professionals about their health status and options;
  - better understand how their status compares with other patients with a similar condition;
  - share their data and help the broader patient community.
- allow **healthcare professionals** to:
  - track the evolution of their patients;
  - enable a different outcome-based conversation;
  - better inform and enhance clinical decisions based on the patient perspective.
- allow **patient organisations** to:
  - assess the status and dynamics of their patient population;
  - increase engagement with other healthcare stakeholders in evidence-based advocacy;
  - further contribute to improving the healthcare system.
- allow **health authorities and healthcare providers** to:
  - improve the quality of care through better and more transparent evidence of patient measures and outcomes;
  - drive research agendas and investments in the right areas;
  - ensure the sustainability of healthcare systems in finding ways to improve the allocation of resources.
- allow **pharmaceutical companies and other innovative companies** to use data to:
  - enable ethical utilisation of the observatory data as legally appropriate;
  - generate insights that can be used to support the design and direction of the development of new treatments;
  - generate robust evidence that can be used in submissions to regulators, health technology assessment (HTA) agencies and other decision makers.

It is also expected that the pool of harmonised data that will be generated can be shared with other institutions and consortia (see section ‘Potential synergies with existing Consortia’). Standardised data across geographies can eventually enable comparison of outcomes among different healthcare systems.

Finally, applicants should indicate how their proposal will impact the competitiveness and industrial leadership of Europe by, for example, engaging suitable SMEs.

Potential synergies with existing Consortia

Applicants should take into consideration, while preparing their short proposal, relevant national, European (both research projects as well as research infrastructure initiatives), and non-European initiatives. Synergies and complementarities should be considered in order to incorporate past achievements, available data and lessons learnt where possible, thus avoiding unnecessary overlap and duplication of efforts and funding.

Collaboration agreements

There is the potential for important synergies between the consortium selected under this topic and the one selected under IMI2 JU Call 18 topic 3 (*Improving patient access, understanding and adherence to healthcare information: an integrated digital health information project*). In particular, on the one hand, for instance it could be possible for the consortium selected under topic 2 to leverage the observatory platform in order to to obtain access to and analyse relevant electronic health record (EHR) data, in compliance with applicable regulation, gathered under topic 3. On the other hand, the consortium selected under topic 3 could become an additional important use-case for the observatories and improve their usefulness. Additionally, the perspectives brought by the consortium selected under topic 3 can contribute to development of the governance and operational model of the observatories, under topic 2. It could also help future-proof them as a neutral guardian of patients' health data which could then be made available in the future with the appropriate safeguards for applications, such as those envisaged under topic 3.

To explore these potential synergies between actions funded under these two topics, the selected consortia are expected to cooperate in common boards/structures and provide access to their results for specific activities when relevant. Therefore the grants awarded under IMI2 JU Call 18 topics 2 and 3 will be complementary grants. The respective options under Article 2, Article 31.6 and Article 41.4 of the IMI2 JU Model Grant Agreement[50] will apply. Accordingly, the relevant consortia will conclude collaboration agreement(s) to ensure the exchange of relevant information, exploration of synergies, collaboration where appropriate.

Other potential synergies

The project funded under this topic will build on applicable methodologies and principles established in particular (but not limited to):

- Projects from the IMI2 Big Data for Better Outcomes (BD4BO) programme such as:
  - EHDEN – for infrastructure and principles of data standardisation;
  - BD4BO disease-specific projects – for their principles of establishing the usefulness of PROs and real world evidence (RWE) in decision making and establishing the value of interventions;
  - DO-IT – for its informed consent principles and recommendations amongst others Patient
- engagement projects such as EUPATI and PARADIGM;
- OMOP CDM (OHDSI) can provide a common model to encode data as well as important analytical tools.
- Projects suggesting novel treatment options and establishing patient survey mechanisms (e.g. BIOCYCLE).

Industry consortium

The industry consortium is composed of the following EFPIA companies:

- Takeda (lead)
- AbbVie
- Eli Lilly
- Hoffmann-La Roche Ltd
- Medtronic
- Pfizer
- Sanofi
- Novartis

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

- Juvenile Diabetes Research Foundation (JDRF)
- Trial Nation

[50] See: https://www.imi.europa.eu/sites/default/files/uploads/documents/reference-documents/h2020-mgaimi_en_v5.pdf.

The industry consortium will contribute to the 'horizontal phase' of the project by providing the following expertise:

- medical knowledge for the disease areas;
- regulatory expertise;
- health outcomes and RWE expertise;
- legal expertise;
- financial and business planning expertise;
- digital technologies expertise;
- expertise in public-private partnerships related to clinical research in the health care ecosystem.

This expertise will be provided for the following tasks to be executed in collaboration with the public consortium:

- identification/ design of the underlying requirements (medical, legal, regulatory, etc.);
- business plan including governance model, structure, and sustainability;
- interactions with regulators and health care authorities for the acceptability of the PROs and of the observatories;
- selection of the digital technologies to measure PROs;
- development of methods to analyse the PROs.

Moreover, the industry consortium will contribute to the disease-specific 'vertical phase' by providing medical and regulatory experts for the disease areas, as well as expertise in digital technologies, health outcomes and RWE.

Indicative duration of the action

The indicative duration of this action is 60 months.

Future project expansion

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

In the context of this topic, a restricted Call may be launched as part of a future IMI2 JU Annual Work Plan to expand the work to include additional data sources, therapeutic areas and/or health economic analysis, leveraging the success achieved. This would help to maximise the long-term impact of the project and to engender continued future successes in making outcomes and value concepts and their application in healthcare and clinics being more fruitful and efficient.

Indicative Budget

The indicative in-kind and financial contribution from EFPIA partners and IMI2 JU Associated Partners is EUR 11 435 000.

This contribution comprises an indicative EFPIA in-kind contribution of EUR 10 385 000, of which EUR 900 000 financial contributions, and an indicative IMI2 Associated Partners in-kind contribution of EUR 1 050 000, of which 882 000 financial contributions.

The allocation of the financial contribution from EFPIA partners and Associated Partners to the beneficiaries receiving JU funding 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 Partner, it is anticipated that some elements of the contributions will be non-EU/H2020 Associated Countries in-kind contributions.

The financial contribution from IMI2 JU is a maximum of EUR 10 478 000.

Applicant consortium

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

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

This may require the applicant consortium to mobilise, as appropriate, the following expertise:

- solid experience in measuring health outcomes, creating appropriate methodologies that allow the capture of patient insights and integrating these methodologies appropriately to gain broad acceptance;
- access to existing real-world data and technology to query the data, together with experience in creating and operating patient registries that capture patient's input and preferences;
- demonstrated ability to build strong relationships with the health authorities and patient organisations of at least three different European countries where there is desire and willingness to co-create these observatories together with the industry;
- strong legal skills including GDPR / data governance aspects but also in broader healthcare law;
- digital architecture and technical skills, including data linkage skills, to set up and/or adapt and operate the appropriate infrastructure in full compliance with GDPR and cybersecurity requirements;
- technical capabilities to create the right digital solutions that will allow individual patients to monitor their outcomes in accordance with the agreed standards;
- expertise in data mining, machine learning, computational biology and modelling expertise and resources;
- biostatisticians and epidemiologists to combine and analyse the data and publish regularly on the outcomes;
- medical expertise across the disease areas;
- social scientists to ensure a robust and socially acceptable model for the collection of data;
- expertise in planning, developing and drafting communications to a range of audiences (including, but not limited to, medical, patient, academic and policy maker audiences);
- strong project management expertise.

Very importantly, the applicant consortium should include among their participants, either as members of the consortium or demonstrated willingness to contribute as experts:

- patient advocacy groups in the respective disease areas and the respective countries to ensure that the patient voice is appropriately heard, captured and interpreted;
- national bodies, such as regulatory agencies and/or HTA agencies and/or health authorities in the respective countries/regions to ensure that the observatories will become part of the national/regional healthcare ecosystems.

Data management

In their short proposal, applicants should give due visibility to 'data management'. At stage 2, applicants should include a draft data management plan (DMP) in the full proposal, outlining how research data will be handled and made available during the project and after it is completed.

Dissemination, exploitation and communication activities

In their short proposal, applicants should give due visibility to the dissemination, exploitation and communication of the project's results. At stage 2, in their full proposal, applicants should further develop these activities.

Partnership with the industry consortium

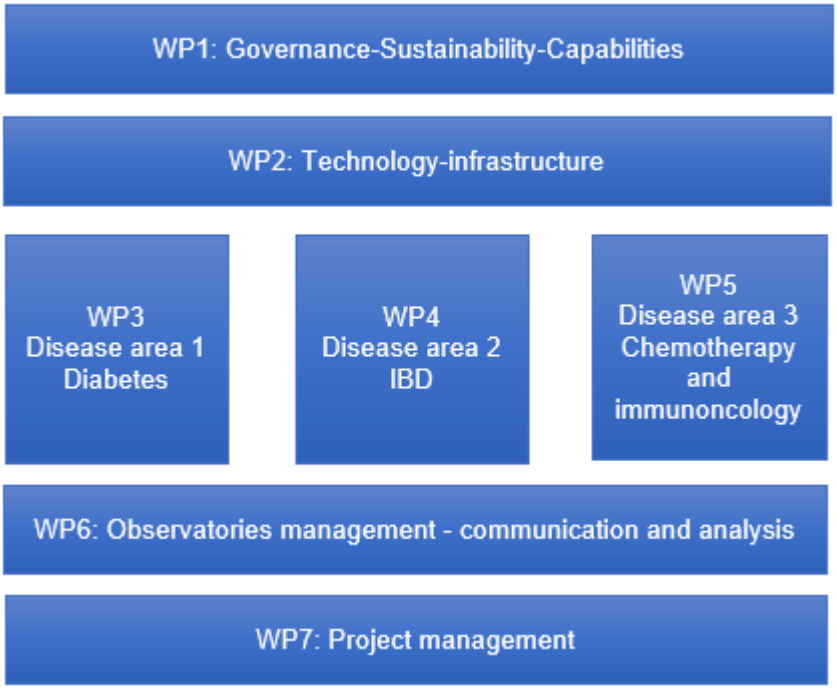
In their short proposal, applicants should outline a strategy to create a successful partnership with the industry consortium.

Suggested architecture of the full proposal

The applicant consortium should submit a short proposal which includes their suggestions for creating a full proposal architecture, taking into consideration the industry participation including their contributions and expertise provided below.

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 should 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.

The architecture outlined below for the full proposal is a suggestion. The architecture of the full proposal should be designed to fulfil the objectives and key deliverables within the scope of this proposal.



Work package 1: Governance - Sustainability - Capabilities

- design of the specific governance principles and structures including legal structures, funding and operating model in the given countries in a way to ensure long-term sustainability. This should include the governance and operating procedures for the creation and maintenance of the observatories, including their relationship with patient organisations, health authorities both at regional/national and above country level and commercial entities. Important elements for the design of the appropriate governance model would be:
  - the long-term sustainability of the model;
  - the possibility to scale it to further disease areas;
  - the interoperability of the data collected with health data derived from EHRs, registries, academic researchers, etc.;
  - the development of a robust consenting process in compliance with the GDPR and other relevant legal and regulatory requirements;
  - the creation of an ethics council to watch over the observatories to build strong trust levels among patients and society.
- methodology for identifying the appropriate measurement standards ensuring they reflect patients' priorities and validating them. In order for any measurement/reporting tool to be truly useful to patients, it should offer them the opportunity to improve their communication with their HCP and/or the healthcare system more broadly. It is therefore an important part of the mission of the observatories to choose standards that reflect patients' priorities but also integrate these standards with the broader stakeholders in order to gain broader acceptability;

- identify the capabilities and capacity required for the collection, analysis and dissemination of health data in the observatories, including the required capabilities for data analysis and administration, and staff the observatories appropriately.

Work package 2 – Technology - Infrastructure

Identify the appropriate technology that will allow the capture of relevant information from patients and enable real-time information sharing with patients. Set up or adapt the appropriate technology, including tools and a platform, that would allow the collection and management of patient-generated data taking into consideration the possible scalability of the project as well as the interoperability of this data with health data derived from other sources (EHR, registries etc.).

Work packages 3 – 5

These work packages will focus on each disease area, aiming to enhance the value of treatment and care for patients through the collection of patient-generated data, the analysis of best care practices as well as the development and validation of digital e-health tools and technologies. The ultimate aim is to increase the wellbeing of patients through improvements in patient care that have been developed with greater insights from patients generated by the observatories.

Specific common objectives are:

- identify the appropriate measurement standard for the respective disease/outcome and ensure validation by the stakeholder community;
- create the methodology to answer the specific research questions identified by the consortium as the most pertinent to the respective disease;
- provide input to the design of technologies in WP2.

Work package 3 – Diabetes types 1 and 2

- to focus on the analysis and validation of key outcomes measures and assess their usefulness for diabetes care and contribution to health economic aspects of the healthcare system;
- to use state of the art analytical techniques to demonstrate ideal levels of care based on the validated outcomes data together with other data types such as EHR and patient-generated data;
- to stratify people with diabetes according to outcomes to improve the understanding of diabetic endotypes;
- to develop a digital decision-making system which can be used by healthcare professionals in clinical practice for more personalised treatment of people with type 1 and type 2 diabetes.

The following sub-work packages are proposed to achieve WP3's goals:

- WP3.1: Collecting, refining and validating existing outcome measures to enable solid assessment of the value of a treatment:
    - weighting outcome measures and understanding their impact on the quality of life and care of patient segments;
    - weighting outcome measures and understanding their appropriateness for the cost of care analyses;
    - development of a digital decision-making tool, based on outcomes that could be used by HTA bodies to aid in the assessment of new therapies and treatments.
- WP3.2: Analysing and validating clinical, patient-reported and real-world data to enable the development of a novel segmentation of patients to attribute to them the right level of care:
    - deployment of computational biology approaches for assessment and analysis of large multivariate datasets (e.g. outcomes-data derived from both EHRs and clinical trials) to divide patients into more precise and personalised segments;
    - development and validation of new recommendations of treatment, care and approaches for the newly-defined patient segments based on the comparative assessment of the performance of established treatments for type 1 and type 2 diabetes.

- WP3.3: Development of a clinical digital decision-making tool, based on outcomes and healthcare experience, for healthcare providers to aid in the assessment of treatment choice.

Work Package 4 – Inflammatory bowel disease

- to establish and validate a key set of key outcomes **and healthcare experience** measures that matter to patients in IBD, especially related to the assessment of disease severity based on patient-reported outcomes;
- to develop digital tools to collect these data directly from patients;
- to assess the acceptance and usability of these tools in patients suffering from IBD;
- to collect a set of patient-generated data using these tools and assess how these outcomes data sets compare to and complement other measures of patient outcome derived from clinical assessments, registries and EHR data;
- to better understand patient endotypes in IBD;
- to better understand how outcomes vary with patient endotypes and clinical practice and assess their potential use for improving patient care and system efficiency in the care of IBD;
- to utilise the PRO data to develop a simple scoring algorithm to indicate a patient's risk of not showing an adequate response to their existing IBD therapy (and which could prompt his/her treating physician to re-evaluate the treatment strategy);
- to support the development of digital decision-making tools which can be used by healthcare professionals in clinical practice for more personalised treatment based on patient and disease characteristics, treatment history and risk factors.

Work Package 5 – Side effects of chemotherapy and immuno-oncology

- to establish and validate a key set of core, patient-relevant, outcomes and health care experience measures that matter to patients with chemotherapy and immune-oncology side effects, and to develop digital tools to collect these data directly from patients;
- to assess the acceptance and usability of these tools in patients suffering from the side effects of chemotherapy or immune-oncology;
- to collect a set of patient-generated data using these tools and assess how these outcome data sets compare to and complement other measures of patient outcomes derived from clinical assessments, registries and EHR data;
- to better understand how outcomes and experience with healthcare vary across patients and across clinical practice and assess the potential for improving patient care and system efficiency in the care of cancer patients;
- to better understand patient segments across chemotherapy or immuno-oncology side effects;
- to support the development of digital decision-making tools which can be used by healthcare professionals in clinical practice for more personalised treatment of patients with side effects of chemotherapy or immune-oncology.

Work Package 6 – Observatory management: communication and analysis

- establish the operation of the observatories, including continuous support to patients and other stakeholders for using the technology, collecting feedback and data;
- generate regular publications to demonstrate the value added of the observatories and the lessons learned;
- manage the gateway for users of the data (including patient-level data, whether identifiable or anonymised, and aggregated data) to be able to access the data;
- define the appropriate operational and maintenance plan to ensure the technical, organisational and financial sustainability after completion of the project. Explore with partners possible expansion into additional diseases as well as possible integration with EHR and registry data.

Work Package 7 – Project management

Take responsibility for overall project management of the project, including (but not limited to) finance management for the project as a whole; meeting management and organisation (for the project as a whole); administration of communication activities; and supporting the reporting to and communication with the IMI office. WP7 will not be responsible for managing the activities of the individual work packages.

Topic 3: Improving patient access, understanding and adherence to healthcare information: an integrated digital health information project

Topic details

Topic code	IMI2-2019-18-03
Action type	Research and Innovation Action (RIA)
Submission and evaluation process	2 stages

Specific challenges to be addressed

The ability to access and understand high-quality health information is central to health literacy, and this affects the day-to-day decisions citizens make in the management of their health and care [1] that will ultimately determine adherence to treatment [2]. A lack of adherence is an established public health concern, with significant effects on the individual patient, as well as healthcare systems as a whole [3].

A multitude of health-related information resources are now available to patients, tapping into demands for greater engagement with personal healthcare. This digital era, however, is compromised by two major concerns. Firstly, the sheer volume of information available has become disorientating to users, many of whom have poor health literacy [4] to start with, and do not know which source to trust for up-to-date guidance. Distribution of this information across different source locations only compounds the issue. Secondly, existing health-related resources are generally not personalised to their specific needs or health literacy level, and therefore large amounts of the information available are irrelevant to the patient[51]. Indeed, product information is a prime example of this phenomenon, with little direct evidence to suggest that patients are actively reading, understanding and adhering to details in the patient leaflet (PL)[52]. Bearing in mind that the product information is considered for most products to be the primary risk minimisation measure, this paradigm clearly needs to change.

There is therefore the need to lay the foundations for the application of digital technologies to health information in order to transform citizens' understanding of their health and care, thereby promoting adherence to prescribed treatments, and ultimately contributing to better outcomes. The topic is consistent with the EU Digital Single Market Strategy, which highlights the need and opportunity to introduce a digital transformation of health and care[53], and is aligned with the IMI Strategic Research Agenda under Axis 4 'Patient Tailored Adherence Programmes'[54]. The topic is also consistent with the key benefits noted in the European Medicines Agency (EMA) Action Plan on e-Product Information (ePI)[55] and subsequently in the draft key principles for electronic product information published by EMA[56] following an EMA/HMA/EC stakeholder workshop.[57] During the workshop, this topic was presented alongside other initiatives in the context of a future vision for electronic product information in the broader digital health landscape, and the EMA also shared details of their mapping of ongoing ePI initiatives, illustrating the very considerable degree of interest and activity in this area at the present time.

[51] The most frequently quoted example of this is pregnancy information for male patients.
[52] The authoritative source of information provided to patients about their medicine is the patient leaflet which must be provided unless all information can be included on the outer packaging (Directive 2001/83/EC Article 58). This single document is provided to all patients irrespective of their health literacy, patient profile, medical history, or preference. In addition, the current format of the package leaflet is widely acknowledged to need improvement (Report from the European Commission on the shortcomings of product information published 22 March 2017)
[53] Communication on Transformation of Health and Care in the Digital Single Market (April 2018)
[54] IMI Strategic Research Agenda.
[55] EMA Product Information Action Plan was published on 10 October 2017
[56] Electronic-product-information-human-medicines-european-union-draft-key-principles - consultation period 31-Jan-19 to 31-Jul-19
[57] European Medicines Agency (EMA) / Heads of Medicines Agencies (HMA) / European Commission (EC). Stakeholder presentations and the workshop report including details of the mapping of ongoing initiatives have been published. See: https://www.ema.europa.eu/en/events/european-medicines-agency-ema-heads-medicines-agencies-hma-european-commission-ec-workshop

Need and opportunity for public-private collaborative research

While there are already digital tools available that enable patients to access product information electronically (e.g. electronic Medicines Compendium (eMC) in the UK, LIF in Denmark, FASS in Sweden, and the Gebrauchsinformation 4.0 project in Germany)[58], and ePI texts may also be available via health authority websites, these do not at this time comprehensively address the broader information needs noted above, there is limited flexibility to tailor the information available to individual needs, and equivalent digital tools are not available to all patients in all countries.

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. The project must balance the need for interoperability with national healthcare systems, align with other key principles mentioned in the EMA ePI draft key principles document, address concerns from industry to enhance the effectiveness of the ePI as a primary risk minimisation measure, and provide all of this in an intuitive and user-friendly design which meets citizens' unmet needs as noted above. This includes:

- perspectives from patient and healthcare professional organisations to understand patient health information/literacy needs and ensure that proposed solutions are fit-for-purpose, acceptable to all stakeholders and truly value-added from the user perspective, and to enable measures to be defined of relevance to these stakeholders;
- academic and research institutions and appropriate health literacy experts who can support the development of appropriate methodology to test patient understanding and impact and contribute to development of appropriate key performance indicators (KPIs) in relation to the project objectives;
- current providers of ePIs and associated product information to enable existing best practices/expertise to be leveraged, and other technology organisations who can develop and integrate the envisaged technology platform and digital applications that will be needed for the proof of concept testing, including considerations for data integration;
- public sector partners who can contribute to the identification of trusted sources of product information, electronic health records and health education materials for use within the project framework;
- contributors with appropriate expertise in the gathering/use/analysis of real-world data and risk-benefit assessment, to measure the effectiveness of the platform as a risk minimisation tool;
- advice from regulators (i.e. EMA, national competent authorities) to consider alignment with wider telematics initiatives and the impact of the proposed approaches on the current/future regulatory framework for the provision of health information to patients;
- contributors with legal and data privacy, as well as social science and ethical expertise to ensure that questions in relation to these areas can be addressed.

The establishment of a public-private partnership offers a unique mechanism for these diverse stakeholders to engage to deliver the range of input and expertise necessary for achieving the project aims and ensuring that a practical and sustainable solution is found.

Scope

The principle objective of this topic is to demonstrate how the use of an integrated, digital, user-centric health information solution could enable a tangible improvement in the ability of citizens to access and understand reliable, relevant health information from different sources.

Access to and understanding of health information are key components determining health literacy, and the health literacy level of a citizen underlies their decision-making in regarding to management of their health and care, including adherence to treatment. Accordingly, a secondary objective will be to measure how improved access to and understanding of health information translates into higher levels of treatment adherence, safer use of medicines and consequently better health outcomes, with new insights into how health information can be optimised to act as an effective risk minimisation measure.

The topic objectives will be achieved by a phased approach, in which later stages build on the outputs of the earlier research activities in an agile manner:

[58] For example, see the Swedish FASS website at http://www.fass.se; mp3 audio files on http://www.laakeinfo.fi, videos on https://www.indlaegssedler.dk, and the 'Gebrauchsinformation 4.0 project in Germany: www.gebrauchsinformation4-0.de

1. **Establishing stakeholder needs and development of appropriate KPIs**

Research will be conducted to establish an in-depth understanding of citizens'[59] expectations and aspirations for the provision of healthcare information in a digital setting to form the basis for future project activities and design-planning for technology development. Specific contexts/patient journeys will be mapped at this stage either on specific therapy areas or other product-type scenarios, such as non-prescription medicines or vaccines. The needs of different patient populations, including vulnerable patients, will also be considered. KPIs will be developed in relation to the two key objectives outlined above to enable the measurement of the success of the proposed integrated digital health information approach versus the current paradigm (which typically relies on paper-based product information for the patient and/or fragmented digital sources).

2. **Technology platform and digital solution**

Development of an **underlying open source technology platform,** and a **digital solution** to enable testing and measurement of the effectiveness of a digital approach to meet defined user needs.

The initial focus will be on product information, electronic health records (EHRs) and a two-way communication channel with the patient. Appropriate, trusted data sources will be linked to the platform taking into account applicable data security and General Data Protection Regulation (GDPR[60]) considerations. A digital solution with tailored information in line with patient needs will be developed for the proof of concept testing of understanding and acceptability. Alignment with the key principles on the common standard for ePI coming from the EMA Action Plan will also be taken into account[61]. Depending on technical progress with product information and EHRs, the latter stages of the project may include a wider range of trusted health educational materials (HEMs) within the platform, with the aim of further enhancing patient understanding.

3. **Evaluation of the ability of digital solutions to enhance risk minimisation approaches through the generation of real-world evidence**

Feedback gathered via the digital tool can be used to assess understandability and options can be evaluated for how to further assess the effectiveness of the platform as a risk minimisation tool.

Ongoing: Development and execution of a sustainability plan

A sustainability plan will be developed over the life of the project which details recommendations for how successful concepts/technology approaches will be carried forward and implemented into the digital healthcare ecosystem at the national/regional level in a sustainable and practical manner. The draft plan will be developed early in the life of the project and adapted in an agile manner based on the project outcomes.

Any form of promotional materials will **not be in scope** for this project.

Expected key deliverables

The key deliverables will be an **open-source technology platform** and **digital technology solution**(s) that have been developed for testing.

- The **open-source technology platform** will integrate information from regulator-approved product information and electronic health records in the wider context of digital health. The platform will aim to make such information available via an application programming interface (API) to allow other companies/developers to use this as a basis for further market-specific applications, offering flexibility for the future evolution of the digital ecosystem.
- The **digital technology solution** will allow digital information to be presented to the patient in a tailored, user-friendly manner to more effectively serve the needs of patients in the management of their own health and care. A range of digital functionality will be built into the digital solution and tested with user groups to measure the effectiveness in improving understanding, adherence to treatment, and health outcomes.

[59] Including patients, healthcare professionals and members of a patients' support network.
[60] See https://ec.europa.eu/info/law/law-topic/data-protection_en.
[61] EMA Product Information Action Plan was published on 10 October 2017.

For example:

- a user-friendly view of the patient's medical history and other pertinent characteristics;
- tailored versions of the ePI dependent on patient circumstances and health literacy needs. A variety of formats will be made available based on the approved PLs, and integration across PLs for different products to generate a single 'treatment ePI' will also be investigated;
- the solution will incorporate additional digital functionality to enhance the user experience and support understanding, adherence and health outcome measures. These features will be fully defined during the research studies but may include features such as dosage reminders, comprehension tests, linkage to healthcare systems to receive e-prescriptions or book appointments, and other off-the-shelf capabilities that already exist in different EU Member States;
- users will have the ability to send information to the platform to be aggregated and analysed to improve outcome measures;
- depending on progress with EHRs and ePI, the platform may also look to identify defined health educational materials at different health literacy levels that will help the patient understand their health, medical diagnosis, and prescribed treatments.

Other deliverables will include the following:

- a **series of study reports** will be published presenting the outcomes of research studies which seek firstly to demonstrate the benefit that this integrated digital approach offers to patients in accessing and understanding health information from the identified sources (primary objective), and in turn to applying this to enable improved adherence to treatment and health outcomes (secondary objective). Details of the KPIs developed for measurement of success in relation to these two objectives will be described;
- an evaluation will be completed to assess the potential ability of digital solutions to enhance risk minimisation approaches through the generation of real-world evidence;
- at the end of the project, the project team will publish **a white paper** that outlines the next steps that should occur in the EU to take advantage of the research findings from the proof of concept test phases. Depending on the results and demonstration of the success of different concepts, this may include a recommendation on adoption of the technology platform/digital solution as the starting point for national or regional implementation (with appropriate modifications), adoption of elements of the solution for further development, and what changes (if any) would be needed to EU legislation/regulation to allow for introduction of these elements;
- identification and **publication of key stakeholder needs** and preferences in terms of information, personalisation and functionality, which will then be used as a basis for design planning for a suitable digital solution;
- identification and publication of a set of **data source specifications** for integration into the digital solution via:
  - identification of the data standards for, and key elements of, electronic medical records and medical alerts for inclusion;
  - utilisation of regulator-approved product information in the appropriate data standard according to emerging ePI standards.
- report on the **key features of future data standards** for ePIs that would optimise functionality in relation to the provision of health information for consideration by regulators[62].

Expected impact

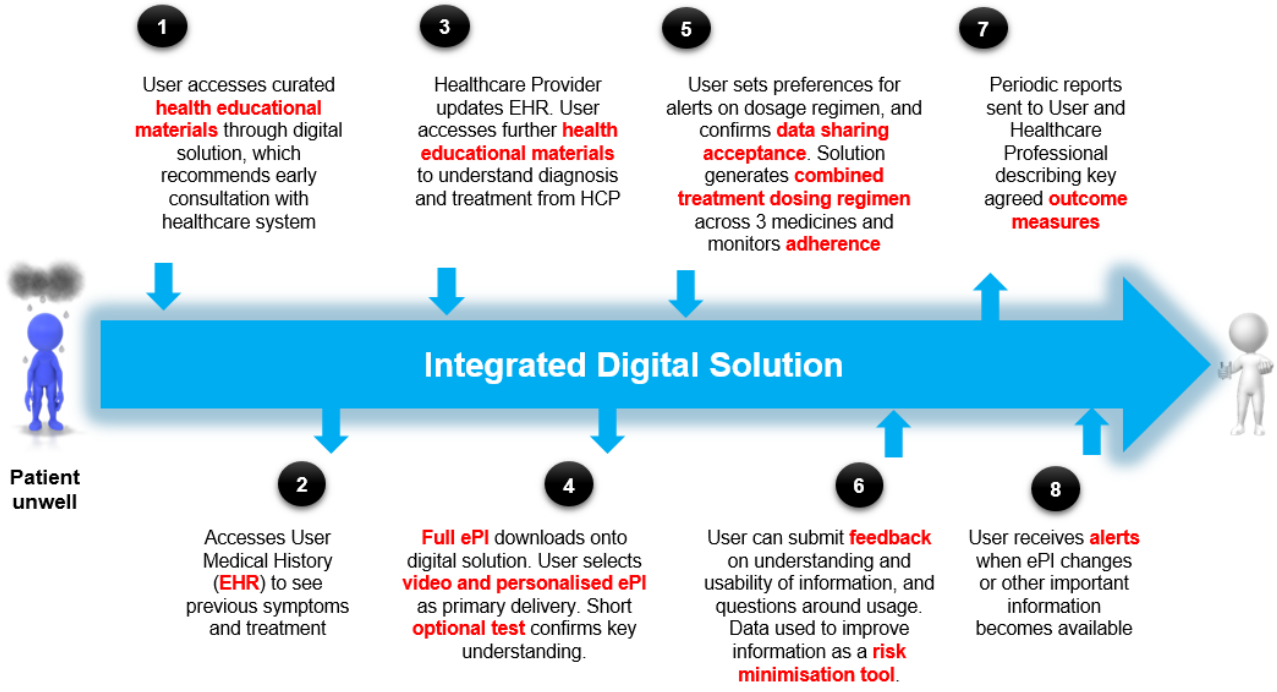
Applicants should describe how the outputs of the proposed project will contribute to the following impacts and include baseline, targets and metrics to measure impact:

- allow individual patients to easily access **trusted health information, tailored to be relevant** to their specific needs. **Empower these patients** and better prepare them for informed interaction with national healthcare systems;

[62] Accordingly, the option of Article 28.2 IMI2 JU Grant Agreement regarding results contributing to standards should be activated and included in the text of the future funded action's Grant agreement.

- further build patients' (digital) health literacy, so allowing for **better decision-making concerning their health care**, **disease prevention** and **health promotion**, to **maintain or improve quality of life** throughout the course of life;
- positively **impact healthcare at a societal level** through **enhanced adherence, better use of resources, and improved overall patient outcomes**; the approach may offer **particular benefits in complex scenarios**, for example where patients are managing multiple morbidities;
- improve the effectiveness of ePIs as a **primary risk minimisation measure** by surfacing greater insights on access, understanding and the usability of the information provided to them;
- the **technology platform/tools** developed for the purposes of the project will be made available **open-source**, and will be accessible to other companies/developers to use this as **a basis for further market-specific applications** which can accommodate the specifics of local digital ecosystems, allowing flexibility to best support longer-term implementation of the integrated digital healthcare approach;
- the implementation will enable relevant and approved updated trusted health information to be pushed in a timely manner to ensure adherence with changes in safety or usage information to continue to enhance patient adherence and safety after and with patient permission to receive alerts pertinent to them;
- the **digital approach and technology developed** under the project has the potential to transform the patient experience as they engage with and manage their health and care throughout their healthcare journey. The figure below illustrates how such a journey may be envisaged in the future, in an environment in which digital information sources are integrated effectively and tailored to the needs of the individual.

Figure 1. Illustrative use case (prescription scenario)



Applicants should indicate how their proposal will impact the competitiveness and industrial leadership of Europe by, for example, engaging suitable small and medium-sized enterprises (SMEs).

Potential synergies with existing consortia

This proposal is expected to develop synergies, build on results, and avoid duplication of efforts with existing consortia and current e-PI/EHR initiatives at national, EU, and international level. The development of the global IDMP (ISO)[63] standard for the product database can further be regarded as a potential synergy to this project. Applicants should assess existing opportunities for synergies with other ongoing initiatives at a

[63] Identification of Medicinal Products (International Organization for Standardization). See https://www.ema.europa.eu/en/human-regulatory/overview/data-medicines-iso-idmp-standards-overview

regional or national level, in particular in the fields of ePI and EHR and demonstrate in their proposals how they will synergise with such initiatives in order that the project can leverage relevant expertise to the maximum degree

Collaboration agreements

There is the potential for important synergies between the consortium selected under this topic and the one selected under IMI2 JU Call 18 topic 2 (Health Outcomes Observatories – empower patients with tools to measure their outcomes in a standardised manner creating transparency of health outcomes). On the one hand, for instance, while the consortium selected under this topic 3 should have access to sufficient EHRs and patients to meet its own objectives, this consortium could also leverage the observatory platform in order to obtain access to and analyse additional relevant electronic health record (EHR) data, in compliance with applicable regulation, gathered under topic 2. On the other hand, the consortium selected under this topic could become an additional important use-case for the observatories under topic 2 and improve their usefulness. Additionally, the perspectives brought by the consortium selected under topic 3 can contribute to development of the governance and operational model of the observatories, under topic 2. It could also help future-proof them as a neutral guardian of patients' health data which could then be made available in the future with the appropriate safeguards for applications, such as those envisaged under topic 3.

To explore these potential synergies between actions funded under these two topics, the selected consortia are expected to cooperate in common boards/structures and provide access to their results for specific activities when relevant. Therefore the grants awarded under IMI2 JU Call 18 topics 2 and 3 will be complementary grants. The respective options under Article 2, Article 31.6 and Article 41.4 of the IMI2 JU Model Grant Agreement[64] will apply. Accordingly, the relevant consortia will conclude collaboration agreement(s) to ensure the exchange of relevant information, exploration of synergies, collaboration where appropriate.

Industry consortium

The industry consortium is composed of the following EFPIA companies:

- Pfizer (Lead)
- Astra Zeneca
- Bayer
- Grunenthal
- Lilly
- Medidata
- Mylan
- Novartis
- Roche
- UCB

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

- Datapharm
- Medicines for Europe

The scope of the research proposed is wide-ranging, and hence the industry contributors are offering functional expertise across a range of disciplines aligned to the project scope and objectives. These areas of expertise include: knowledge of development and maintenance of product information, and its central place in pharmacovigilance and risk management/minimisation methodologies; the importance of health literacy and the provision of high quality medical information; the use of real-world data to improve understanding of product safety and effectiveness; business technology expertise concerning development of systems; processes, and data standards to support regulatory processes; and knowledge of development and implementation of EHR systems.

[64] See: https://www.imi.europa.eu/sites/default/files/uploads/documents/reference-documents/h2020-mgaimi_en_v5.pdf

Indicative duration of the action

The indicative duration of the action is 60 months.

Indicative budget

The indicative in-kind and financial contribution from EFPIA partners and IMI2 JU Associated Partners is EUR 9 280 000

This contribution comprises an indicative EFPIA in-kind contribution of EUR 9 070 000 and an indicative IMI2 JU Associated Partners in kind contribution of EUR 210 000.

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.

The financial contribution from IMI2 JU is a maximum of EUR 9 280 000.

Applicant consortium

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

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

This may require mobilising, as appropriate the following expertise:

- **patient groups/healthcare professional groups** to ensure that the perspective of the end user is taken into account fully in the research scope, the development of appropriate KPIs relating to the two key objectives, and also for the proof of concept testing;
- **academic and research institutes** specialising in the **provision/use/understanding of health information**, who can support the definition of appropriate KPIs relating to the two key objectives, and development of an appropriate methodology for testing to demonstrate patient understanding and impact;
- expertise **in gathering/use/analysis of real-world data and risk-benefit assessment**, to consider the effectiveness of the platform as a risk minimisation tool;
- expertise on the **legal, ethical, social science and GDPR questions** arising from the proposed work;
- **technology partners**, including SMEs, who have proven experience **in electronic health records, provision of health information (for example current leaders of national electronic product information initiatives)**, platform integration and development of user-centric solutions within a highly secure environment, and provision of business/regulatory information technology. User-centric solutions need to be designed with the patient journey in mind, covering measures which will improve patient adherence to treatment (e.g. adherence checks), patient understanding of the product information (e.g. novel interactive question and answer features), and the delivery of novel forms of personalised product information (e.g. video, pictorial, digital assistant) based on defined criteria coming from EHRs or other data-entry methods. **Interest from SMEs** who can offer technical expertise that could support the development of the technology envisaged under the project is welcomed;
- ideally, **national competent authorities** would be part of the applicant consortium to ensure alignment with national initiatives.

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

- applicants should demonstrate access to appropriate data sources spanning product information and EHRs in at least one country. It is proposed to conduct the study in several markets;
- existing relevant digital technologies that can be further developed during the project.

Experience and engagement with relevant digital health initiatives

Applicants should demonstrate how they will seek to take advantage of established/planned digital health initiatives within relevant member states, in particular in relation to ePIs and EHRs.

Interaction with regulators

In their proposals, applicants should have a plan for engaging with regulators (for example, seeking scientific advice from the European Medicines Agency and/or national competent authorities). This is to ensure alignment with any new e-labelling principles across the region, but also to consider the potential impact on legislation to allow the development of recommendations for the introduction of successfully proven solutions in due course. At a minimum, it is anticipated this will occur prior to initiation of testing activities in the specific Member States and during the development of implementation recommendations in the later phases of the project. Suitable resources should be dedicated to these activities.

Data management

In their short proposal, applicants should give due visibility to 'data management'. Applicants should include proposals for how concerns relating to data privacy/GDPR may potentially be addressed. At stage 2, applicants should include a draft data management plan (DMP) in the full proposal, outlining how research data will be handled and made available during the project and after it is completed.

Dissemination, exploitation and communication activities

In their short proposal, applicants should give due visibility to the dissemination, exploitation and communication of the project's results. At stage 2, in their full proposal, applicants should further develop these activities.

Partnership with the industry consortium

In their short proposal, applicants should outline a strategy to create a successful partnership with the industry consortium.

Sustainability planning

In their short proposal, applicants should outline how they have considered the longer-term sustainability of the project outputs.

Suggested architecture of the full proposal

The applicant consortium should submit a short proposal which includes their suggestions for creating a full proposal architecture, taking into consideration the industry participation including their contributions and expertise provided below.

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.

The architecture outlined below for the full proposal is a suggestion. The architecture of the full proposal should be designed to fulfil the objectives and key deliverables within the scope of this topic.

The proposed project should be phased with an initial focus on product information, then moving on to linkages with electronic health records, and the development of a two-way communication channel to the patient to assess the potential of the platform as an effective risk minimisation tool. A final phase of the

proposed project should focus on the expansion of content within the platform to include a wider scope of health educational materials will be considered after the project has proven the utility of the integrated platform across product information and EHRs. In each phase of the proposed project, attention will be paid to ensuring that the platform is delivering a *meaningful* effect on patient understanding and adherence before moving to the next stage.

Phase 1: Establishing stakeholder needs and development of appropriate KPIs

Research activities to define key patient/user needs and preferences in terms of information, personalisation and functionality as described above across product information and EHRs. Testing scenarios will be assessed during this phase. In addition, technology contributors/partners will be assessing the feedback and analysing its feasibility and complexity for consideration in technology development planning. KPI development will begin to enable measurement of enhanced understanding/adherence during the planned studies.

Phase 2: Sourcing, developing, testing, and measuring the effectiveness of digital solutions to meet defined user needs through a series of proof-of-concept projects

Work packages across both of the initial information areas (product information & EHR) will manage the next phase of activities during which technologies will be built and tested in initial proof–of-concept studies.

In parallel, the technical development and evaluation of the ability of digital solutions to enhance risk minimisation approaches through the generation of real-world data will begin, so that this element of functionality can be incorporated into the digital tool as a basis for further testing. The work packages will proceed in parallel.

Phase 3a: Sourcing, developing, testing, and measuring the integrated digital solutions to meet defined user needs in a proof-of-concept study

Proof-of-concept testing of the fully integrated prototype digital solution to demonstrate a benefit on identified measures relevant to patient health.

Phase 3b: Extension to include health educational materials

This last phase will only proceed if Phase 3a is successful and will look to identify and include trusted sources of health educational material to further enhance patient understanding. The methodology will be developed to define how such sources may be identified, assessed, and included (either linked or embedded) within the platform and tested with users.

Ongoing: Development and execution of a sustainability plan

A sustainability plan will be developed over the life of the project, and then executed to allow the development of recommendations based on project outputs that would consider how successful concepts will be carried forward and implemented. The initial plan will be developed at an early stage of the project, and then adapted in an agile manner in response to project outcomes. Horizon-scanning/landscape mapping to allow for identification of relevant digital health initiatives will also occur during the life of the project to ensure that the project outputs can be integrated successfully into the wider digital health ecosystem. Explore future case scenarios and drive thought leadership for next generation activities relevant to product information.

References

[1] Sabate E (2003). World Health Organization. Adherence to Long Term Therapies. Evidence for Action. Geneva. WHO. Available at: https://www.who.int/chp/knowledge/publications/adherence_report/en/

[2] Medication adherence is defined as 'the extent to which the patients' behaviour matches agreed recommendations from the prescriber' and thus illustrates the importance of the patients' decisions. See: Horne RWJ, Barber N , Elliot R , et al. Concordance, adherence and compliance in medicine taking. Report for the national coordinating centre for NHS service delivery and organization R & D (NCCSDO), 2005. http://www.netscc.ac.uk/hsdr/files/project/SDO_FR_08-1412-076_V01.pdf

[3] Viswanathan M, Golin CE, et al. Interventions to Improve Adherence to Self-administered Medications for Chronic Diseases in the United States: A Systematic Review, 4 Dec. 2012. https://doi.org/10.7326/0003-4819-157-11-201212040-00538

[4] Health literacy entails 'people's knowledge, motivation and competencies to access, understand, appraise, and apply health information in order to make judgments and take decisions in everyday life concerning healthcare, disease prevention and health promotion to maintain or improve quality of life during the life course'. Sorensen K et al. (2012), Health literacy and public health: A systematic review and integration of definitions and models BMC Public Health 12:80 https://doi.org/10.1186/1471-2458-12-80

Topic 4: Establishing international standards in the analysis of patient reported outcomes and health-related quality of life data in cancer clinical trials

Topic details

Topic code	IMI2-2019-18-04
Action type	Research and Innovation Action (RIA)
Submission and evaluation process	2 stages

Specific challenges to be addressed

Patient-centeredness is increasingly identified as a critical component of quality health care [1]. As such, health-related quality of life (HRQOL) and other patient-reported outcomes (PRO) that quantify how a patient feels or functions during treatment are increasingly considered as important endpoints in cancer clinical trials. Data on these endpoints are increasingly used to inform benefit-risk evaluations for regulatory marketing authorisation purposes. These endpoints are also useful in the context of reimbursement decision-making, where they are instrumental in evaluation of added therapeutic benefit and documentation of the value of surrogate endpoints such as progression-free survival (PFS) or overall response rate (RR). Moreover, information on HRQOL and PROs may also be used to enable better communication and shared decision making between patients and their treating physician, improving outcomes, treatment satisfaction and care.

Numerous efforts have been undertaken to standardise the way HRQOL and PRO data are conducted and reported in cancer clinical trials. These include recommendations to standardise reporting and drafting of clinical trials [2][3], translations in clinical trials [4]**Error! Reference source not found.**, and how to develop and standardise measures for use in clinical trials [5]. However, there are no agreed standards on how to analyse HRQOL and PRO data in clinical trials and subsequently, interpret the findings. The various ways data are analysed and interpreted make it difficult to compare results across trials, and hinder the application of research findings to inform physicians, patients, caregivers, policy makers, reimbursement authorities and other stakeholders. Lack of standardisation can lead to variation in the analysis of results and could result in two near-identical trials being analysed in different ways, leading to potential differences in data interpretation.

A number of systematic reviews from randomised controlled trials (RCTs) have highlighted the current lack of standardisation in this field and reported the following key findings [6][7][8]:

- a lack of clear HRQOL and PRO research objectives;
- a lack of standardisation of basic statistical terms such as compliance and completion rates;
- the use of suboptimal statistical practices and a variety of statistical methods not well justified with respect to analysing HRQOL and PRO data;
- the use of a variety of approaches to handling missing data.

There is an urgent need to develop clear standards and guidelines, endorsed by a broad range of stakeholders, to improve how HRQOL and PRO data are analysed in cancer clinical trials. This would also help promote HRQOL and PROs as potential primary or co-primary endpoints (when relevant) in cancer clinical trials. Such standards will support the full use and understanding of HRQOL and PROs in drug development and drug and device approval by regulators and health technology assessment (HTA) bodies, but importantly it will also support better communication of PRO results to clinicians and patients with the potential to inform and improve shared decision-making.

Need and opportunity for public-private collaborative research

This initiative aims to establish a multi-stakeholder consortium with the overall objective to standardise and develop recommendations for the analysis and interpretation of HRQOL and PRO data in cancer clinical trials. The focus of this topic is to achieve a consensus on the analysis methods of HRQOL and PRO data in RCTs. However, as other study designs (e.g. single arm studies, basket trials) are also starting to play an important and innovative role in cancer drug development, there is general agreement that guidelines and best practices also need to be developed for these trial designs. Moreover, once these new standards and guidelines are

developed, it is critical to validate them using existing data from academic and pharma-led clinical trials. Finally, PRO findings based on these recommended analyses must be communicated in a simple and accurate way to clinicians, patients and other stakeholders.

To be able to address this challenge, the concerted efforts of different experts from various organisations are needed. It is critical to have a broad based consortium to include a wide range of experts and organisations. For instance, patient groups and their representatives, healthcare decision makers, regulators and representatives from HTA authorities and other public health bodies are needed, as well as experts from the pharmaceutical industry. Small and medium-sized enterprises (SMEs) may also play a role in the development of data visualisation software which should demonstrate added value to the regulatory and HTA bodies.

Scope

The scope of this Call topic is to develop recommendations for the different analyses and interpretations of HRQOL and PRO endpoints in cancer clinical trials that will be tailored towards addressing specific research objectives within each clinical trial. This Call topic aims for a global scope and is of strong interest to individuals from various regulatory and HTA bodies, key cancer organisations, the pharmaceutical industry, specialised vendor organisations, academic societies and international patient organisations. The buy-in of these various key stakeholders is crucial, as this will help identify a set of similar expectations, facilitate the implementation of these recommendations, and harmonise the analysis and interpretation of HRQOL and PRO data on a global scale.

The main objectives are to:

- achieve international consensus, across stakeholders, on the optimal use of HRQOL and PRO data in cancer clinical trials;
- improve the quality of statistical analysis of HRQOL and PRO data in cancer clinical trials;
- improve the standards of reporting of HRQOL and PRO data, and as such the interpretability of the data. It is hoped that this will result in more reliable interpretation, and ultimately faster dissemination, of HRQOL and PRO findings, as well as cross-referencing within and between different cancer settings, whenever this is deemed feasible.

Expected key deliverables

The work should lead to several important key deliverables and consensus documents that are aligned with relevant stakeholders; alignment with regulatory and HTA bodies will be especially important as this will be critical to successful implementation. Continuous collaboration throughout the project with representatives from patient advocacy groups is vital to ensure the patient-centricity of the research recommendations, dissemination strategies and patients' understanding of educational programmes.

The deliverables below should be achieved during the 48 months duration of the project.

- Work towards the development of internationally agreed consensus-based guidelines and recommendations for HRQOL and PRO analysis for RCTs, supported by relevant publications:
  a) recommendations to support the development of industry guidelines for the design, analysis and interpretation of HRQOL and PRO findings from cancer clinical trials;
  b) recommendations to support the development of regulatory guidance, such as European Medicines Agency (EMA) Points to Consider, and HTA guidelines for the design, analysis and interpretation of HRQOL and PRO findings from cancer clinical trials;
  c) recommendations to support the European Society for Medical Oncology (ESMO) and American Society of Clinical Oncology (ASCO) guidelines on assessing clinical benefit using HRQOL and PRO data from cancer trials;
  d) recommendations for dissemination strategies and educational programmes designed specifically to improve patients' understanding of HRQOL/PRO and empower their abilities for shared decision making;
  e) recommendations for clinically meaningful change for HRQOL/PRO instruments used in cancer clinical trials.
- Delivery of a case study database to retrospectively validate consensus recommendations;

- A freely accessible toolbox providing recommendations for the communication, presentation and visualisation of HRQOL and PRO findings from cancer RCTs, including templates that are freely available to all users and promoted in all literature;
- Evaluate the feasibility of developing recommendations for non-RCTs, using single-arm studies as a case study (this should be closely linked to the main recommendations for RCTs to ensure uniformity in terminology and synergy of complementary ideas);
- A sustainability and capacity building plan to ensure that recommendations for PRO analysis in cancer clinical trials remain constantly up to date and relevant, including establishing an ongoing governing advisory board (with defined roles and responsibilities) to give advice on future updates to the recommendations.

Recommendations will be widely disseminated, where appropriate, and made available through a publicly accessible website that also allows access to other deliverables; use of this website's resources, along with implementation of the recommendations by regulatory agencies and HTAs, will be instrumental in ensuring the success of this initiative.

Expected impact

A consensus and clear set of agreed methodological recommendations for the statistical analysis of HRQOL and PRO data in cancer studies will improve their interpretability. This is an important prerequisite for better adoption and increased use of these outcomes in various decision-making contexts (regulatory approval, HTA/reimbursement decisions, shared decision making between physicians and patients). Importantly, the expected outcomes of this initiative will be of mutual benefit to all stakeholders involved, including the most important beneficiary of healthcare, the patient. Reaching a broad international consensus is a prerequisite for a broader adoption of HRQOL and PRO data and is likely to result in:

- more reliable findings and faster dissemination of HRQOL and PRO data in cancer studies;
- advances in statistical science and improved statistical practice in cancer studies;
- improved interpretability of the data because of greater familiarity with standardised reporting;
- broader use and adoption of PRO data to inform benefit-risk evaluation in regulatory appraisals, added benefit evaluation in HTAs and reimbursement decision processes as well as shared treatment decision making contexts;
- better and improved shared decision making between patients and their treating physicians which may lead to improved patient satisfaction, an increased likelihood of adherence to treatment, higher likelihood of treatment success and a reduction in health-care cost;
- better and more efficient use of increasingly finite research and healthcare funding;
- improved and more efficient clinical trial designs that also investigate the cancer patient perspective on treatment outcomes.

Applicants should indicate how their proposal will impact the competitiveness and industrial leadership of Europe by, for example engaging suitable small and medium-sized enterprises (SMEs).

Potential synergies with existing consortia

Applicants should take into consideration, while preparing their short proposal, relevant national, European (both research projects as well as research infrastructure initiatives), and non-European initiatives. Synergies and complementarities should be considered in order to incorporate past achievements, available data and lessons learnt where possible, thus avoiding unnecessary overlap and duplication of efforts and funding. Proposals should document how collaboration will be achieved.

Possible synergies and collaborations will exist with the following initiatives and it is vital for the success of this project that close collaboration and alignment with these institutions should be sought by the applicants:

- The Setting International Standards in Analysing Patient-Reported Outcomes and Quality of Life Endpoints Data (SISAQOL) Consortium, managed by the European Organisation for Research and Treatment of Cancer (EORTC), currently working on guidelines for the analysis of PRO data;
- The Standard Protocol Items: Recommendations for Interventional Trials (SPIRIT)-PRO/ Consolidated Standards of Reporting Trials (CONSORT)-PRO (https://www.equator-network.org/reporting-guidelines/spirit-pro/) who recently published standards and are collaborating on standards for designing clinical trials, including non-RCT cancer trials;
- The Critical Path Institute (C-PATH - https://c-path.org/): a group working on PRO in the United States and working on the important area of developing electronic PRO measurements;

- EMA who have developed guidelines on PRO assessment; [9]
- The Food and Drug Administration (FDA) who have recommendations on PRO assessment in label claims, although limited guidance in terms of statistical analysis or interpretation; [10]
- The International Society for Quality of Life Research (ISOQOL; http://www.isoqol.org/) and International Society for Pharmacoeconomics and Outcomes Research (ISPOR: https://www.ispor.org/) working groups;
- Health Canada (https://www.canada.ca/en/health-canada.html) and the Japanese Clinical Oncology Group (http://www.jcog.jp/en/) who are developing new efforts towards making PRO an important national endpoint;
- Oncology societies that have made major steps in oncology: ASCO (https://www.asco.org/) and ESMO (https://www.esmo.org/).
- Study data from existing EU-funded (from the FP6/FP7/H2020 research portfolio) RCTs and observational studies addressing palliative, end-of-life and survivorship care could be potentially used to validate the recommendations for statistical analyses developed in this initiative, if feasible.

Industry consortium

The industry consortium is composed of the following EFPIA companies:

- Boehringer Ingelheim (lead)
- AbbVie
- Bayer
- Bristol-Myers Squibb
- Merck KGaA
- Pfizer

The industry consortium will contribute the following expertise and assets:

- in-depth knowledge of the advantages and disadvantages of various statistical methods and how they can be matched to identified research objectives;
- contributing to the review of clinically important responders and clinically important differences for various instruments and developing best practice recommendations for future instruments including outcome item banks;
- participation at all consensus meetings; making proposals, discussing options and contributing to guideline drafting and review;
- validating guideline recommendations by re-analysing existing data-sets and implementing them in prospective case studies;
- discussing and assessing the operational feasibility of implementing guideline recommendations in future cancer studies;
- contributing to developing educational tools and dissemination materials.

Indicative duration of the action

The indicative duration of the action is 48 months.

Indicative budget

The indicative in-kind and financial contribution from EFPIA is EUR 2 900 000.

This contribution comprises an indicative EFPIA in-kind contribution of EUR 2 000 000 and EUR 900 000 as financial contribution to the beneficiaries receiving JU funding in the selected action.

At stage 1, applicants should provide a suggested allocation of the total financial contribution (EUR 3 182 000) in the budget of their short proposal in order to achieve the proposed objectives.

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.

The financial contribution from IMI2 JU is a maximum of EUR 2 282 000.

Applicant consortium

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

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

To be successful, the applicant consortium will need to effectively combine the expertise of the various stakeholders in order to harmonise and standardise HRQOL and PRO analysis for cancer RCTs. Therefore, the successful consortium should have representatives from these key stakeholders or demonstrate plans to bring in necessary stakeholders and in-depth knowledge, as appropriate:

- regulatory affairs expertise with a proven track record of interacting with key regulatory agencies;
- representatives from HTA agencies;
- biostatisticians, epidemiologists, psychologists, and HRQOL and PRO researchers with experience in cancer RCTs (mandatory as participants);
- clinicians and other health-care professionals with experience in the design and conduct of cancer randomised clinical trials;
- representatives from academic medical and methodological societies;
- experts in the visualisation and presentation of HRQOL and PRO data;
- cancer patient advocacy groups, with knowledge and experience in cancer clinical trials (for activities in work package 7).

Optional:

- representatives from key cancer/medical journals;
- experts (including SMEs) in communication and knowledge dissemination;
- experts in interaction and communication with an international, multi-disciplinary stakeholder group.

The applicant consortium is also expected to have access to closed, completed cancer randomised controlled trial datasets with HRQOL/PRO assessments. Ideally, such data sets will be international and collected in the academic based clinical trial setting. The applicant consortium is expected to possess the necessary project management skills suitable for the consortium activities including organising and conducting consensus meetings.

The resources allocated should be adequate for the complexity and size of the consortium.

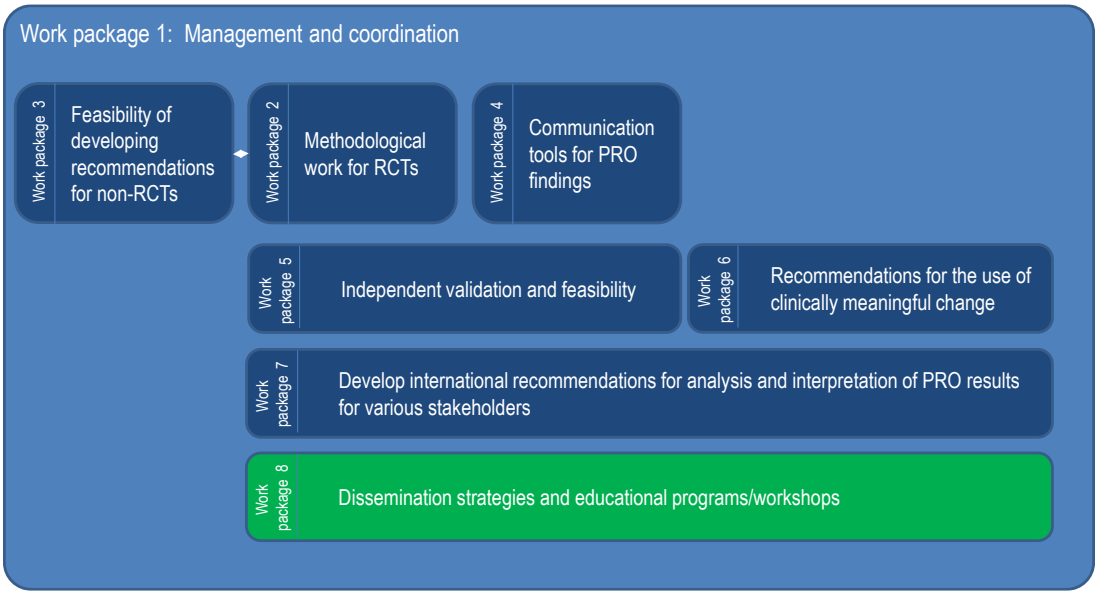
Suggested architecture of the full proposal

The applicant consortium should submit a short proposal which includes their suggestions for creating a full proposal architecture, taking into consideration the industry participation including their contributions and expertise provided below.

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.

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

The below architecture for the full proposal is a suggestion. The architecture of the full proposal should be designed to fulfil the objectives and key deliverables within the scope of this call topic.



Work package 1 – Management and coordination

The goals of this work package are to:

- establish a working governance structure, ensuring that various key stakeholder groups are well-represented;
- establish an internal communication structure to ensure the harmonisation of work across project teams;
- organise project-wide meetings;
- budget administration;
- communicate with the project team and relevant external stakeholders to ensure alignment and uptake of recommendations;
- establish an independent ethics advisory task force to help ensure all ethical aspects of the research and their recommendations conform to H2020 standards and norms.

Industry contribution:

- project leader;
- coordination across different work packages (including overall scientific and strategic oversight).

Expected applicant consortium contribution:

- project coordinator;
- professional project management expertise (daily operational support with project meetings, reporting and internal communication), see also section on applicant consortium.

Work package 2 – Methodological work for cancer RCTs

The goals of this work package are to:

- identify and update valid PRO objectives for RCTs and translate them into estimands;
- set criteria to help design the timing and frequency of PRO assessments (including baseline), balancing the need for assessments at clinically relevant time points and reducing patient burden;
- set criteria to assess quality of collected PRO data, ensuring that there is enough good quality data available to respond to the PRO objectives;
- set criteria to identify appropriate statistical methods to analyse PRO data;
- match appropriate statistical methods to valid PRO objectives;

- provide recommendations on the interpretation of PRO findings based on the trial objectives, data quality and statistical methods used;
- ensure close communication with work package 3, ensuring that the key criteria needed for drawing conclusions of PRO findings are correctly represented in the communication tools for various stakeholders;
- provide guidelines on when an update of the methodological work would be needed.

Work package 3 – Feasibility of developing recommendations for non-RCTs, with single-arm studies as a case study

The goals of this work package are to:

- identify case studies in which PROs were used in single-arm cancer clinical trial studies;
- identify the needs of various stakeholders to assess PROs in single-arm studies;
- identify valid PRO objectives that can be addressed by single-arm studies and set criteria needed to evaluate PROs in single-arm studies as well as criteria to evaluate the potential bias for single arm, open-label studies;
- evaluate aspects of RCT recommendations that can be adapted to single-arm studies.

It is recommended that this work package be closely linked to the main work for RCTs to ensure uniformity in terminology and synergy of complementary ideas.

Work package 4 – Communication tools for PRO findings from cancer clinical trials

The goals of this work package are to:

- set criteria and general guidelines for presentation and visualisation of PRO findings from cancer RCTs – this should be done in close collaboration with work package 2;
- identify the needs of various stakeholders (regulatory, HTA, patients, clinicians, journals, academics) on how they want the PRO results from clinical trials to be reported;
- produce templates for the visualisation and presentation of PRO findings that would fit the needs of different stakeholders;
- provide guidelines on when an update of the communication tools would be needed.

Work package 5 – Independent validation and feasibility of methodological work and communication tools

The goals of this work package are to:

- manage and coordinate the use of research data including legal and ethical considerations;
- identify case studies for this project:
    - retrospective cancer clinical trials data with HRQOL/PRO assessment;
    - prospective cancer clinical trials that will include a HRQOL/PRO assessment.
- using the case studies, implement and assess the feasibility of the approaches from work packages 2–3, including identifying gaps and recommending solutions for each of these gaps;
- provide guidelines on when additional validation and feasibility checks would be needed.

Work package 6 – Develop international recommendations for the terminology and definitions of clinical meaningful change in cancer clinical trials

The goals of this work package are to:

- identify best practices to develop clinical meaningful change research objectives for the most commonly used HRQOL/PRO instruments in cancer trials that clearly differentiate group level differences and individual level differences. Recommendations need to recognise the wide-range of terminologies currently used in the literature which include, but are not limited to minimum clinically important differences (MCIDs) / minimum important differences (MIDs) and responder thresholds;
- investigate whether these approaches can be generalised to emerging new instruments and item banks;

- Develop final recommendations for the use of terminology and definitions in HRQOL/PRO assessments in cancer trials that are agreed by the main stakeholders including regulatory agencies, HTA agencies as well as ESMO and ASCO;
- Provide guidelines on when updates of recommendations would be needed.

Work package 7 – Develop international recommendations for analysis and interpretation of PRO results for various stakeholders

The goals of this work package are to:

- identify a procedure to ensure recommendations are based on a consensus and that key experts and stakeholder groups are well-represented;
- ensure that the needs of the various stakeholders are considered in the final recommendations including feedback from representatives of leading patient advocacy organisations;
- provide final recommendations based on the combined results from work packages 2, 4, 5 and 6 for the various stakeholders to:
    - support the development of industry guidelines for the design, analysis and interpretation of PRO findings from cancer clinical trials;
    - support development of regulatory and HTA guidelines for the design, analysis and interpretation of PRO findings from cancer clinical trials;
    - support ESMO and ASCO guidelines on assessing clinical benefit.
- provide guidelines on when an update of the recommendations would be needed.

Work package 8 – Dissemination strategies and educational programmes/workshops

The goals of this work package are to:

- provide a continuous dissemination and communication plan (including social media) to ensure that project results are communicated to both internal and external stakeholders;
- provide an educational tool based on the work from the different work packages for different stakeholders;
- ensure close collaboration with all Work package leaders to ensure proper and efficient dissemination of results from the various work packages are disseminated;
- a feasibility plan and guidelines for updating relevant PRO objectives, statistical methods and handling of missing PRO data based on future developments in methodology and changes in the cancer clinical trial environment. The goal is to have a live document that will be available for all stakeholders in the long-term;
- provide educational tools and develop required knowledge to assess, analyse and interpret PRO data in cancer clinical trials for all relevant stakeholders including patients.

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[3] Zikos, E., et al., *Health-related quality of life in small-cell lung cancer: a systematic review on reporting of methods and clinical issues in randomised controlled trials.* Lancet Oncol, 2014. **15**(2): p. e78-89.

[4] Koller, M., et al., *Translation procedures for standardised quality of life questionnaires: The European Organisation for Research and Treatment of Cancer (EORTC) approach.* Eur J Cancer, 2007. **43**(12): p. 1810-20.

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[6] Bottomley, A., et al., *Moving forward toward standardizing analysis of quality of life data in randomized cancer clinical trials.* Clin Trials, 2018. **15**(6): p. 624-630.

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[9] EMA (CHMP): *Reflection paper on the regulatory guidance for the use of healthrelated quality of life (HRQL) measures in the evaluation of medicinal products.* 2009.

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Topic 5: Accelerating research & innovation for advanced therapy medicinal products

Topic details

Topic code	IMI2-2019-18-05
Action type	Research and Innovation Action (RIA)
Submission and evaluation process	2 stages

Specific challenges to be addressed

Curative or near curative therapies for rare and orphan diseases have been a long-held desire for many in the biomedical research and development arena, including patients. Rare diseases are often very severe, genetically driven illnesses with high morbidity and mortality that place a large burden on families of patients and healthcare systems. Though these diseases are relatively rare, the costs of medicines are high, even for many that provide only marginal benefit. Gene therapy and cell therapy provide an opportunity for a curative, single treatment for many of these devastating diseases, eliminating the need for chronic treatment. This topic aims to accelerate the research and development of advanced therapy medicinal products (ATMPs) by filling gaps in our knowledge base in, and tools for, gene and cell therapy. This will provide medicines developers and regulators with the information they need to more swiftly move these potentially transformative medicines forward so that they can benefit patients in need.

The goal of gene and cell therapy is to provide, with a single treatment, sustained therapeutic levels of transgene expression or cell activity, with potentially life long duration. This can be achieved employing classical viral vectors and cells transformed using viral vectors, or by novel means based on non-viral technologies, cellular encapsulation, etc. [1][2] Challenges to this goal are immunological and non-immunological factors that may impact persistent expression and eligibility for treatment. [3] [4] [5] Patients with pre-existing neutralising antibodies (nAbs) due to natural viral infections that result in cross-reactive antibodies, or perhaps due to prior exposure to viral gene therapy capsids, are typically excluded from treatment [6][7]. After treatment, patients are also excluded from redosing due to the high titer nAb response to the dose of vector [8]. Additionally, some patients, when treated systemically with gene/cell therapy, mount an immune response to transduced cells that have resulted, in some instances, in damage to targeted liver and muscle tissues [9]**Error! Reference source not found.**. Molecular features, such as concatemer state and integration mechanism, may influence persistence which in turn may be impacted by age and tissue target [10]**Error! Reference source not found.**. Consequently, the potential dilutional impact of tissue division and growth on persistence requires deeper molecular understanding to develop efficacious and long-lasting gene/cell therapy products.

Conventional medicinal product characterisation, clinical safety/efficacy, and regulatory requirements already pose challenges to developing treatments for rare monogenic diseases. These challenges are amplified for gene and cell therapies due to knowledge gaps in our understanding of these ATMPs for viral or non-viral approaches. By addressing these existing knowledge gaps, we hope to accelerate and improve the feasibility of product development and decrease development time and costs to bring effective new advanced therapies to patients. For many aspects of ATMP biology and safety, regulatory agencies have to consider theoretical concerns in this emerging field, largely due to a lack of supporting data and evidence. This can be a major burden for the efficient development of ATMPs.

To streamline regulatory requirements, it would be highly beneficial to continue to build a greater understanding and evidence-base of essential performance parameters needed in the field of gene/cell therapy. Those parameters include: persistence of gene/cell therapy efficacy; potential for re-treatment; the impact of host immunology on patient inclusion and product efficacy; the molecular characterisation of common features of each delivery modality and the possibility of creating ’plug-and-play’ platform approaches; and the delineation of the right balance between the standards for product characterisation, safety, and the value of the medicine.

Need and opportunity for public-private collaborative research

Collaboration between public and private partners is essential and will enable directed research to solve the challenges posed in this topic; provide learning opportunities for the next generation of scientists in the ATMP area; and foster open scientific interaction in the public domain. Much of the expertise in gene and cell therapy lies in academia, however, clear data important for ATMP development regarding host responses, persistence of efficacy, redosing, and safety is lacking. Working together in this public-private partnership, combining the deep expertise and innovation in vector design, adeno-associated virus (AAV) biology, cell biology, and immunology that resides in academia, with growing industry ATMP development expertise and data emerging from clinical trials, as well as regulatory expertise lying in regulatory agencies, will create synergies that will enable the building of a data-driven consensus around ATMP biology, immunology, and persistence. This in turn will support the development of guidance by regulators on the development of ATMPs.

Scope

The main focus of this topic is to develop a product characterisation framework and methodologies that are limited to the pre-competitive space. Though much of the work will be to understand aspects of gene or cell therapy in general without a particular disease focus, there may be some work that utilises disease models to accomplish the appropriate characterisation. The disease focus will be on non-oncological, monogenic rare diseases. Therefore, this topic intends to utilise both therapeutically relevant systems, as well as model systems that rely on the use of marker transgenes. In order to develop such a framework, there is a need for a coordinated and substantive effort to acquire and analyse the currently available data and then design preclinical and clinical studies to fill the knowledge gaps. This information will help to address gene/cell therapy risks and also guide product developers and regulators to determine and implement an appropriate and effective characterisation framework to enable efficient and safe development of gene/cell therapies.

The main objectives of the topic, intended to address existing knowledge/data and tools gaps focused on viral-mediated gene therapy and cell therapy, are to:

1. develop better, standardised models for predicting product immunogenicity in humans;
2. build our understanding of gene/cell therapy drug metabolism inside a host and explore any loss of efficacy (persistence), particularly with non-integrating viral vectors or cell therapy;
3. understand the clinical factors around pre-existing immunity limiting patient access to ATMP therapy, and adaptive immune responses affecting product safety, efficacy and persistence, including for integrating vectors-based therapies;
4. engage regulators to ensure that the models and data generated through the funded action will provide the necessary information to support regulatory filings and to address regulatory and safety concerns.

Specifically, the scope of the project is expected to address the following points:

- **Develop better, standardised models for predicting ATMP immunogenicity in humans:** some aspects of human immunology are not adequately captured in current pre-clinical models. Improving these models would enable development of regimens for modulating humoral and cellular immune responses to cell and gene/cell therapy products. Specific areas to address for each ATMP type are:
    - Gene Therapy: predictive tools for testing immunogenic properties of viral or non-viral delivery systems, or their combinations, to enable the design of vectors that will evade immune recognition in order to: 1) treat a higher proportion of patients; 2) achieve successful transfer of the therapeutic gene protein to the target cells; and 3) mitigate the risk of immunotoxicity on target organs.
    - Somatic cell therapy: expand on current paradigms in transplantation immunology using innovative *ex vivo* and *in vivo* systems. Aim for a deeper understanding of mechanisms that influence acute immune responses at the site of implantation and how the nature of disease affects long term immunity against therapies using autologous, allogeneic, or xenogeneic non-germline cells.
    - Tissue engineered products: develop new models to investigate the innate and adaptive immunity that contribute to the inflammatory response to natural and artificial scaffold structures.
- Characterise host, tissue, and target cell metabolic responses to gene/cell therapy vectors and transgene products to understand persistence: As many rare genetic diseases manifest in childhood

and the cells in the target organs in young patients continue to divide, it is of interest to characterise the dilution of the therapeutic effect, which is most likely different depending whether viral or non-viral vectors may have been used. Specifically, it needs to be investigated whether there is a dilution effect in children and/or in specific organs or tissues. It is of interest to characterise the metabolism of the vector genome in different cell types to understand whether rates of degradation, episomal maintenance, or integration vary from cell to cell, and to define strategies to improve the persistence of vector genomes. Prospective paediatric samples may be obtained to explore how the levels of expression are affected by growth.

- Understand the clinical factors around pre-existing immunity limiting patient access to ATMP therapy, and adaptive immune responses to gene/cell therapy drug substance and product: in order to address challenges of potential immunologic barriers, the funded action is expected to:
    - develop novel protocols for the modulation of immune responses to capsids, cells, and transgene products, or induction of tolerance to expressed transgene products, as well as components and materials used for non-viral vectors, or induction of tolerance to expressed transgene products;
    - develop cohesive metrics for immunological characterisation applicable in gene and cell therapies, for both patient inclusion and post-treatment monitoring phases;
    - develop standardised pathways for the characterisation of pre-existing immunity to gene/cell therapy products, including memory T-cells and neutralising and binding antibodies;
    - establish a geographically diverse prospective biobank from treated and untreated donors with matching cell, serum, and plasma samples to enable the evaluation of the pre-existing and adaptive immunity, assuring that appropriate informed consent is obtained, and privacy maintained;
    - develop and standardise innovative characterisation/functional assessment methods for gene/cell therapy drug substances and products;
    - evaluate the safety risk of administering viral and non-viral vectors in the presence of humoral and/or cellular immunity;
    - evaluate novel approaches to allow for vector re-administration in order to re-establish therapeutic protein levels.
- Engage with regulators to ensure the results of the funded action will support regulatory filings and address regulatory and safety concerns: specifically, concerns such as insertional mutagenesis/carcinogenicity, vector shedding, viral clearance, material biocompatibility, degradability, safety, and persistence, need to be addressed. In addition, since large amounts of data are generated across the field it is important to explore, jointly with regulators, how to bring this information together in a meaningful way to potentially address issues across a class of products. It is expected that the models and data generated through this funded action will provide the information needed to support the alignment efforts and the development of harmonised guidance through the International Council for Harmonisation (ICH), and optimise the risk-benefit of the ATMPs covered in this initiative. Therefore, the funded action is expected to:
    - gather examples, develop criteria and evaluate options to standardise differences in regulatory requirements across countries;
    - identify and address scientific gaps in current knowledge and generate new evidence/systems to support the development of improved standards for safety, while enabling accelerated product development;
    - identify mechanisms for unified regulatory approaches to key issues in gene/cell therapy development, including environmental assessments, the characterisation of replication competent viruses, viral clearance/shedding, patient screening criteria, and long-term follow up for persistence and delayed adverse events;
    - explore, and where feasible, enable developments that effectively and appropriately allow new developments to benefit from and utilise existing regulatory analogies or frameworks;
    - conduct a comprehensive review of clinical data and prepare a package (or white paper) aimed at evaluating the theoretical risk of insertional mutagenesis and formulating recommendations to the regulatory agencies.

Expected key deliverables

The expected key deliverables to be achieved during the duration of the funded project are:

- **in vitro**, **ex vivo**, and animal models with better translatability of the immune responses to gene/cell therapy; once in place these models should be sustainable;
- deep understanding of how host cells and tissues metabolise gene/cell drug products and how this affects persistence;

- identification of immunogenicity hurdles and potential solutions, for de-immunisation or immunomodulation that can improve overall efficacy and minimise patient risk along with a standardised vector characterisation platform;
- during the first year, the consortium is expected to develop a plan for which issues will benefit the most from a comprehensive database(s) to address regulatory needs;
- a sustainable, beyond the timeframe of the action, prospective biobank of samples obtained with appropriate informed consent and privacy from healthy volunteers and patients treated with gene or cell therapies;
- optimised and validated specific methods and models, which will increase regulatory acceptance and thereby facilitate the regulatory success of future gene therapy projects;
- standardised methods and gold standards to better characterise the products, such as potency, dose, and various quality properties.

Expected impact

Primarily, the action funded under this topic will fill gaps in our knowledge base around gene/cell therapy host responses which will allow for the data-driven development of a product characterisation framework to aid researchers, developers and regulators to more rapidly move effective and safe gene/cell therapies forward.

Understanding the host immune responses and the prevalence of pre-existing immunity in humans in broad geographic areas will be instrumental for finding the best immune-modulating regimens, thus increasing patient access to advanced medicines. Understanding the determinants of immunogenicity may enable re-dosing with gene/cell therapy products, while studying the mechanisms of persistence will help to define the optimal age for gene/cell therapy intervention.

Finally, joint efforts across pharma, biotech, academia, and regulatory functions will inform patient inclusion criteria, limit sub-therapeutic dosing, and define the impact of the pre-existing and adaptive immunity on the efficacy and persistence of gene/cell therapy. This broad understanding will help to focus industry resources on actual (not theoretical) risks and will facilitate the harmonisation of regulatory requirements. These improvements will, in turn, enable accelerated cures for rare diseases via a defined regulatory framework.

Applicants should also indicate how their proposal will impact the competitiveness and industrial leadership of Europe by, for example engaging suitable small and medium-sized enterprises (SMEs).

Potential synergies with existing Consortia

Applicants should take into consideration, while preparing their short proposal, relevant national, European (both research projects as well as research infrastructure initiatives), and non-European initiatives. Synergies and complementarities should be considered 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

- Pfizer (lead)
- Astellas
- Bayer
- Janssen
- Lonza
- Novartis
- NovoNordisk
- Sanofi
- Spark Therapeutics
- Takeda
- Viscofan

The industry consortium will contribute the following expertise and assets:

- Anonymised existing or prospective data from clinical trial cohorts from industry partners supplementing the academic cohorts;
- Personnel with in-depth knowledge in the fields of experimental and clinical immunology, cell and *in vivo* biology, virology/vectorology, histology, genetic toxicology, omics, chemistry manufacturing and

controls (CMC) analysis, medical affairs, statistics, regulatory, bioethics, epidemiology and non-clinical development;
- Know-how and means to support the establishment of the federated database including legal advice, setting up the database, and making analysis feasible, accessible and sustainable over time;
- A cash contribution, detailed in the indicative budget section, for supporting the derivation of a novel methodology for the modulation of immune responses to capsid and transgene products, and autologous or allogeneic gene-modified or unmodified transplanted tissues and cells. Similarly, develop protocols to induce tolerance to expressed transgene products or to autologous or allogeneic gene-modified or unmodified cell products. Also, for the design of improved hybrid vectors that have a higher efficiency of concatermerisation, and full-length vector genome reconstitution, and to accommodate transgenes that exceed the packaging capacity of AAV. Details will be decided by the full consortium at stage 2 when preparing the full proposal.

Indicative duration of the action

The indicative duration of the action is 60 months.

Indicative budget

The indicative in-kind and financial contribution from EFPIA partners is EUR 15 752 500.

This contribution comprises an indicative EFPIA in-kind contribution of EUR 14 500 000. The total financial contribution available from the EFPIA partners for activities in relation to the objectives of this action is EUR 1 252 500. The allocation of the EUR 1 252 500 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.

The financial contribution from IMI2 JU is a maximum of EUR 11 773 000.

Applicant consortium

The applicant consortium will be selected on the basis of the submitted short proposals. The applicant consortium is expected to address all the research objectives and make key contributions to the defined deliverables in synergy with the industry consortium, which will join the selected applicant consortium in preparation of the full proposal. Therefore, the consortium should mobilise all relevant expertise, skillsets and stakeholders to implement proposed activities in order to achieve the objectives of the topic. This may require mobilising, as appropriate the following:

- groups with experience and relevant skillsets in research and development and regulation of gene and cell therapy ATMPs, including experience with AAV biology and production, drug delivery, tissue engineering, predictive organ-tissue models, *in silico* simulation, cell biology and production, cell biology and production, transgenic animals, immunology, virology/vectorology, histology, omics, and *in vivo* experimentation;
- state-of-the-art experience and expertise in the establishment of databases, data harmonisation, database management and data security;
- experience in translating and conveying data for regulatory purposes;
- access to clinical cohorts and samples from patients dosed with gene or cell therapies.

The applicant consortium should engage with relevant patient organisations and incorporate patient input and active involvement into the project.

In addition to academic groups, relevant small and medium-sized enterprises (SMEs) are encouraged to participate in the applicant consortium.

The size of the consortium should be proportionate to the objectives of the project.

Suggested architecture of the full proposal

The applicant consortium should submit a short proposal, which includes their suggestions for creating a full proposal architecture, taking into consideration the industry participation including their contributions and expertise provided above and below.

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.

The consortium is expected to have a strategy for the translation of the relevant project outputs into regulatory and clinical practice. A plan for interactions with regulatory agencies / health technology assessment bodies with relevant milestones and resources allocated should be proposed.

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

The architecture outlined below for the full proposal is a suggestion. The architecture of the full proposal should be designed to fulfil the objectives and key deliverables within the scope of this proposal.

Work package 1 – Management, coordination, and dissemination

The goals of this work package will be as follows:

- general oversight and coordination;
- dissemination of research results and data amongst the consortium and into the public domain via workshops, publications, and presentations.

Expected applicant consortium contribution: project management including coordination of work package deliverables, periodic reporting and budget administration, dissemination of scientific results.

EFPIA consortium contribution: overall leadership of project goals, communication, and dissemination of project results.

Work package 2 – Develop better, standardised models for predicting product immunogenicity in humans

The goals of this work package will be as follows:

- develop models for evaluation of the impact of pre-existing immunity or of adaptive immunity on product efficacy and/or safety using *in vitro* cell-based assays and/or various routes of administration in relevant animal species, in combination with immune phenotyping methods (e.g. IgG profiling on protein arrays and multiplexed targeted protein profiling for innate and adaptive immunity key factors);
- expand on current mechanistic understanding of innate immune response during initial ATMP exposure, the priming of the adaptive response, and the maturation of the immune response against targeted tissues that can provide a basis for the rational design of immunomodulation protocols that can be evaluated in work package 4 for clinical application.

Expected applicant consortium contribution:

- innovative models of interactions between immune cells and target cells;
- next generation technologies for assessing immunity in those models across a breadth of immune cells and receptor repertoires;

- identification of cellular and/or protein biomarkers that could contribute to potential stratification of patients in order to reduce the risk of deleterious immune responses;
- application of the most relevant models (e.g. humanised rodent, non-human primates) already in use or under development;
- strategies for investigating the role of patient genotype on the anti-ATMP response, with consideration for how to mitigate for small numbers of subjects;
- translation of mechanisms learned from *in vivo* and *in vitro* systems to clinical approaches for immunomodulation or immunosuppression of the response to ATMP (in alignment with WP4);
- using the knowledge and patient samples from work package 4, develop methods to determine the predictive value of *in vivo* and *in vitro* models.

EFPIA consortium contribution:

- selection and prioritisation of models with an emphasis on those dealing with cellular immune responses;
- models, including *in vitro* and *in vivo* for evaluation;
- expertise in cellular immune assays including assay development, validation, and data interpretation;
- scientific input for innovative approaches to develop additional models;
- data management / bioinformatics infrastructure.

Work package 3 – Build our understanding of gene/cell therapy drug metabolism inside a host and explore any loss of efficacy (persistence), particularly with non-integrating viral or non-viral vectors or cell therapy

The goals of this work package will be as follows:

- WP3 broadly aims to understand the molecular stability and metabolism of AAV-derived therapeutic vector genomes, both wild type size and oversized, in target tissues, as well as that of non-viral approaches. This provides a unique opportunity to identify the main advantages and disadvantages of both systems, and to integrate their use to modulate response for a more effective and safe treatment. Characterisation of the effect of vector genome dilution, as a consequence of target tissue growth, and thereby therapeutic potential, will be addressed. Additionally, characterisation of the metabolism of the therapeutic vector genome in different cell types will be explored. Finally, strategies to improve the persistence of vector genomes as well as to generate hybrid vectors to accommodate transgenes that exceed the packaging capacity of AAV or non-viral counterparts will be investigated.
- identify strategies to mitigate loss of vector genomes and explore the idea of stabilising non-integrated AAV or non-viral vector genomes within the target cell;
- characterise the metabolism of the vector genome in different cell types to understand whether rates of degradation, episomal maintenance, or integration vary from cell to cell;
- design improved hybrid vectors that have a higher efficiency of concatermerisation, and full-length vector genome reconstitution.

Expected applicant consortium contribution:

- small and large animal models of disease. Focus on central nervous system (CNS), muscle and liver;
- development and utilisation of technology to measure vector copy number, vector genomic structure, monomers, concatemers, epigenetic status of vectors over time in relevant tissues;
- development of and utilisation of tools to analyse the cellular milieu to identify factors which govern vector stability and genomic structure.

EFPIA consortium contribution:

- disease relevant animal models;
- registry of results from pre-clinical data;
- prospective paediatric patient data and samples.

Work package 4 – Understand the clinical factors around pre-existing immunity limiting patient access to ATMP therapy, and adaptive immune responses affecting product safety, efficacy and persistence, including for integrating vector-based therapies

Objective: Perform translational and clinical research with the intent of standardising existing analytics based on biobanked samples, and the development of the new immune-modulatory protocols.

The goals of this work package will be as follows:

- establish a geographically diverse prospective biobank from treated and untreated donors with matching cell, serum, and plasma samples to enable evaluation of the pre-existing and adaptive immunity; assure that informed consent is properly obtained and strict adherence to privacy is maintained;
- develop standardised pathways for characterisation of pre-existing immunity to gene/cell therapy products, including macrophages, natural killer (NK) cells, memory T-cells, and other cells, and neutralising and binding antibodies;
- develop cohesive metrics for immunological characterisation, applicable for gene and cell therapies, for both patient inclusion and post-treatment monitoring;
- standardise assays for use in safety and persistence biomarker monitoring;
- develop and standardise innovative characterisation methods for the analytical evaluation of therapeutic drug substance to assess function, potency, quality, and microbiological load;
- establish novel protocols for the modulation of immune responses to capsid and transgene products, non-viral vector components, and autologous or allogeneic gene-modified or unmodified transplanted tissues and cells. Similarly, develop protocols to induce tolerance to expressed transgene products or to autologous or allogeneic gene-modified or unmodified cell products;
- evaluate safety risks when dosing viral gene therapies in the background of humoral and/or cellular immunity against the virus.

Expected applicant consortium contribution:

- organisation of biobanking from healthy volunteers and recipients of cell and gene therapies from broad geographic areas;
- characterisation of the relationship between binding antibodies and neutralising antibodies. Define the interplay between humoral immunity, complement activation, and cell-mediated immunity. Establish models to allow prediction of innate immune responses. Discern mechanisms of activation of memory T-cell and NK-cell activation and their role in loss of transgene expression. Expand knowledge regarding non-antibody mediated neutralisation;
- define metrics for immunological characterisation, applicable for gene and cell therapies, for both patient inclusion and post-treatment monitoring;
- develop and standardise of innovative characterisation methods for the analytical evaluation of therapeutic drug substance (characterisation/functional assessments of potency, quality, and microbiological load), especially for products used in cell-based assays and *in vivo* models from WP2;
- use animal models developed in WP2 to access modulatory/intervention strategies. The learning and knowledge derived from WP2 will be used to inform this goal of developing novel animal models and establishing novel protocols for the modulation of immune responses to capsid and transgene or cell products, as well as induction of tolerance to vectors, expressed transgene products, and autologous or allogeneic gene modified or unmodified cell products;
- conduct nonclinical studies to identify potential adverse events when dosing the presence of viral vector immunity.

EFPIA consortium contribution:

- prospective data from clinical samples;
- alidation of immunosuppressive protocols in animal models.

Work package 5 – Engage regulators to ensure that the models and data generated through this project will provide the necessary information to support regulatory filings and to address regulatory and safety concerns

The goals of this work package will be as follows:

- enable data-driven regulatory requirements. Identify and address scientific gaps in current knowledge in order to generate improved and data-driven standards for safety while enabling accelerated product development. This may include key issues in gene/cell therapy development, including environmental assessments, characterisation of replication competent virus, viral clearance in the manufacturing process, genetically-modified organism (GMO) issues such as viral shedding after administration, patient screening criteria, and long-term follow up for persistence and delayed adverse events such

as those related to insertional mutagenesis. This will enable a move from theoretical concerns to data driven risk assessments that can be used to update regulatory requirements;
- identify opportunities for regulatory harmonisation. Conduct a landscape analysis of regulatory requirements and gather examples, develop criteria and evaluate options to standardise differences in regulatory requirements across countries. Utilise project efforts to guide the development of ATMP specific ICH guidelines;
- perform a landscape analysis of regulatory requirements and identify differences in existing requirements in order to develop recommendations for regulatory harmonisation;
- publish a white paper(s) outlining the results of the data analysis and regulatory landscape analysis with specific recommendations for updated regulatory requirements;
- participation in meetings or workshops with regulators to drive acceptance of consortium-recommended regulatory harmonisation;
- create predictable regulatory pathways for innovation. Work with regulators to develop a more predictable path to implementing innovative systems and technology such as the qualification of novel biomarkers (e.g. transgene expression) for use as endpoints in clinical trials, the use of standardised manufacturing platforms, improved comparability strategies and the utilisation of predictive immunogenicity strategies, engage with health authorities, take advantage of regulatory tools and procedures such as Innovation Task Force (ITF); the European Medicines Agency (EMA) (including the committee on Advanced Therapies) scientific advice (SA) and qualification advice as well as national scientific advice.

Expected applicant consortium contribution:

- based on the plan generated, develop a prospective database where non-competitive data can be collected such as replication competent virus testing, vector shedding, and long-term follow up. The database should be set up to ensure patient confidentiality and protect competitive corporate intelligence. Compile data and perform cross-sectional analysis to determine actual experience related to the unique risks of cell and gene therapy to enable a move from theoretical to data-driven recommendations for regulatory requirements.

EFPIA consortium contribution:

- share non-competitive data related to regulatory requirements such as replication competent virus testing, vector shedding, and long-term follow up to allow for a cross-sectional analysis of data to enable a move from theoretical to data-driven recommendations for regulatory requirements;
- contribute to landscape analysis of regulatory requirements and develop recommendations for regulatory harmonisation.

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Topic 6: Supporting the development of engineered T cells

Topic details

Topic code	IMI2-2019-18-06
Action type	Research and Innovation Action (RIA)
Submission and evaluation process	2 stages

Specific challenges to be addressed

Despite recent advances in cancer treatment, the unmet medical need in oncology remains high. In the European region, cancer causes 20 % of deaths and is the second cause of death after cardiovascular diseases, with 3 million new cases and 1.7 million deaths each year. Cancer is also a leading cause of death in children and adolescents around the world [1].

Engineered T cells, including chimeric antigen receptor (CAR) and T-cell receptor (TCR) engineered T cells, combine features of cell therapy, gene therapy, and immunotherapy. With two distinct autologous CD19 CAR-T-cell therapies approved by Food and Drug Administration (FDA) in 2017 and European Medicines Agency (EMA) in 2018, cellular immunotherapy is emerging as a promising new treatment modality for a broad range of cancers. Allogeneic approaches are also being developed in order to overcome some of the challenges of autologous therapies. Although CAR-T-cell therapies have been largely successful in treating haematological malignancies, they have not been as effective in treating solid tumours [2].

These complex medicinal products have the unique ability to self-amplify and persist in treated patients. Their translation from basic and pre-clinical research to clinical trials therefore poses many challenges that slow down clinical development [3]**Error! Reference source not found.**. They have been associated with unique specific acute toxicities, with cytokine release syndrome (CRS) and neurotoxicity being two most commonly observed toxicities. Animal models often fail to predict toxicities associated with the use of CAR-T cells and frequently overestimate the efficacy of the treatment, as they do not accurately reflect the tumour microenvironment (TME). Although new mouse models have recently been shown to be able to recapitulate human efficacy, CRS and neurotoxicity of anti-CD19 CAR-T cells, efforts are still needed to optimise and extend these models to other tumour antigens [2][3][4][5][6][7]. The use of alternative, non-genotoxic and non-myeloablative methods to induce lymphodepletion or better schemes for administrating existing regimens may also contribute to decreased toxicity associated with engineered T cells [3][8].

The need for good manufacturing practice (GMP)-compliant manufacturing may also constitute a specific hurdle in the timely translation to the clinic. Issues may be related to the consistency of clinical batches, the characterisation of the final product, and definition and evaluation of specific potency criteria. The standardisation of analytical procedures would improve comparability of CAR-T-cell batches and of clinical results from patients included in different trials and/or receiving CAR-T cells from different origins [3]**Error! Reference source not found.**.

In addition, there is an increasing consensus among stakeholders that patient engagement is critical to fostering patient access to innovative therapeutic solutions and delivering better patient health outcomes.

Need and opportunity for public-private collaborative research

Advancing therapeutic T-cell engineering requires progress on multiple fronts, including the development of pre-clinical models with high translational potential to predict the safety and efficacy of engineered T cells; the optimisation of lymphodepletion regimens and better understanding of their impact on the safety and efficacy of engineered T cells; and better control and industrialisation of cell manufacturing sciences and regulatory compliance in the development of engineered T cells.

To address such a wide range of complex issues, there is a need for strong cooperation amongst industry, biotechs, academia, patient organisations, policymakers, public health experts and regulators, bringing their diverse expertise in the following fields:

- development of relevant pre-clinical models of safety and efficacy;

- standardisation of analytical methods;
- collection of public or existing biological and clinical data related to engineered T cells and lymphodepletion;
- modelling (pharmacokinetics/pharmacodynamics (PK/PD) / lymphodepletion);
- biostatistics;
- quality profiles and regulatory aspects of the manufacturing of engineered T-cell therapies;
- patient access to treatments.

This Call topic also represents an opportunity to enable patients to better reflect their perspectives in CAR and TCR engineered T-cell development. Through meaningful patient engagement, all stakeholders involved in the development of medicinal products should benefit from each other's expertise and develop a better understanding of how diverse viewpoints can positively drive better medicines.

Scope

The overall objective of the call topic is to support the development of autologous and allogeneic engineered T-cell therapies, including CAR and TCR engineered T cells. The Call topic addresses both haematological and solid tumours.

The objectives of the Call topic are:

- Optimisation of existing pre-clinical models, tools and pharmacodynamic (PD) markers to predict toxicities associated with engineered T cells, such as CRS, neurotoxicity, graft-versus-host disease (GvHD), off-target toxicity of gene editing technologies and insertional mutagenesis linked to the use of viruses. Development of new models and tools if needed.
- Optimisation of existing pre-clinical models, tools and PD markers to predict the efficacy of engineered T cells, including assessment of anti-tumour activity, pharmacokinetics (PK) (trafficking, homing, infiltration, persistence) and PK/PD modelling. Development of new models and tools, such as patient derived xenograft (PDXs) models relevant for the heterogeneity of the tumour and potentially to study the role of TME in the case of haematological malignancies, as well as syngeneic models.
- Comparison of existing analytical methods used pre- and post-infusion of engineered T cells to define gold standard methods. New technologies may also be developed. Methods related to quantification and characterisation of engineered T cells pre-infusion (product), assessment of the clinical fate of engineered T cells (homing, persistence, expansion and efficacy), immune monitoring of patients (kinetics of reconstitution of immunity, profiling of engineered T cells and immune response to engineered T cells), and assessment of off-target toxicity of gene editing technologies and insertional mutagenesis linked to the use of viruses, both pre- and/or post-infusion.
- Creation of a database with historical existing clinical and biological data from patients receiving lymphodepleting regimens. Modelling of the impact of the different lymphodepleting agents on immune cells. Development of relevant *in vivo* models to evaluate new lymphodepleting regimens.
- Expert discussion on the implementation of regulatory guidance for engineered T cells, including European Pharmacopoeia and GMP for advanced therapy medicinal products (ATMPs) to define standard product profiles.
- Determination of the role(s) of patients in each research and development (R&D) stage. Development of patient-friendly communication tools to improve the patient journey, and materials to facilitate the training of healthcare providers (HCPs) on engineered T-cells to better respond to patient needs.
- Expert discussion on the best path to ensure broad patient access to engineered T cells.

Expected key deliverables

The expected key deliverables will be public and should include the following:

- **Deliverable 1:** Pre-clinical models, pharmacodynamic markers or tools with high translational potential to predict safety of engineered T cells, including CRS, neurotoxicity, GvHD and off-target toxicity of gene editing technologies and insertional mutagenesis linked to the use of viruses.
- **Deliverable 2**: Pre-clinical models, pharmacodynamic markers or tools with high translational potential to predict efficacy of engineered T cells and the role of TME, including anti-tumour activity and pharmacokinetics (trafficking, homing, infiltration, persistence) and PK/PD modelling.
- **Deliverable 3**: Gold standard analytical methods used both pre- and post-infusion of engineered T cells, including quantification and characterisation of engineered T cells pre-infusion (product),

assessment of clinical fate of engineered T cells (homing, persistence, expansion and efficacy/potency), immune monitoring of patients (kinetics of reconstitution of immunity, profiling and immune response to engineered T cells) and assessment of genetic modifications pre- and/or post-infusion (off-target toxicity of gene editing technologies and insertional mutagenesis linked to the use of viruses).

- **Deliverable 4:** Optimised lymphodepletion regimens for engineered T cells, based on analysis/modelling of existing lymphodepletion data and development of new *in vivo* models to evaluate the impact of different lymphodepleting regimens on engineered T-cell expansion and persistence.
- **Deliverable 5**: Customised European Pharmacopoeia and GMP for ATMPs for engineered T cells to achieve standard product profiles.
- **Deliverable 6:** Communication tools for patients and healthcare providers on engineered T cells, including tools to increase the capability of patients to understand and contribute to R&D of engineered T cells, reliable and patient-friendly communication tools to improve the patient journey and to raise awareness among HCPs of patient concerns.
- **Deliverable 7:** White paper on equitable patient access to engineered T cells across EU member states.

Expected impact

Applicants should describe how the outputs of the project will contribute to the following impacts and include baseline, targets and metrics to measure impact.

At the levels of the R&D process, regulatory pathways and/or health technology assessment (HTA), patient access processes, clinical and healthcare practices, the impact would be:

- the development of safer and more effective engineered T-cell therapies;
- the opportunity to compare data generated from standardised analytical methods;
- increased industrial competitiveness;
- broader patient access to engineered T-cell therapies;
- an increased awareness among HCPs of patients' concerns.

In addition, patients will benefit from the project outputs by:

- better understanding the mode of action and procedures of their treatment;
- having a better consideration of their perspectives by being a key actor of the whole R&D process;
- facilitated interactions with HCPs.

For society, the impact could be:

- a better understanding of these complex therapies by the public (complexity, efficacy and safety);
- a better understanding and evidence-based development of engineered T cells might also contribute to decreasing their cost;
- improved synergies between industry, small and medium-sized enterprises (SMEs) and academic organisations.

Applicants should indicate how their proposal will impact the competitiveness and industrial leadership of Europe by, for example, engaging suitable SMEs.

Potential synergies with existing consortia

Applicants should take into consideration, while preparing their short proposal, relevant national, European (both research projects as well as research infrastructure initiatives), and non-European initiatives. Synergies and complementarities should be considered in order to incorporate past achievements, available data and lessons learnt where possible, thus avoiding unnecessary overlap and duplication of efforts and funding.

In particular, potential applicants should consider any relevant work/result from other IMI2 JU projects as far as these are accessible (e.g. IMI2 - Call 15, topic 4: Emerging translational safety technologies and tools for interrogating human immuno-biology).

Industry consortium

The industry consortium is composed of the following EFPIA companies and partners:

- Servier (lead)
- Bayer
- Janssen Pharmaceutica
- Nanostring
- Takeda.

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

- European Hematology Association (EHA).

The industry consortium will contribute with major assets such as:

- clinical experience of engineered T-cell therapies;
- chemistry manufacturing and controls (CMC);
- regulatory issues;
- communication & dissemination;
- education & training;
- managing expert boards;
- standardisation of monitoring tools/systems.

Moreover, the industry will also contribute with the following expertise:

- project management;
- legal/compliance;
- modelling;
- IT support;
- biostatistics;
- bioinformatics;
- molecular biology;
- cell biology;
- market access;
- patient advocacy / engagement.

Indicative duration of the action

The indicative duration of the action is 60 months.

Indicative budget

The indicative in-kind and financial contribution from EFPIA partners [and IMI 2 JU Associated Partner] is EUR 8 733 000.

This contribution comprises an indicative EFPIA in-kind contribution of EUR 6 158 000 and an indicative IMI2 JU Associated Partner in kind contribution of EUR 2 575 000.

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

The financial contribution from IMI2 JU is a maximum of EUR 8 733 000.

Applicant consortium

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

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

This may require mobilising, as appropriate, the following expertise and contribution with a major focus on:

- development of pre-clinical models and tools (*in vitro* and *in vivo* models);
- cellular and molecular biology;
- pharmacometrics (PK-PD) / modelling;
- regulatory / HTA;
- health economics.

In their short proposal, applicants should demonstrate that they have access to historical data, as well as existing cohorts, of patients treated with engineered T-cells and/or receiving lymphodepletion regimens.

Patient organisations will be considered as key partners of the funded action. They will contribute by collecting concerns and needs from patients and caregivers, actively taking part in the R&D process and ensuring patient-friendly communication.

Moreover, the applicant will also contribute with the following expertise:

- imaging;
- immunology;
- CMC/GMP;
- clinicians with lymphodepletion experience;
- project management.

Suggested architecture of the full proposal

The applicant consortium should submit a short proposal which includes their suggestions for creating a full proposal architecture, taking into consideration the industry participation including their contributions and expertise provided below.

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.

The architecture outlined below for the full proposal is a suggestion. The architecture of the full proposal should be designed to fulfil the objectives and key deliverables within the scope of this proposal.

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

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

Work package 1 – Project management, coordination, communication and long-term sustainability

Description:

The goals of this work package are to support optimal project management in compliance with scientific and ethical standards, implement the strategy of the consortium, and ensure appropriate dissemination of the project progress and outcomes.

Proposed objectives:

- define work expectations of different work streams, deliverables, dates and activities, and review progress regarding adherence to budget, timelines and quality (by all consortium members);
- ensure legal and contractual management;
- ensure the set-up of a joint governance structure (by all consortium members);
- quality assessment of documents;
- define project interdependencies, stakeholders and risks;
- ensure ethics management;
- ensure appropriate communication within the consortium;
- ensure dissemination of the project progress and outcomes (project website, conference talks, social media presence, a project newsletter, abstracts, publications);
- communication to the wider public.

Industry contribution: will include co-leading this work package, including management of legal, contractual, ethical and quality assessment aspects, and contributing to the definition of the dissemination and communication plan.

Expected applicant consortium contribution: will co-lead in partnership with industry consortium and work together to define the governance structure and full work plan, will participate in communication and data dissemination.

Work package 2 – Patient involvement

Description:

The goal of this work package is to guarantee that the patient perspective is taken into account.

Proposed objectives:

- promote engagement of patients all along the R&D process;
- ensure adequate communication on engineered T-cell therapies to patients and their family/caregivers;
- ensure that HCPs are sensitised to patient needs;
- propose solutions for equitable patient access to engineered T cells;
- propose solutions to guarantee broad patient access to engineered T cells.

Industry contribution: communication and dissemination, education and training, collaboration with patient advocacy groups, management of expert boards, knowledge of pharmaceutical life-cycle process, market access.

Expected applicant consortium contribution: patient expertise, communication, national health care authorities and societies, health economics.

Work package 3 – Models and tools to assess safety of engineered T cells

Description:

The goal of this work package is to optimise and/or develop pre-clinical models, pharmacodynamic markers and tools with high translational potential to predict the safety of engineered T-cell therapies.

Proposed objectives:

- map existing pre-clinical models relevant to assess the safety of engineered T cells and identify gaps/needs;
- optimise existing models and develop new models or tools to better predict the safety of engineered T cells;
- preclinical models may include models of CRS, neurotoxicity, GvHD;
- off-target toxicity of gene editing technologies and insertional mutagenesis linked to the use of viruses could also be addressed.

Industry contribution: clinical knowledge of engineered T-cell safety concerns, preclinical models.

Expected applicant consortium contribution: pre-clinical models including *in vivo* and *in vitro* models, technologies, immunology.

Work package 4 – Models and tools to assess efficacy of engineered T cells

Description:

The goal of this work package is to optimise or develop models, pharmacodynamic markers and tools with high translational potential to predict the efficacy of engineered T-cell therapies.

Proposed objectives:

- map existing pre-clinical models relevant to assess the efficacy of engineered T cells and identify gaps/needs;
- optimise existing *in vitro* and *in vivo* models and develop new models and biomarkers to better predict efficacy of engineered T cells; the development of new models relevant to studying the impact of tumour heterogeneity and the role of TME would be a plus;
- Efficacy parameters may include the assessment of anti-tumour activity (predictive *in vitro* assays and *in vivo* models) for haematological and solid tumours or any other relevant biomarkers for engineered T cell expansion and persistence;
- the development of tools and models to assess the pharmacokinetics of engineered T cells, including trafficking, homing, infiltration and persistence could also be included (imaging, molecular biology);
- immunocompetent mouse models to study epitope spreading;
- PK/PD modelling based on the data generated in the different models (and if possible, on clinical data available).

Industry contribution: expertise in modelling, *in vivo* and *in vitro* preclinical models, PK.

Expected Applicant consortium contribution: pre-clinical models including *in vivo* and *in vitro* models, imaging, PK data, cell therapy PK/PD modelling.

Work package 5 – Gold standard analytical methods used both pre- and post-infusion of engineered T cells

Description:

The goal of this work package is to optimise/develop analytical methods and define gold standard analytical methods to be used for both pre- and post-infusion of engineered T cells.

Proposed objectives:

- Analytical methods to be standardised may include but are not limited to the assessment/quantification of engineered T cells, rapid and less product consuming assays to assess microbiological safety, assessment of the clinical fate of engineered T cells (homing, persistence and efficacy), immune monitoring of patients (kinetics of reconstitution of immunity, profiling of engineered T cells and immune response to engineered T cells) and assessment of off-target toxicity of gene editing technologies and insertional mutagenesis linked to the use of viruses.
- Technologies such as quantitative polymerase chain reaction (qPCR), antibody – and targeted protein (via protein-microarrays, and targeted multiplex bead-arrays), flow cytometry, next generation sequencing (NGS), single cell analysis, replication competent lentivirus (RCL), omics may be addressed.
- Development of new tools and methods if needed.
- Technologies could be first developed using relevant *in vitro* models and could then be validated on batches/clinical samples that may be provided by clinicians treating patients with commercially available or academic engineered T cells.

Industry contribution: CMC, translational, analytics, bioinformatics, standardisation of monitoring tools/systems.

Expected applicant consortium contribution: Molecular biology, imaging, immunology.

Work package 6 – Development of optimal lymphodepletion /conditioning regimen

Description:

The goal of this work package is to develop lymphodepletion models to better understand the impact of lymphodepletion on engineered T-cell safety and efficacy, and to optimise or develop new conditioning regimens.

Proposed objectives:

- collect existing biological and clinical data from patients who received lymphodepleting regimens in the context of allograft transplantation and/or CAR-T cells and create an easy to access database by pooling collected data;
- meta-analysis of the data;
- modelling of the different existing lymphodepleting regimens (based on collected data);
- development of relevant *in vivo* models (preclinical) to optimise or test new conditioning regimens and address key questions.

Industry contribution: clinical expertise, *in vivo* and *in vitro* preclinical models, PK, bioinformatics and IT.

Expected applicant consortium contribution: historical data, literature review, bioinformatics, modelling, pre-clinical models, immunology.

Work package 7 – Data integration

Description:

The goal of this work package is to create and manage an IT platform where all data collected and generated in the context of the consortium will be stored.

Proposed objectives:

- develop an IT platform to allow easy, compliant and secured access to all the data collected or generated during the project to all members of the consortium and will be made publically accessible at the latest stage;
- consider the sustainability of the platform.

Industry contribution: IT platform accessible to all members of the consortium.

Expected applicant consortium contribution: IT and suitable data sets.

Work package 8 – Customised European Pharmacopoeia and GMP for ATMPs for engineered T cells

Description:

The goal of this work package is to address some regulatory and quality aspects of manufacturing in order to achieve a standard product profile.

Proposed objectives:

- biological and pharmaceutical characterisation of the products (i.e. potency activity, release assays, appearance);
- critical quality attributes;
- quality control, including safety tests such as RCL;
- recommendations on the practical implementation of GMP for ATMPs and pharmaceutical requirements;
- some technologies developed in WP5 could also be applicable for this work package.

Industry contribution: CMC, regulatory.

Expected applicant consortium contribution: Academic Centres, contract development and manufacturing organisations (CDMOs) or any other organisations that are interacting with regulatory health authorities, CDMOs, with access to academic centres.

References

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[4] June CH, Sadelain M. Chimeric Antigen Receptor Therapy. N Engl J Med. 2018 Jul 5;379(1):64-73.

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[8] Turtle CJ, Riddell SR, Maloney DG. CD19-Targeted chimeric antigen receptor-modified T-cell immunotherapy for B-cell malignancies. Clin Pharmacol Ther. 2016 Sep;100(3):252-8.

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 18 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-IMI2-2019-18-two-stage**
Type of actions	**Research and Innovation Action (RIA)**
Publication Date	**26 June 2019**
Stage 1 Submission start date	**26 June 2019**
Stage 1 Submission deadline	**26 September 2019 (17:00:00 Brussels time)**
Stage 2 Submission deadline	**26 March 2020 (17:00:00 Brussels time)**
Indicative Budget	
From EFPIA companies and IMI2 JU Associated Partners	EUR 85 871 760
From the IMI2 JU	EUR 74 866 000

Call Topics

IMI2-2019-18-01 Central repository of digital pathology slides to support the development of artificial intelligence tools	The indicative contribution from EFPIA companies is EUR 37 771 260 The financial contribution from IMI2 JU is a maximum of EUR 32 320 000	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.
IMI2-2019-18-02 Health Outcomes Observatories - empower patients with tools to measure their outcomes in a standardised manner creating transparency of health outcomes	The indicative contribution from EFPIA companies is EUR 10 385 000 The indicative IMI2 JU Associated Partners contribution is EUR 1 050 000 The financial contribution from IMI2 JU is a maximum of EUR 10 478 000	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.

IMI2-2019-18-03 Improving patient access, understanding and adherence to healthcare information: an integrated digital health information project	The indicative contribution from EFPIA companies is EUR 9 070 000 The indicative IMI2 JU Associated Partners contribution is EUR 210 000 The financial contribution from IMI2 JU is a maximum of EUR 9 280 000	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.
IMI2-2019-18-04 Establishing international standards in the analysis of patient reported outcomes and health-related quality of life data in cancer clinical trials	The indicative contribution from EFPIA companies is EUR 2 900 000 The financial contribution from IMI2 JU is a maximum of EUR 2 282 000	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.
IMI2-2019-18-05 Accelerating research & innovation for advanced therapy medicinal products	The indicative contribution from EFPIA companies is EUR 15 752 500 The financial contribution from IMI2 JU is a maximum of EUR 11 773 000	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.
IMI2-2019-18-06 Supporting the development of engineered T cells	The indicative contribution from EFPIA companies is EUR 6 158 000 The indicative IMI2 JU Associated Partners contribution is EUR 2 575 000 The financial contribution from IMI2 JU is a maximum of EUR 8 733 000	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.

Annex III - IMI2 Call 19 topic text

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[65] 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[66].

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[67], 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)[68] is the main reference for the implementation of research priorities for IMI2 JU. The scientific priorities for 2019 for IMI2 JU have been prepared based on the SRA.

Applicant consortia fulfilling the specific eligibility criteria (see Conditions for this Call) are invited to submit a research and innovation action proposal to the topic of this Call and address all its aspects. The size and composition of each consortium should be adapted so 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.

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[65] 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.

[66] http://www.who.int/medicines/areas/priority_medicines/en/

[67] 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.

[68] 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[69] and Clinical Trial Regulation (EU) 536/2014[70] (and/or Directive 2001/20/EC[71)] and any relevant legislation[72].

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[73], 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).

[69] 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.

[70] 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.

[71] 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.

72 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.

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

Restricted Call to maximise impact of IMI2 JU objectives and scientific priorities

Topic details

Topic code	IMI2-2019-19-01
Action type	Research and Innovation Action (RIA)
Submission and evaluation process	single stage

Specific challenges to be addressed by public-private collaborative research

A major challenge in life sciences, in particular within the medicines development process, is the scale of the investment required, the stepwise approach, very long development timelines and the successful involvement of relevant stakeholders. They are, through close collaboration, in a position to bring the critical mass of expertise, knowledge and resources to address the vast challenges ahead.

The Innovative Medicines Initiative 2 Joint Undertaking (IMI2 JU) provides the unique framework required to drive major and fundamental new innovations by enabling unique collaborative partnerships among public and private stakeholders. Such partnerships have the potential to deliver well beyond the initially expected outputs. The efficient harnessing of such unique outcomes would be extremely valuable for the achievement of the IMI2 JU objectives, as well for the benefit of citizens and public health.

Certain IMI2 JU topics, launched under IMI2 JU Calls for proposals that are now closed, anticipated in their corresponding Annual Work Plans the need for a stepwise approach. Thus, these Annual Work Plans informed potential applicants that IMI2 JU could at a later stage publish a subsequent, restricted Call for proposals, addressing the consortia selected under initial topics.

Scope, key deliverables and applicant consortium

The scope of the restricted Call will be to support further research activities in those exceptional cases where it is necessary to enable successful consortia to build on the achievements of their initial action, move onto the next step of the challenge, and maximise the impacts of the initial action results.

Proposals will be evaluated by experts on the basis of the award criteria ‘excellence’, ‘impact’ and ‘quality and efficiency of the implementation’, in line with the Article 15 of the Horizon 2020 Rules for Participation (Regulation No 1290/2013). Within these criteria, the experts will focus on the points listed below and the proposals should therefore address them in detail:

- the very high relevance for successfully addressing the IMI2 JU objectives and scientific priorities;
- how the proposed activities relate to an area with a high unmet need in the context of public health and industrial challenges as relevant. This should also include a landscaping exercise to demonstrate that no similar effort of the same extent is already ongoing at national, European or global level;
- the need for the proposed activities to (in a timely fashion) seamlessly build on and add value to the already remarkable results achieved by the applicant consortium in the initial action, which may include intellectual properties (IP) and ethical constraints as relevant;
- the scope of proposed activities must fall beyond the scope of the initial action (e.g. initial objectives and its financial and temporal framework);
- the specific circumstances justifying the fact that only the initial consortium (with some justified modifications of the partners list, if any, to cover the expertise needed for the newly proposed activities) can carry out the follow-up activities successfully. For instance, the initial consortium represents a unique and effective partnership with the expertise, equipment, methodologies, or access to unique resources and IP rights, that are not available from another consortium;
- how the proposed activities build on and benefit from the strong foundations established in the initial action, e.g. governance, workflows, procedures;

- the applicants will also need to justify how the proposed activities are needed to further maximise the public-private partnership value of IMI2 JU as demonstrated both by: 1) the success of the initial public private partnership; and 2) a substantial amount of in-kind and financial contributions brought to the action by contributing partners, i.e EFPIA constituents and affiliated entities and, when relevant, by IMI2 JU Associated Partners[74].

Accordingly, applicants should define key specific deliverables addressing the challenges identified by their proposal and enabling the achievement of its objectives. They should also define deliverables that would be sustained beyond the duration of the funded action, and how this would be achieved along with any key results that would be expected to be made openly accessible.

Additional condition for participation[75]

This Call is:

- restricted to the initial consortia of actions funded under topics published in the IMI2 JU Annual Work Plans of 2014 and of 2015, since only these actions are sufficiently advanced in their implementation to be considered for follow-up activities, and;
- limited to those actions derived from topics where the corresponding work plan already informed potential applicants about the possibility of a later restricted Call (see list of eligible actions under the Call conditions).

If the action selected under this Call starts before the end date of the initial Grant Agreement, the applicants must demonstrate in their proposal how proper collaboration between the two actions will be ensured.

Expected impact

Applicants should describe how their proposal will uniquely contribute to the following impacts and include baseline, targets and metrics to measure impact.

Funded actions are expected to significantly:

- enhance the impacts already delivered by the consortium in the initial action;
- improve the drug development process;
- have public health benefits and improve European citizens' health and well-being;
- contribute to the EU's industrial leadership including small and medium-sized enterprises (SMEs);
- have an impact on regulatory, health technology assessment, and healthcare practices, if relevant;
- further maximise the IMI2 JU public-private partnership value by harnessing support from different stakeholders, including the mobilisation of funds through the inclusion of contributing partners – not necessarily involved in the initial project – to reflect the public-private character of IMI2 JU actions. These mobilised contributions must be in addition to those already committed by any contributing partners when the initial project(s) began.

Indicative duration of the action

The indicative duration of the action is 24 months.

However, the consortium may propose a different duration if properly justified.

[74] Contributing partners: EFPIA companies or organisations associated to EFPIA, and Associated Partners to IMI2 JU contributing resources to the action may report it as their in-kind or financial contribution to the IMI2 JU. If the contributing entity is not yet an affiliate or a constituent entity of an IMI2 Member other than the Union (i.e. EFPIA), or an Associated Partner at the time of the proposal submission, and the proposal is selected for funding, such a legal entity is invited to become an affiliate or a constituent entity of an IMI2 Member, other than the Union, or an Associated Partner in accordance with the IMI2 JU Statutes prior to the signature of the relevant Grant Agreement.

[75] Article 9(5) 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.

Indicative budget

Applicant consortia will be competing for the maximum total financial contribution from IMI2 JU of EUR 20 000 000.

Within this budgetary envelope, each proposal must include a sound justification of the budget requested, taking into account the proposed in-kind contributions from contributing partners, i.e. EFPIA constituents or affiliated entities and/or, when relevant, IMI2 JU Associated Partners.

Proposals above the threshold will be invited in order of ranking to prepare a Grant Agreement within the limits of the available overall budget.

Single stage proposal

While preparing their proposal, applicants are requested to pay due attention to all the following points:

Data management

In their proposal, applicants should give due visibility to data management including use of the data standards. A full 'data management plan' (DMP) as a distinct deliverable must be delivered within the first 6 months of the action. The DMP needs to be kept up to date with the needs of the action and as such be updated as necessary during its lifetime.[76]

Dissemination, exploitation and communication

In their proposal, applicants must provide a draft plan for the exploitation and dissemination of results. A full plan as a distinct deliverable must be delivered within the first 6 months of the project.[77] The proposed communication measures for promoting the action 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 action.

Sustainability

In their proposal, applicants must describe a sustainability plan beyond the end of the Grant Agreement. This plan may be updated during the action lifetime and could include:

- identification of results that may need sustainability solutions;
- identification of potential end-users for these results;
- a proposed sustainability roadmap.

Sufficient resources should be set aside for activities related to the sustainability of the project results. This may involve engaging with suitable biological and medical sciences research infrastructures (RIs).[78]

Patient and healthcare provider engagement

Applicants are encouraged to include a strategy to engage with patients, learned societies and healthcare providers as relevant to ensure the project results impact on healthcare practices.

Synergies

Applicants should briefly present an environment scan of relevant existing initiatives to ensure synergies and complementarities, and avoid unnecessary overlap and duplication of efforts and include a plan on how they propose to synergise with these initiatives.

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[76] 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

[77] As an additional dissemination obligation under Article 29.1 of the IMI2 JU Grant Agreement will apply

[78] http://www.corbel-project.eu/about-corbel/research-infrastructures.html

Regulatory strategy

Applicants are expected to have a strategy for the translation of the relevant outputs into the regulatory practice to promote the uptake of the results e.g. qualification advice, qualification opinion when relevant. A plan for interactions with regulatory agencies/health technology assessment bodies /payers, with relevant milestones and sufficient resources, should therefore, be proposed.

Note on the template for preparing your proposal

When using the IMI2 JU single stage proposal template, applicants should ensure that in addition to all the information to be provided as standard in the relevant sections, they also address the following points specific to this restricted Call for proposals:

Under the section **Excellence**:

Section 1.1 Objectives

- Explain how the proposal addresses the specific challenge and scope of the topic text of the restricted Call for proposals to maximise the impact of IMI2 JU objectives and scientific priorities, as set out in the relevant IMI2 Annual Work Plan;
- Indicate the initial action (acronym - Grant Agreement number) and the related Call topic published in the IMI2 JU Annual Work Plan of 2014 or of 2015 to which their proposal relates;
- Explain how the proposal addresses the specific challenge and scope of the restricted Call for proposals (i.e. the topic text) and meet all key objectives as set out in the topic text.

In particular, applicants should address the following points:

- the very high relevance for addressing successfully the IMI2 JU objectives and scientific priorities;
- how the proposed follow up activities relate to an area with a high unmet need in the context of public health and industrial challenges as relevant. This should also include demonstration that no similar effort of the same extent is already ongoing at national, European or global level;
- the need for the proposed follow up activities to seamlessly build on and add value to the already remarkable results achieved by the applicant consortium in the initial action in a timely fashion; this may include intellectual properties (IP) and ethical constraints as relevant;
- the scope of proposed follow up activities must fall beyond the scope of the initial action (e.g. initial objectives and financial and temporal framework);
- the specific circumstances, justifying the fact that only the initial consortium (with some justified modifications to the list of partners, if any, to cover the expertise needed for the new proposed activities) can carry out follow up activities successfully. For instance, the initial consortium represents a unique and effective partnership as expertise, equipment or methodologies, or access to unique resources and IP rights are not available from another consortium;
- how the proposed follow up activities build upon and benefit from the strong foundations established in the initial action, e.g. governance, workflows, procedures, success in completing all planned relevant deliverables.

In addition, applicants should justify that the proposed follow up activities are needed to further maximise the public-private partnership value of IMI2 JU as demonstrated by both: 1) the success of the initial public private partnership; and 2) by a substantial amount of in-kind and financial contributions brought to this new action by contributing partners, i.e. EFPIA constituents and affiliated entities and, when relevant, by IMI2 JU Associated Partners.

Section 1.2 Concept and methodology

- Define specific, important key deliverables addressing the challenges identified by their proposal and enabling the achievement of its objectives. This should include consideration for sustainability beyond the duration of the funded action and how this would be achieved, along with any key results expected to be made openly accessible.

Under the section **Impact**:

Section 2.1 Expected impact

- Demonstrate how the outputs of the project will contribute to each of the expected impacts mentioned in the relevant Call topic text; in particular how it will enhance the impacts already delivered by the consortium in the initial action.

Under the section **Implementation**:

Section 3.1 Project work plan — Work packages, deliverables and milestones

- Provide a brief presentation of the overall structure of the project work plan; including a sound justification for the budget requested together with the contribution from EFPIA/Associated Partners. Applicants should justify the proposed total duration of the action.

Section 3.2 Management structure, milestones and procedures

- If the start of the proposed action overlaps with the duration of the initial Grant Agreement, explain how the collaboration between the two actions would be ensured.

Section 3.3 Consortium as a whole

- Provide a justification in case of modifications to the initial consortium. If new members are included, applicants should justify how they bring expertise needed for the new proposed follow up activities.

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 additional conditions shall apply to this IMI2 JU Call for proposals:

- The Call is restricted to the initial consortia of actions funded under topics published in the IMI2 JU Annual Work Plans (AWPs) of 2014 and of 2015, since only these actions are sufficiently advanced in their implementation to be considered for follow-up research activities.
- In addition, it is limited to those actions derived from topics where the corresponding work plan already informed potential applicants about the possibility of a later restricted Call as listed below.

AWP year	Call	Topic number	Topic title	Project acronym	Project number	Project website
2014	1	1	Translational approaches to disease modifying therapy of type 1 diabetes Mellitus (T1DM)	INNODIA	115797	https://www.innodia.eu/
2015	3	1	RADAR-CNS	RADAR-CNS	115902	https://www.radar-cns.org/
2015	3	2	Assessing risk and progression of prediabetes and type 2 diabetes to enable disease modification	RHAPSODY	115881	https://imi-rhapsody.eu/
2015	3	3	Linking clinical neuropsychiatry and quantitative neurobiology	PRISM	115916	https://prism-project.eu/en/prism-study/
2015	4	1	Enabling platform on medicines adaptive pathways to patients	ADAPT-SMART	115890	https://www.infographic.adaptsmart.eu/
2015	5	2	Diabetic Kidney Disease Biomarkers (DKD-BM)	BEAt-DKD	115974	https://www.beat-dkd.eu/
2015	5	5	Evolving models of patient engagement and access for earlier identification of Alzheimer's disease: Phased expansion study	MOPEAD	115985	https://www.mopead.eu/
2015	6	1	Development of Quantitative System Toxicology (QST) approaches to improve the understanding of the safety of new medicines	TransQST	116030	http://transqst.org/
2015	6	2	Establishing impact of RSV infection, resultant disease and public health approach to reducing the consequences	RESCEU	116019	http://resc-eu.org/
2015	6	4	Development of an outcomes-focused data platform to empower policy makers and clinicians to optimize care for patients with hematologic malignancies	HARMONY	116026	https://www.harmony-alliance.eu/
2015	7	3	Pathological neuron-glia interactions in neuropathic pain	NGN-PET	116072	http://ngn-pet.com/
2015	7	5	A comprehensive 'paediatric preclinical POC platform' to enable clinical molecule development for children with cancer	ITCC-P4	116064	https://www.itccp4.eu/
2015	7	6	Coordination and Support Actions (CSA) for the Big Data for Better Outcomes programme	DO-IT	116055	http://bd4bo.eu/index.php/portfolio/do-it/

Applicants intending to submit a proposal in response to the IMI2 - Call 19 should read this topic 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-J TI-IMI2-2019-19-single-stage**
Type of actions	**Research and Innovation Action (RIA)**
Publication Date	**26 June 2019**
Submission start date	**26 June 2019**
Submission deadline	**26 September 2019 (17:00:00 Brussels time)**
Indicative Budget	
From EFPIA companies and IMI2 JU Associated Partners	to be defined based upon selected proposals
From the IMI2 JU	EUR 20 000 000

Call Topic

IMI2-2019-19-01 **Restricted Call to maximise impact of IMI2 JU objectives and scientific priorities**	The indicative contribution from EFPIA companies is to be defined based upon selected proposals. The financial contribution from IMI2 JU is a maximum of EUR 20 000 000	Research and Innovation Action (RIA) Single stage submission and evaluation process. Proposals submitted will be evaluated and ranked in one single list. Several proposals might be invited to conclude a Grant Agreement, depending on the budget availability and their ranking.

LIST OF ACRONYMS

Acronym	Meaning
AAV	Adeno-associated virus
ABAC	Accrual Based Accounting System
AD	Alzheimer's disease
AD (HR)	Administrator
AER	Average error rate
AI	Artificial Intelligence
AMR	Antimicrobial Resistance
API	active pharmaceutical ingredient
API	Application Programming Interface
ASCO	American Society of Clinical Oncology
AST (HR)	Assistant
ATMPs	Advanced Therapy Medicinal Products
AWP2019	Annual Work Plan 2019
CA (Budget)	Commitment Appropriation
CA (HR)	Contractual Agent
CAR	Chimeric Antigen Receptor
CDISC	Clinical Data Interchange Standards Consortium
CDMO	Contract Development and Manufacturing Organization
CEOi	Global CEO Initiative
CFAST	Coalition for Accelerating Standards and Therapies
CFS	Certificates on Financial Statements
CMC	Chemistry Manufacturing and Controls
CNS	Central Nervous System
CONSORT	Consolidated Standards of Reporting Trials
C-Path	Critical Path Institute
CPD	Continuing professional development
CRO	Contract Research Organisation
CRS	Cytokine Release Syndrome
CSA	Coordination and Support Action
CSC	Common Support Centre (European Commission)
CV	Cardiovascular
DG AGRI	Directorate-General Agriculture and Rural Development (European Commission)
DG HR	Directorate-General Human Resources and Security (European Commission)
DG GROW	Directorate-General for Internal Market, Industry, Entrepreneurship and SMEs (European Commission)
DG RTD	Directorate-General for Research and Innovation (European Commission)
DG SANTE	Directorate-General for Health and Food Safety (European Commission)
DMP	Data Management Plan
DPO	Data protection officer
E&T	Education & Training
EBiSC	European induced pluripotent stem cell
EC	European Commission
ECA	European Court of Auditors
EDPS	European Data Protection Supervisor
EEG	Electroencephalograph
EFPIA	European Federation of Pharmaceutical Industries and Associations
EHR	Electronic Health Record
EMA	European Medicines Agency
eMC	electronic Medicines Compendium
EORTC	European Organisation for Research and Treatment of Cancer
ePI	electronic Product Information

Acronym	Meaning
ERA	environmental risk assessment
ESFRI	European Strategy Forum on Research Infrastructures
ESMO	European Society for Medical Oncology
EU	European Union
FASS	Farmacevtiska specialiteter i Sverige
FDA	Food and Drug Administration
FG	Function Group
fNIH	Foundation for the National Institute of Health
FTE	Full-Time Equivalent
FP	Full Proposal
FP7	Seventh Framework Programme
FWC	Framework Contract
GA	Grant Agreement
GAP	Global Alzheimer's Platform
GB	IMI2 JU Governing Board
GDPR	General Data Protection Regulation
GLP	Good Laboratory Practice
GMO	Genetically Modified Organism
GMP	Good Manufacturing Practices
GPCRs	G-protein-coupled receptors
GvHD	Graft versus Host Disease
H2020	Horizon 2020 is the biggest EU Research and Innovation programme ever with nearly EUR 80 billion of funding available over 7 years (2014 to 2020) – in addition to the private investment that this money will attract. It promises more breakthroughs, discoveries and world-firsts by taking great ideas from the lab to the market. Horizon 2020 is the financial instrument implementing the Innovation Union, a Europe 2020 flagship initiative aimed at securing Europe's global competitiveness. For more information, click here: http://ec.europa.eu/programmes/horizon2020/en/what-horizon-2020
HCP	Health Care Professional
HCPs	Health Care Providers
HCT	Human challenge trials
Helmsley Charitable Trust	Leona M. and Harry B. Helmsley Charitable Trust
HEMs	Health Educational Materials
HMA	Heads of Medicines Agencies
HR	Human resources
HRQOL	Health-Related Quality of Life
HTA	Health Technology Assessment
HTS	High-throughput screening
IAC	Internal Audit Capability
IAPO	International Alliance of Patients' Organisations
IAS	Internal Audit Service of the European Commission
IBD	Inflammatory Bowel Disease
ICC	Internal Control Coordinator
ICD	International Classification of Diseases
ICH	International Council for Harmonisation
ICHOM	International Consortium for Health Outcomes Measurement
ICS	Internal Control Standards
ICT	Information Communications Technology
IDMP	Identification of Medicinal Products
ILG	Industry Liaison Group
IMI1 JU	Innovative Medicines Initiative 1 Joint Undertaking
IMI2 JU	Innovative Medicines Initiative 2 Joint Undertaking
IMI JU	Innovative Medicines Initiative Joint Undertaking

Acronym	Meaning
INHAND	International Harmonization of Nomenclature and Diagnostic Criteria
IP	Intellectual properties
iPS cells	Induced pluripotent stem cells
ISA	IMI2 JU Information System for Absences
ISOQOL	International Society for Quality of Life Research
ISPOR	International Society for Pharmacoeconomics and Outcomes Research
IT	Information Technology
ITF	EMA Innovation Task Force
ITI-PF&S	Innovative therapeutic interventions against physical frailty and sarcopenia
JDRF	Juvenile Diabetes Research Foundation
JUs	Joint Undertakings
KM	Knowledge Management
KPI	Key performance indicator
LIF	Läkemedelsindustriföreningens
MAPPs	Medicines adaptive pathways to patients
MCID	Minimum clinically important difference
MEP	Member of the European Parliament
MID	Minimum important differences
MOA	mechanisms-of-action
MRI	Magnetic resonance imaging
MS	Multiple sclerosis
MTA	Material transfer agreement
nAbs	neutralizing antibodies
ND4BB	New Drugs for Bad Bugs
NGS	Next Generation Sequencing
NHP	Non-human primates
NIMH	National Institute of Mental Health
NK	Natural killer
OAC	Obesity Action Coalition
OECD	Organisation for Economic Co-operation and Development
OHDSI	Observational Health Data Sciences and Informatics
OMOP CDM	Observational Medical Outcomes Partnership Common Data Model
OLAF	European Anti-Fraud Office
PA	Payment Appropriation
PBT	persistent, bioaccumulative and toxic
PD	Pharmacodynamics
PEC	Predicted Environmental Concentration
PET	Positron emission tomography
PFS	Progression-free survival
PiE	pharmaceuticals in the environment
PIL	Patient information leaflet
PK	Pharmacokinetics
PM	Person/month
PMDA	Pharmaceuticals and Medical Devices Agency
PPP	Public-private partnership
PRO	Patient Reported Outcomes
QoL	Quality of life
qPCR	quantitative Polymerase Chain Reaction
QST	Quantitative sensory testing
R&D	Research and development
RA	Rheumatoid arthritis
RAE	Risk assessment exercise
RCL	Replication Competent Lentivirus
RCSA	Risk and control self-assessment
RCTs	Randomized controlled trials

Acronym	Meaning
RepER	Representative error rate
ResER	Residual error rate
RIA	Research and Innovation Action
RIs	Research Infrastructures
RP	Reporting Period
RR	Response rate
SA	Scientific Advice
SC	IMI2 JU Scientific Committee
SAICM	Strategic Approach to International Chemicals Management
SEDIA	European Commission's Single Electronic Data Interchange Area – under Funding & tender opportunities
SEND	CDISC SEND Controlled Terminology
SEND	Standardization for Exchange of Nonclinical Data
SGGs	Strategic Governing Groups
SISAQOL	Setting International Standards in Analysing Patient-Reported Outcomes and Quality of Life Endpoints Data
SLC	Solute carriers
SMEs	Small and medium-sized enterprises
SPIRIT	Standard Protocol Items: Recommendations for Interventional Trials
SOFIA	IMI2 JU Submission of Information Application
SOP	Standard operating procedure
SP	Short Proposal
SRA	IMI2 JU Strategic Research Agenda
SRG	IMI2 JU States Representatives Group
T1D	Type 1 diabetes
T2D	Type 2 diabetes
TA	Temporary Agent
TCR	T Cell Receptor
TME	Tumor microenvironment
TTG	Time to Grant
TTP	Time to Pay
UK	United Kingdom
US	United States
WHO	World Health Organisation
WP(s)	Work Package(s)

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