



Amended Annual Work Plan and Budget for 2020

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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-2020-08 adopted on 28.02.2020

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NOTICE

For UK applicants: Please be aware that following the entry into force of the EU-UK Withdrawal Agreement* on 1 February 2020 and in particular Articles 127(6), 137 and 138, the references to natural or legal persons residing or established in a Member State of the European Union are to be understood as including natural or legal persons residing or established in the United Kingdom. UK residents and entities are therefore eligible to participate in calls in this work plan.

* Agreement on the withdrawal of the United Kingdom of Great Britain and Northern Ireland from the European Union and the European Atomic Energy Community

Chronology and list of reviews

Version	Date of the adoption by the Governing Board	Items
Version 1.0	13.12.2019	Annual Work Plan and Budget for 2020
Version 2.0	28.02.2020	<p>Update of the following sections:</p> <ul style="list-style-type: none"> ▪ Notice ▪ 2.1 Executive Summary ▪ 2.2.1 Objectives & indicators - risks & mitigations ▪ 2.2.2 Scientific priorities for 2020 ▪ 2.2.3 Call management (planning, evaluation, selection, ...) ▪ 2.2.4 Activities to support and monitor ongoing projects ▪ 2.3 Call management rules ▪ 3 Budget ▪ List of acronyms <p>Insertion of Annex II - IMI2 JU Call 21 topic text</p>

1 Introduction

In 2020, IMI2 JU will continue to focus on its core activity of launching Calls for proposals for projects that address key challenges highlighted in the IMI2 JU Strategic Research Agenda in areas such as diabetes/metabolic disorders, neurodegeneration, immunology, infection control (including vaccines), translational safety, digital health, and oncology. This will be in principle the last year of allocation of funding for IMI2 JU and as such will be a pivotal year in terms of budget commitment for the Programme Office.

In addition, the 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 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, healthcare systems, patients and European society at large.

Pierre Meulien

Executive Director

2 Annual Work Plan Year 2020

2.1 Executive Summary

In order to continue to bring value to the EU citizen, we will execute the strategic research agenda of IMI2 JU through the launch of four new Calls for proposals based on the scientific priorities set out in section 2.2.2.

We will continue to successfully manage and connect a growing portfolio of projects ensuring sound budget management and close monitoring of project performance.

The IMI2 JU will continue with its programme of regular project reporting, mid-term reviews and audits of beneficiaries.

The close monitoring of project performance will also allow the IMI2 JU to demonstrate the added value of the programme to the EU and facilitate continued communication to target audiences. Efforts to engage with key stakeholders such as patients and SMEs will continue as will those related to improving the dissemination of project results.

Given the importance of demonstrating the impact of the programme to the EU citizen, reporting and dissemination activities will be complemented by socio-economic impact studies.

In order to maximise the impact of IMI2 JU projects and extend the reach of the programme, we will actively seek to involve industries other than the pharmaceutical industry when these industries facilitate the achievement of the goals of IMI2 JU. Given the global nature of the challenges being addressed these outreach activities will also focus on bringing on board actors from outside the EU and countries associated to H2020.

2.2 Operations

2.2.1 Objectives & indicators - risks & mitigations

The key objectives for IMI2 JU operations in 2020 are identified by the Governing Board in the Annual Work Plan and by the Management at operational level.

Key operational objectives for 2020 as follows:

- 1. complete the execution of the 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 by embedding dissemination in all stages of the project lifecycle.**

IMI2 KPIs

Reporting on measuring and outcomes on the ten following Key Performance Indicators will be provided yearly as part of the IMI2 JU Annual Activity Reports for year 2020 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 JU Strategic Research Agenda (SRA) and addressed by IMI2 JU projects.	Based on the SRA and including the WHO priority medicines therapeutic areas: - expressed as a number of areas reflected in the IMI2 JU portfolio; - complemented by the number and budget of grant agreements that delivered them.	IMI2 JU Regulation ¹ 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 IMI2JU 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 JU 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	0	50

¹ Council Regulation (EU) No 557/2014 of 6 May 2014 establishing the Innovative Medicines Initiative 2 Joint Undertaking (IMI2 JU), OJ L 169, 7.6.2014, p. 54–76.

			development process by providing the support for the development of tools, standards and approaches to assess efficacy, safety and quality of regulated health products'		
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KPI	Definition	Comment	Relates to	Baseline	Target
3	<p>New or improved guidelines, methodologies, tools, technologies or solutions accepted by regulatory authorities for use in the context of R&D, specifically for:</p> <ul style="list-style-type: none"> - 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. 	<ul style="list-style-type: none"> - 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. 	<p>IMI2 JU Regulation objective b1, b2, b4, b5 and b6:</p> <p>b1: 'increase the success rate in clinical trials of priority medicines identified by the WHO'</p> <p>b2: 'reduce the time to reach clinical proof of concept in medicine development...'</p> <p>b4: 'develop diagnostic and treatment biomarkers for diseases clearly linked to clinical relevance and approved by regulators'</p> <p>b5: 'reduce the failure rate of vaccine candidates in phase III of clinical trials through new biomarkers for initial efficacy and safety checks'</p> <p>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'</p>	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.	<ul style="list-style-type: none"> - 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. 	<p>IMI2 JU Regulation objective b3 and b4:</p> <p>b3: 'develop new therapies for diseases for which there is a high unmet need...'</p> <p>b4: 'develop diagnostic and treatment biomarkers for diseases clearly linked to clinical relevance and approved by regulators'</p>	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.	<p>IMI2 JU Regulation objective a:</p> <p>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...';</p> <p>and IMI2 JU Regulation recital 8:</p> <p>'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.'</p>	0	EUR 300 Million

KPI	Definition	Comment	Relates to	Baseline	Target
6	Share of IMI2 JU projects whose resources/outputs are made accessible beyond the consortia partners (with or without fee), such as major databases, bio-banks, <i>in silico</i> tools, training materials, clinical trial networks, guidance etc.	<ul style="list-style-type: none"> - 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. 	<p>IMI2 JU Regulation objective a, b2 and b6:</p> <p>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...'</p> <p>b2: 'reduce the time to reach clinical proof of concept in medicine development'</p> <p>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'</p>	0	50%
7	Co-authorships and cross-sector publications between European researchers on IMI2 JU projects (sectors include academia, small and mid-sized companies, pharma, regulators, patient organisations, etc.).	<ul style="list-style-type: none"> - Expressed as net figure - Complemented by the number and budget of grant agreements that delivered them. 	<p>IMI2 JU Regulation objective a:</p> <p>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...'</p>	0	1500

KPI	Definition	Comment	Relates to	Baseline	Target
8	New tools and processes generated by IMI2 JU projects that have been implemented by the industry participants of IMI projects.	<ul style="list-style-type: none"> - 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. 	<p>IMI2 JU Regulation objective a, b2 and b6:</p> <p>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...'</p> <p>b2: 'reduce the time to reach clinical proof of concept in medicine development'</p> <p>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'</p>	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.).	<ul style="list-style-type: none"> - Complemented by the number and budget of grant agreements that delivered them. 	<p>IMI2 JU Regulation objective a, and b1:</p> <p>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...'</p> <p>b1: 'increase the success rate in clinical trials of priority medicines identified by the WHO'</p>	Share of IMI JU projects involving patient organisations: (participants /advisory boards etc. 40%)	80%

10	Support to SMEs: share of SMEs participating as formal IMI2 JU project beneficiaries.	- To be complemented by the number of SMEs benefitting from IMI project support in other ways.	H2020 priority; IMI2 JU 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 IMI JU project beneficiaries: 15.96%	20%
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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 management is a strategic element of planning activities as their identification enables the IMI2 JU to effectively customise its objectives and prioritise actions.

Following the risk assessment exercise carried out by the Programme Office in view of this AWP, the main risks that might challenge the achievement of the objectives planned by IMI2 JU on 2020 relate to:

- Achievement of the cap (30% of total eligible costs) set out for non-EU in-kind contribution therefore, some research topics matching the IMI2 JU Strategic Research Agenda (SRA) might not be developed.
The IMI2 JU has limited control on this risk because its Member representing the pharmaceutical industry proposes the identification of call topics. However, the risk might be mitigated through i) continuous monitoring of in-kind contribution; ii) communication actions with EFPIA and the IMI2 JU Associated Partners; iii) supporting the development of other topics (e.g. cross sectional approach involving more EU-based participants); and iv) EFPIA's plan to limit non-EU pre-proposed topics.
- Completion of the H2020 research programme, which will be implemented through calls for proposals launched at the latest by 31 December 2020. In these circumstances, delays in defining annual scientific priorities and call topics might affect the IMI2 JU programme and budget execution. In order to control this risk, the Programme Office has planned extensive preparatory consultations as well as a fixed plan of call development stages shared with Members and Stakeholders.
- The volatility of the external environment, surrounding the IMI2 JU activities might affect the final implementation and the future of the IMI2 JU programme and operational activities during 2020. The IMI2 JU has a limited control of this kind of risk and completely depends on the decisions of its Members and stakeholders. In order to mitigate related risks, the Programme Office will operate proactively in order to have timely directions and will follow up any political development that may affect its strategy. To that purpose, the implementation of IMI2 JU communications strategy will be a key element to demonstrate, in a spirit of openness and transparency, the benefit of the partnership to EU citizens; this should contribute to mitigating possible negative perceptions or misconceptions about IMI2 JU objectives. The Programme Office will also maintain close relationships with key decision-makers to ensure they have an informed view of the way IMI2 JU works and its achievements.
- Low participation of industry from sectors other than the pharmaceutical industry due to misperception of IMI2 JU objectives and challenges of the legal framework (e.g. absence of matching with EU funds and acknowledgement, IP rules). In order to mitigate this risk, the IMI2 JU will i) ensure proactive outreach strategies; ii) explore with potential industry partners the specific issues and the alternative approach that might be taken.
- Limited cross-project collaboration, exploitation of assets and infrastructures generated, and dissemination of IMI project outcomes. The reasons triggering this risk factor might include i) an extensive opt-out of the open access to research data, ii) challenges in exploitation and dissemination of projects, or iii) lack of sustainability measures. To that purpose, the mitigating measures put in place by the IMI2 JU aim at i) informing on the scope of open access and the possibility to partially opt-out, based in the H2020 existing documents; ii) enhancing and communicate on the catalogue of projects tools available (IMI2 JU website); iii) involving the IMI2 JU advisory bodies (States Representatives Group, Scientific Committee and the Strategic Governing Groups) in defining sustainability and identifying possible solutions considering the project objectives and outcomes and assets generated.

2.2.2 Scientific priorities for 2020

The IMI2 JU activities for 2020 are fully in line with the objectives as set out in Article 2 of the IMI2 JU Regulation. 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 wellbeing.

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 2020 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 2020, IMI2 JU has identified nine 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 2020 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 2020 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 2020 would then be updated accordingly.

To implement the 2020 priorities, IMI2 JU will initiate four 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 2020.

Topics launched based on this Annual Work Plan 2020 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.

A. Neurodegeneration and other neuroscience priorities

Activities in 2020 will address the following topics:

- 1. Rare neurodegenerative and neurocognitive diseases clinical platform development:** The main scope of this topic will be to develop a clinical platform for rare neurodegenerative and neurocognitive diseases (RND), ready to test new therapies in a streamlined and efficient way, delivering more effective, targeted interventions that can slow or stop RND. Additionally, the research on a rare neurological disorder will be used to get insights into more complex diseases with similar genetic linkage.
- 2. Complement in neurodegenerative diseases.** The main interest is around building knowledge on the druggable targets in the complement system, as neuroinflammation is widely implicated in a wide range of chronic neurodegenerative conditions, but much about the specific role of complement remains to be defined. The project will build up on the significant advances in genetic and biomarker domains made for Alzheimer's disease (AD), focusing on delivering a profile of the status of complement activity in Parkinson's disease (PD), Huntington disease (HD), amyotrophic lateral sclerosis (ALS) (or possibly subtypes of these), with corresponding suggestions of what novel therapeutic approaches/ targets could be most effective.

Expected impact:

- Foster the collaboration of the main stakeholders that are academic researchers, patients and patient advocacy groups, industry and regulatory bodies as well as reimbursement agencies to build up innovative trial methodologies appropriate for the rarity of the diseases
- Leverage the growing pipeline of therapeutic RND approaches developed by European pharma industry
- Develop the knowledge of the role of complement in PD, ALS, HD and other neurodegenerative diseases, using the technical foundations established in AD
- Apply innovative approaches in the research methodologies that will be performed (system biology analysis; complete patient biomarkers' profiling; in vivo testing of tool compounds/ antibodies in specific animal models)

Type of actions:

Research and innovation actions

B. Infection control including vaccines

Activities in 2020 will address the following topics:

Expansion of the AMR accelerator platform. There is still a critical need for new antibiotics. The objective is to build on the Antimicrobial Resistance (AMR) Accelerator Programme launched in 2018. The aim is to expand activities and accelerate scientific discoveries in antimicrobial resistance (AMR) and to progress a pipeline of potential therapeutic, biologic and preventive medicines & procedures. This may include host pathogen interaction (e.g. anti-virulence targets), host directed and immune therapies, alternative approaches (e.g. novel delivery systems), *in silico* tools (big data, machine learning, artificial intelligence (AI)) for optimising use of available data (Clinical Trials, pharmacokinetics/pharmacodynamics (PK/PD), physiologically based pharmacokinetic (PBPK), Imaging, non-clinical safety studies). The solutions should help preventing recurrent infections, improve quality and longevity of life and reduce significantly the use of antibiotics.

3. Academia and industry united innovation and treatment for tuberculosis (UNITE4TB).

Tuberculosis (TB) is one of the top ten causes of death worldwide. In 2017, 10 million people fell ill with the disease with 1.6 million associated deaths in both adults and children. The objectives of UNITE4TB topic are to develop and implement innovative, state of the art adaptive clinical trial designs to the field of TB regimen development able to define the therapeutic dose for existing experimental New Chemical Entities (NCE's) within treatment combinations, The topic outputs will define the duration and composition of novel treatment combinations, that will shorten or simplify the standard of care as well as prospectively validating biomarkers against the relapse endpoint. In addition, the funded action is expected to develop clinical trial simulations, evaluate new technologies to monitor and enhance treatment adherence, and develop an understanding of population pharmacogenomics in all forms of active TB.

4. Development of innovative personalized diagnostics and patient-guided therapies for the management of sepsis-induced immune suppression.

The proposed topic is addressing sepsis, a global health priority being targeted by many countries and the World Health Organization (WHO). If not recognized early and managed promptly, sepsis can lead to septic shock, multiple organ failure and serious consequences including death. There are approximately 30 million sepsis patients per year worldwide. The primary aim of this topic is to develop diagnostic tools for characterizing sepsis or injury-induced immunosuppression in order to target personalized management and therapeutic solutions for improving outcomes and decreasing the occurrence of secondary healthcare-associated infections (HAI). The main objectives will be to reduce mortality and decrease secondary HAI through diagnostic and therapeutic approaches including (i) implementation of an immune-based personalized diagnostic test to clearly identify sepsis patients in an immune-suppressed state and (ii) introduction of innovative immuno-modulators in order to restore immune homeostasis. The project generated from the topic will also aim to demonstrate the medical and economic value and benefits of this approach to improve patient outcomes (organ dysfunction, disability, mortality, etc.), decrease infectious HAI complications, and reduce healthcare costs.

5. Innovations to accelerate vaccine development and manufacture.

Vaccination is one of the greatest achievements in healthcare. However, developing a vaccine remains costly, time consuming, and risky (approximately EUR 800 million, 11 years in clinical development with <10% chance of entering the market). Advances in immunology, disease modelling, in silico modelling, including the analysis of big data and the application of machine learning (ML) artificial intelligence (AI), provide opportunities to innovate, de-risk and accelerate the vaccine-development process. Many of these advances have occurred in the academic sector. These advances can be harnessed to nurture and expand a vaccines innovation ecosystem by bringing together academics, small & medium size enterprises (SMEs) and industry. The overall objective of the topic is to accelerate and de-risk the development of new vaccines by incorporating scientific and technological advances from the academic and biotech sectors into industry and developing more predictive biological and mathematical models of vaccine performance.

The topic is structured as four subtopics, addressing how to integrate and standardise into the vaccine-development programme four key areas of challenge. Subtopics 1 and 4 are centred on developing in silico model platforms for the immune system and biomanufacturing, respectively, which should be sustainable after the completion of the project; and subtopics 2 and 3 seek to widen the use of controlled human infection models (CHIMs) and next-generation in vitro models and assays in vaccine development. All subtopics in the programme relate to the use of novel modelling technologies (biological or mathematical) to accelerate the development of vaccines. Hence, by bringing together stakeholders from all areas of vaccine R&D (preclinical, clinical and manufacturing), the programme offers a unique opportunity to explore and open up an interdisciplinary dialogue on the future use, acceptance and further co-ordinated development of these technologies.

6. **Modelling the impact of monoclonal antibodies and vaccines on the reduction of antimicrobial resistance:** Monoclonal antibodies (mAb) and vaccines can reduce antimicrobial resistance (AMR) but quantifying their impact is methodologically challenging. This topic has the main objective to quantify the burden of disease and health care costs caused by AMR and the impact of the monoclonal antibodies and vaccines, to prepare the ground for cost-effectiveness modelling to select the best intervention strategy which could reduce such a burden. A systematic review of the literature should clarify the initial structure of the model, the potential parameters and the gaps that will be filled by a retrospective review of relevant hospital databases throughout Europe and globally. Finally, while many data are currently available, the selection of data, their curation and processing should be handled through mathematical modelling to test the effect of mAb and/or vaccination strategies.
7. **Development of therapeutics and diagnostics combatting coronavirus infections:** On 30 January 2020, the novel coronavirus outbreak (COVID-19) was declared by WHO as a Public Health Emergency of International Concern according to the International Health Regulation 2005. Considering the public health and humanitarian implications of the COVID-19 outbreak, there is a need to advance our knowledge of SARS-CoV-2 specifically and the wider coronavirus family in general with the aim of contributing to an efficient patient management and/or public health preparedness and response to current and future outbreaks of coronavirus infection. There is therefore an opportunity to support collaboration of private companies, academia, international organisations, public bodies etc. to accelerate the development of therapeutics and diagnostics to tackle the current and future outbreaks and to contribute the pan-European effort responding to this Public Health Emergency.

Expected impact:

- A pipeline of promising new agents for tackling gram -ve antibiotic-resistant bacterial infections,
- New diagnostics and therapeutic solutions to improve patient outcomes, decrease infectious complications, and reduce healthcare costs for secondary healthcare-associated infections.
- The implementation of state-of-the-art adaptive clinical trial designs to the field of TB regimen development to enable faster validation and delivery of treatment combinations for the world's biggest cause of mortality in infectious disease
- Contributing to the development of a vibrant AMR and TB research environment in the EU, fostering private-public collaboration across EFPIA, Academia, non-governmental organizations (NGOs) and SMEs and strengthening the competitiveness and industrial leadership of Europe.
- More rapid transmission of innovations into de-risking early-stage vaccine development and into increasing efficiencies and reducing costs in the transitioning of the bio manufacturing processes during vaccine development.
- Increased probability of successful Phase 3 efficacy trials and the acceleration of vaccine development, leading to benefits for trial participants and ultimately those with the medical need for the vaccine.
- Determine where mAbs and vaccines will be most useful from health economic and disease burden perspective and with the highest chance of reducing antibiotic consumption and emergence of resistant isolates
- Increase the amount of scientific and value-added information on the potential role of vaccines and mAbs in reducing AMR
- Fast-track development and availability of therapeutics and/or diagnostics to contribute to the response of the ongoing epidemic of COVID-19 and/or future outbreaks of pan-coronaviruses and more generally to contribute to public health preparedness

Type of actions:

Research and innovation actions

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

Activities in 2020 will address the following topics:

- 8. Data lakes.** Many pharma and life sciences companies are currently creating data lakes to bring together internal data to apply analytics and create insights. However, these data often need to be complemented with other data sources. Most health data are generated outside the life sciences, e.g. electronic health records, claims, biobanks etc. In addition, control over health data is starting to shift towards the patient; initiatives and healthcare technology companies already signalling a future where the patient will be in control of data and can decide how and with who to share. To improve our ability to combine data from multiple sources and maximise insights generation from these data, we need a common approach to enable quick and efficient connectivity of data to use for diverse purposes. A fundamental requirement for this to work is to make data findable, accessible, interoperable and reusable (the underlying concepts are known as the FAIR principles). Therefore, the main objectives of this topic are: to create (1) a common set of tooling for managing and FAIRifying data lakes, i.e. the agreement or development of a common and potentially open source toolset, (2) agreement on the necessary key ontologies and standards and (3) to create a market place for datasets or individual-level data to further enhance data fluidity. With a successful implementation, users would be able to find, access and use data which data owner decides to share, and leverage them for different purposes. Data owners could do this at the individual level, e.g. a personal health record, the company level e.g. datasets from the company data lake, or an industry or even global level, e.g. data from an industry collaboration.
- 9. Personalised endpoints.** Personalised medicine has been a focus for the medical field and healthcare systems for many years. The goal is to achieve optimal clinical outcome by providing the right treatment at the right dose and right time to the right person. The hope is that precision medicine will lead to fewer side effects, fewer non-effective treatments and lesser burden on the patients, as well as reduce cost and burden on healthcare. This topic aims to explore ways of implementing personalised healthcare through personalised endpoints. To this end the topic will support activities leveraging information technology, machine learning analysis to create defined patient profiles, not only defined by their medical characteristics but also by their choices and preferred outcomes.
- 10. Returning clinical trial data to patients:** The sharing and secondary use of data collected in a clinical study (interventional and non-interventional) with study participants is still uncommon and rules for sharing not well harmonized within the EU. The objective is to explore the main reasons for this, including the complexities in setting up the infrastructure, processes and a common data format to enable it and the concerns around protecting the integrity of the study, study participants' privacy and confidentiality, maintaining the study blind, and supporting further research projects. This topic would be also a topic for patient and for patient organisations. In addition, the topic support activities for building and move to the next step the results of the Do-IT initiative. The topic intends to tackle the aspect of returning clinical trial data to patient in the following scenarios: Scenario 1 is after the participant leaves the trial (either after screen failure or after unblinding/ the end); Scenario 2 could be during the trial (but not while blinded or for specific data).

Expected impact:

- Patient centric data collection and data re-use
- A coherent and transparent framework to address data privacy and personal integrity issues inherent in the use of health records.
- Allow patients to tailor their care and truly achieve personalised medicine.
- Better patients stratification
- Better adherence to treatment and reduction of off-label use.
- Integration of digital health approaches in clinical practice to enable predictive and precision medicine
- Development and maintenance of standardized, robust and state-of-the-art data management
- Development of new ways to source, manage process, and analyse data in compliance with ethical, General Data Protection Regulation (GDPR) and security standards

Type of actions:

Research and innovation actions

D. Oncology

Activities in 2020 will address the following topics:

- 11. Real-world clinical implementation of liquid biopsy.** Liquid biopsy is a promising concept for patient selection and disease monitoring in drug development and in clinical practice. However, as of today, few clinical studies used liquid biopsies to systematically and prospectively identify eligible patients for clinical studies, therapy selection, therapy monitoring or detection of first signs of efficacy. The overall objective of the topic is to support real-world clinical implementation of liquid biopsies in solid tumour indications. The goal is to evaluate whether liquid biopsies can become a clinical standard that cost-effectively and safely accelerates clinical trial enrolment, as well as therapy decisions, thereby enabling earlier changes to therapy as compared to “response evaluation criteria in solid tumours” (RECIST) in order to tackle emerging treatment resistance and spare patients from overtreatment and burden of invasively collected tumour samples. This should contribute to prolonging progression-free survival and potentially overall survival of cancer patients.
- 12. Microbiome.** Since a number of years, alterations in the microbiome have been associated with the pathology of many human disorders such as inflammatory, neuro-degenerative, metabolic and infectious diseases, nutritional deficits and cancer. The fundamental basic question is whether the observed “microbiome dysbiosis” is causal for disease initiation and its progression or is the consequence of a co-adaptation of the microbes to the disease microenvironment. Increasing evidence from experiments using pre-clinical disease models suggest that many pathologies a potential significant link between the human host response to changes in the microbiome and disease occurrence or severity. Some recent studies have been able to find specific interactions between microbial generated bioactive molecules (i.e. metabolites, bacterial cellular components, etc.) and human host receptors in known disease pathways which might be amenable for therapeutic intervention. In particular for cancer, recent studies indicated a significant correlation of the composition of the gut flora and the efficacy of cancer immunotherapy. This topic will address some key gaps that need to be addressed for translation of microbiome science into true therapeutic opportunities: 1) the lack of well-controlled clinical studies that convincingly demonstrate how/that microbiome manipulation could potentially resolve certain disease phenotypes, at least partially, in humans. 2) the need for definitive exploratory medicine studies which link preclinical hypotheses about human host – microbiota disease interactions with clinical outcomes in disease subject cohorts.3) Finally, due to the overall potential impact of the microbiome on human health and disease a cross-diseases approach should be strived for. To this end the topic will support activities for the understanding of microbiome causality by pursuing studies in volunteers at high-risk for developing immune mediated diseases
- 13. Tumour plasticity.** Drug resistance in cancer is one of the greatest causes of mortality and despite increasing success with targeted therapies in the clinic (including immunotherapy) the mechanisms by which cancer cells evade cell death are still not well understood. Drug combinations are likely to be critical to overcoming drug resistance but are dependent on identifying the cellular programs that cancer cells use to resist therapeutic agents. The overall objective of the topic is to use state-of-the-art single-cell sequencing to understand and overcome drug resistance in cancer by characterising the biology of drug tolerant persister cells, building the capability for such studies across Europe. The topic will address primarily adult tumours, with the provision to include childhood tumours where appropriate models are available at a later stage of the program. To optimise the ability to determine the role of tissue lineage on the biological processes observed in single-cells, it is proposed that the majority (>80%) of the single-cells should be provided from drug treatments in three adult cancers: 1) non-small cell lung cancer (NSCLC); 2) breast cancer; 3) colorectal cancer.
- 14. Proton versus photon therapy for oesophageal cancer – a trimodality strategy.** The main objective of this topic is to examine the value of proton therapy (PT) as a treatment modality through a clinical study in oesophageal cancer. The study will compare outcomes between pencil-beam scanning proton therapy and intensity-modulated radiation therapy (IMRT). The study will determine if proton therapy in a trimodality (radiotherapy-chemotherapy-surgery) treatment; (i) reduces treatment related cardio-pulmonary toxicity (ii) increases loco-regional tumour control and pathological complete response when similar dose or higher dose is delivered, (iii) improves disease-free and overall survival.

Oesophageal cancer is chosen due to its relatively high occurrence in the population and the possibility to extend findings to other cancer types. A second objective is to use the evidence generated during the oesophageal cancer study to reach a consensus on which indications are most suitable for PT treatment by engaging with the broader oncology community including oncologists, healthcare providers, health technology assessment (HTA) agencies, and payers among others.

Expected impact:

- Improved monitoring of disease progress
- Improved selection of patients and inclusion in appropriate clinical trials
- Improved quality of life by preventing in-appropriate medication
- Better knowledge on tumour resistance mechanisms
- Improved understanding of the translational potential of patient-derived tumour models as indicators for the patient situation
- Increased knowledge on the interaction between human organism and microbiota in health and disease
- Access to data for functional studies and further opportunities to identify novel targets and drug combinations that delay or prevent the emergence of drug resistance in cancer
- Development of gold standards for the analysis of single-cell sequencing data
- New and improved standard for the treatment of oesophageal cancer patients and potentially patients with other cancer indications. Refined selection of patients.
- Improve the quality of care through better evidence of benefits and patient outcomes and support reimbursement decisions.

Type of actions:

Research and innovation actions

E. Immunology

Activities in 2020 will address the following topic:

- 15. Early diagnosis, prediction of radiographic outcomes and development of rational, personalised treatment strategies to improve long-term outcomes in psoriatic arthritis.** Autoimmune diseases cover over 100 distinct diseases and syndromes, together affecting approximately 5% of the population of Europe, with two-thirds of the patients being female. The burden of autoimmune disease crosses medical and scientific boundaries, and requires cross-functional collaboration by scientists and physicians with interests in diseases of widely differing organ systems. In addition, there is an increased awareness that immune-mediated mechanisms play a key role in several, if not all, chronic diseases from cancer to metabolic disorders and therefore new immunology based approaches may be game changers for treatment of millions of patients affected by these conditions. The overall scope of this topic is to provide patients and physicians with new tools including clinical data patterns, biomarker profile patterns and imaging analysis for a better control of psoriatic arthritis (PsA). The aim of this topic is to characterise the natural history of PsA from psoriasis to “early” PsA to “full-fledged” PsA (as diagnosed by Classification Criteria for Psoriatic Arthritis – CASPAR - criteria). This characterisation will be based on discovering new biomarkers and endotypes, constructed on genetic, transcriptomic, proteomic and/or clinical markers. To identify those endotypes, artificial intelligence (AI) and machine learning (ML) processes will be needed. In particular, the topic aims at the following specific objectives: 1) to enable rheumatologists, dermatologists and general practitioners to make early diagnosis of PsA in patients with PsO and other rheumatic disorders; 2) to identify early patients at risk of progression to PsA in order to enable earlier interventions and possibly prevent PsA development; 3) to define the factors that predict disease progression in PsA patients, including early prediction of bone/joint damages, leading to the development of more adapted treatment strategies; 4) to develop rational and personalised treatment strategies (e.g. select the optimal first line or second line treatment based on patient characteristics) with optimised outcomes in PsA patients and reduce the disease burden.

Expected impact:

- Improved methods for recognition and diagnosis of autoimmune and inflammatory disorders and a range of treatment options.
- Earlier availability of new, more cost effective therapies to patients most likely to benefit in different geographical regions.
- More precise, targeted treatments yielding long-lived reductions in disease and improved patient quality of life, and fulfilling unmet medical needs in patient care.

Type of actions:

Research and innovation actions

F. Translational safety

Activities in 2020 will address the following topics:

- 16. Pharmacodynamic Drug-drug interaction predictive testing by learning algorithms to enhance safety.** Clinical development usually addresses drug-drug interactions (DDI) from a metabolism standpoint based on in vitro and sometimes in silico information, and ultimately sporadically during late stage clinical trials or even after marketing authorization, i.e. when patients are confronted by polypharmacy. This topic will support activities addressing challenges related to safety issues pertaining to DDI that do not only concern pharmacokinetic, i.e. metabolic (mainly hepatically expressed enzymes) or permeability-related (e.g. efflux transporters such as P-glycoprotein) pathways, but also occur when drugs have opposing functional effects (reduced efficacy issues) and more importantly when drugs have additive or synergetic functional activities in physiological pathways.
- 17. Digital vivarium.** In vivo monitoring of animals in current preclinical studies is done mostly by cage side observation from the husbandry personal. This does not allow detailed monitoring of some phases of the day such as sleeping pattern. Hence the limited ability of this monitoring to translate some findings across species including humans. Digital monitoring technologies provide a great opportunity to develop new methods to monitor the cage environment; monitor the animals for a number of biomarkers (motion, heart rate, temperature, sleep patterns) through observation or wearables and implants; and to develop software to analyse the data and detect abnormalities in some of these functions/parameters. The objective of this topic is to develop those monitoring tools of the future (cages, wearable devices for large animals, sensors) to enhance monitoring of the animal and to detect drug-induced changes that current methods do not allow to observe in animals so far and generate data suitable for use in preclinical toxicological studies. A further aim is a contribution to the 3Rs, reduction, refinement and replacement in the translational safety preclinical field.

Expected impact:

- Improved preclinical models of toxicity
- Decrease the risk presented to patients by drug drug interactions (DDI)
- Reduce dependence on animal models - refinement of pre-clinical safety studies
- Increase developability of candidate drugs

Type of actions:

Research and innovation actions

G. Facilitating Rare Disease therapies (including Advanced Therapy Medical Products) reaching patients in Europe

Activities in 2020 will address the following topics:

- 18. Clinical outcomes assessments for rare diseases.** Regulatory agencies have signalled the importance of including clinical outcomes assessments (COA's) as part of drug development. This is particularly relevant to rare diseases where challenges in advancing and obtaining approval for new therapies include 1) the heterogeneity in clinical disease severity and progression in small populations; 2) the very slowly progressive nature of many rare disease; and 3) the lack of well-defined or established clinical and biomarker endpoints; (4) small populations calling for adapted development and advanced statistical and methods. In the interest of better and faster development of medicinal products for rare diseases, this topic will support activities for consolidated and coordinated efforts towards creating and validating fit-for-purpose COA's by multiple stakeholders (including regulatory agencies). To create a first blueprint for example in a rare neuromuscular disease could be of value. The COA's should include patient reported outcomes (PRO), observer reported outcomes (ObsRo), clinician-reported outcomes (ClinRo), as well as performance-outcomes (PerfO). Coordinated and cooperative participation in COA development efforts and instrument validation with input from patient organizations, clinicians, academic medical centres, industry, regulators, and payers would underscore the importance of a comprehensive public-private partnership approach as well as create avenues to accelerate drug development and approvals
- 19. Defragmenting and shortening the path to rare disease diagnosis by using genetic screening and digital technologies.** Treatment of Rare Diseases is significantly hampered by delayed diagnosis and this topic will focus on diagnosis for the following reasons. Many rare diseases are degenerative, therefore early diagnosis is key. In addition, rare diseases are characterized by a broad diversity of disorders and symptoms that vary not only from disease to disease, but also from patient to patient suffering from the same disease (syndrome). Those symptoms can also and often be very common. Altogether, this leads to a lengthy and burdensome path to diagnosis that has been stated to take on average 8 years and often complicated with misdiagnosis and ineffective treatments, creating a heavy human and societal cost. The topic aims to address the diagnosis gap and, in particular, explore **(a)** the potential for New-born genetic screening for rare diseases. Criteria will be defined to select the gene[s] for the panel as initial use-cases to exemplify the concept and **(b)** Empowering the patient/physician duo with an artificial intelligence/phenotypic database to increase the understanding of disease, develop diagnostic and disease algorithms and identify biomarkers in pre-clinical & early stage of disease.

Expected impact:

- Early detection and Shorter path to diagnosis for Rare Disease Patients
- Early intervention (when available), follow-up, genetic counselling (such as family planning)
- Improved clinical and patient oriented outcomes
- Patient empowerment for smarter referral
- Reduced healthcare inefficiencies
- Enable natural history projects and provide better epidemiological data
- Cost savings for the Healthcare System
- Better and faster development of medicinal products for rare diseases
- Consolidated and coordinated efforts towards creating and validating fit-for-purpose COA's by multiple stakeholders (including regulatory agencies)
- Create avenues to accelerate drug development and approvals
- Advancing COA's in rare disease (for example neuromuscular) could be an important model for subsequent efforts in other rare diseases

Type of actions:

Research and innovation actions

H. Other enablers of research topics

Activities in 2020 will address the following topic:

- 20. Handling of protein drug products and stability concerns.** The overall aim is to address challenges with handling of protein drug products in hospitals, pharmacies and hands of patients. Routine handling or unintentional mishandling of therapeutic protein products may cause degradation that can potentially compromise the clinical safety and efficacy of the product. This topic supports activities that should allow for identification of the risk factors and addressing them in drug production, supply and administration processes. The first objective of this topic is to improve the understanding of real-world stressful drug product handling steps and their effects on protein product quality. The second objective of the topic is to use this understanding for development of guidelines and operating processes to improve the drug product robustness and pharma processes, and to reach more efficient training.

Expected impact:

- Improve quality, safety and efficacy of therapeutic protein products by generating insight and improving development, supply, and use processes.

Type of actions:

Research and innovation actions

I. 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-up research 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 intention is that the restricted Call will be published as a single-stage Call in the second quarter of 2020.

This Call will be:

- restricted to the original consortia of actions funded under topics published in the IMI2 JU Annual Work Plan of 2014, of 2015 and of 2016, 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 actions:

Research and innovation actions

Calls for Proposals

Call number and topics	Indicative Call launch timing	Indicative IMI2 JU funding (in EUR) ^{2,3}	Indicative in-kind contribution (in EUR) from EFPIA entities and Associated Partners
<p><u>IMI2 JU Call 20</u></p> <ul style="list-style-type: none"> ▪ <i>Infection control including vaccines</i> <ul style="list-style-type: none"> ▪ Academia and industry united innovation and treatment for tuberculosis (UNITE4TB) ▪ Innovations to accelerate vaccine development and manufacture ▪ <i>Oncology</i> <ul style="list-style-type: none"> ▪ Tumour plasticity ▪ Proton versus photon therapy for oesophageal cancer – a trimodality strategy ▪ <i>Immunology</i> <ul style="list-style-type: none"> ▪ Early diagnosis, prediction of radiographic outcomes and development of rational, personalised treatment strategies to improve long-term outcomes in psoriatic arthritis ▪ <i>Other enablers of research topics</i> <ul style="list-style-type: none"> ▪ Handling of protein drug products and stability concerns 	21 January 2020	133,009,000	140,209,500
IMI2 JU Call 20 process			
<p>Two-stage call with predefined submission deadline</p> <p>Indicative Call deadline for short proposals: 21 April 2020</p> <p>Indicative Call deadline for full proposals: 5 November 2020</p> <p>Research and Innovation Actions (RIA)</p>			

² Based on estimate of total operational commitment appropriations available in 2020. This includes the carry-over of unused commitment appropriations from 2019 to 2020 for IMI2 JU Calls 14 and 15.

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

Call number and indicative topics	Indicative Call launch timing	Indicative IMI2 JU funding (in EUR) ⁴	Indicative in-kind contribution (in EUR) from EFPIA entities and Associated Partners ⁵
<u>IMI2 JU Call 21</u> Development of therapeutics and diagnostics combatting coronavirus infections	03 March 2020	Up to 45,000,000	0
IMI2 JU Call 21 process			
Single-stage call with predefined submission deadline Indicative Call deadline for proposals: 31 March 2020 Research and Innovation Actions (RIA)			

Call number and indicative topics	Indicative Call launch timing	Indicative IMI2 JU funding (in EUR) ⁶	Indicative in-kind contribution (in EUR) from EFPIA entities and Associated Partners
<u>IMI2 JU Call 22</u> <i>Restricted Call</i> ⁷ Restricted Call to maximise impact of IMI2 JU objectives and scientific priorities	23 June 2020	20,000,000	0
IMI2 JU Call 22 process			
Single-stage call with predefined submission deadline Indicative Call deadline for proposals: 29 September 2020 Research and Innovation Actions (RIA) Restricted Call			

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

⁵ The indicative contribution from EFPIA companies and IMI2 JU Associated Partners will depend on the proposals eventually selected under the Call. See Annex II - IMI2 JU Call 21 topic text.

⁶ The maximum possible rate of co-financing is 100 %.

⁷ The launch of this Call is subject to the assessment of the outcome of the IMI2 JU Call 19 Restricted Call in 2019.

Call number and indicative topics	Indicative Call launch timing	Indicative IMI2 JU funding (in EUR) ^{8,9}	Indicative in-kind contribution (in EUR) from EFPIA entities and Associated Partners
<p><u>IMI2 JU Call 23</u></p> <ul style="list-style-type: none"> ▪ <i>Neurodegeneration and other neuroscience priorities</i> <ul style="list-style-type: none"> ▪ Rare neurodegenerative and neurocognitive diseases clinical platform development ▪ Complement in neurodegenerative diseases ▪ <i>Infection control including vaccines</i> <ul style="list-style-type: none"> ▪ Development of innovative personalized diagnostics and patient-guided therapies for the management of sepsis-induced immune suppression ▪ Modelling the impact of monoclonal antibodies and vaccines on the reduction of antimicrobial resistance ▪ <i>Big data, digital health, clinical trials and regulatory research</i> <ul style="list-style-type: none"> ▪ Data lakes ▪ Personalised endpoints ▪ Returning clinical trial data to patients ▪ <i>Oncology</i> <ul style="list-style-type: none"> ▪ Real-world clinical implementation of liquid biopsy ▪ Microbiome ▪ <i>Translational safety</i> <ul style="list-style-type: none"> ▪ Pharmacodynamic drug-drug interaction predictive testing by learning algorithms to enhance safety ▪ Digital vivarium ▪ <i>Facilitating Rare Disease therapies (including Advanced Therapy Medical Products) reaching patients in Europe</i> <ul style="list-style-type: none"> ▪ Clinical outcomes assessments for rare diseases ▪ Defragmenting and shortening the path to rare disease diagnosis by using genetic screening and digital technologies 	23 June 2020	66,217,098	105,790,500

⁸ Based on estimate of total operational commitment appropriations available in 2020. This is without prejudice to commitment appropriations to be carried over from 2019 to 2020 (to be determined early 2020).

⁹ The maximum possible rate of co-financing is 100 %.

IMI2 JU Call 23 process		
Two-stage call with predefined submission deadline		
Indicative Call deadline for short proposals: 29 September 2020		
Indicative Call deadline for full proposals: 17 March 2021		
Research and Innovation Actions (RIA)		
Overall total IMI2 JU Call 20, Call 21, Call 22 and Call 23	264,226,098	246,000,000

All proposals must conform to the conditions (in particular admissibility conditions, eligibility conditions, selection and award criteria, and type of actions) set out in this amended Annual Work Plan and Budget for 2020.

Budget

The budget for the financial year 2020 is based on the currently available information.

A table overview of the operational budget for 2020 is set out below.

Heading Title 3	Budget 2020.0		Budget 2020 Amendment 1		Amended Budget 2020.1	
	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, including EFTA contribution)	255,971,716	195,055,294	-6,656,650	-4,908,659	249,315,066	190,146,635
Appropriations carried over from 2019	6,314,588		8,623,432	4,537,406	14,938,020	4,537,406
EFPIA and other Members contribution to operational costs		1,000,000			0	1,000,000
Associated Partners contribution to operational costs		1,500,000			0	1,500,000
Total operational costs Title 3	262,286,304	197,555,294	1,966,782	-371,253	264,253,086	197,184,041

The difference between the total budget available for Title 3 and the budget available for new IMI2 JU Calls in 2020 is EUR 26 988. This amount represents IMI JU (FP7) amounts recovered in 2019 from beneficiaries (C4) to be used only with respect to IMI JU related appropriations.

The decrease of the European Union's financial contribution to operational costs is due to a prioritization of and redeployment to climate related activities under Horizon 2020 in the budget adopted for 2020. For IMI2, the budget adopted was thus below the initial Commission proposal, which was underlying the first IMI2 2020 budget. A table overview of the Budget for 2020 is set out in Chapter 3 to this amended Annual Work Plan and Budget for 2020.

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 2020 for new Calls/payments	369,451	4,510,418
50% unused running costs (2019) carried over to operational budget 2020 for new Calls	941,673	
unused appropriations IMI2 (H2020) Call 14 and 15 (2018) – already re-activated in AWP 2020 for Call 20 (new Call to be launched in 2020)	6,314,588	
unused appropriations IMI2 (H2020) Call 19 (2019) – to be re-activated in AWP 2020 for new Calls to be launched in 2020	7,285,320	
IMI JU (FP7) amounts recovered in 2019 from beneficiaries (C4) to be used only with respect to IMI JU related appropriations	26,988	26,988
TOTAL	14,938,020	4,537,406

* breakdown per fund sources of commitment appropriations EUR 369,451: C2 EUR 191,959; C4 EUR 177,492.

* breakdown per fund sources of payment appropriations EUR 4,510,418: C1 EUR 4,233,315; C2 EUR 81,336; C4 EUR 195,767.

2.2.3 Call management (planning, evaluation, selection, ...)

Key activities in 2020 will comprise the launch of four competitive Calls for proposals implementing the 2020 scientific priorities, one responding to the Public Health Emergency regarding the novel Coronavirus outbreak (COVID-19) as declared by the WHO on 30 January 2020. The indicative launch dates are 21 January 2020 for the first call of the year (IMI2 JU Call 20), 3 March for the second call of the year (IMI2 JU Call 21) and 23 June 2020 for the last two calls (IMI2 JU Calls 22 and 23).

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 case of IMI2 JU Call 21, since it addresses a very urgent public health emergency the submission deadline will be limited to four weeks from the publication of the Call 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 for 2020 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)¹¹.

To maximise the efficiency of the calls management, 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

91 ongoing projects will be running at different stages of their life cycle in 2020, with additional projects coming in during the year when the IMI2 JU Calls 18, 19 (launched in 2019) and 21 (launched in 2020) complete the evaluation cycle (as indicated in the second column on the below table– ‘ongoing in 2020’). Most of the 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 24 reviews for projects launched under IMI2 JU Calls 1, 6, 7, 8, 9, 10, 12, 13 and 16.

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’

¹¹ <https://ec.europa.eu/info/funding-tenders/opportunities/portal/screen/home>

The following table presents a forecast of the reporting expected for 2020:

Calls	Ongoing projects in 2020	Reports due after 31/10/2019	Project periodic reports due in 2020					Of which		
			1 st RP in 2020	2 nd RP in 2020	3 rd RP in 2020	4 th RP in 2020	5 th to 7 th RP in 2020	Total reports	Projects ending in 2020	Final reports due in 2020
IMI JU 1										
IMI JU 2										
IMI JU 3										
IMI JU 4										
IMI JU 5										
IMI JU 6	1							1	1	1
IMI JU 7										
IMI JU 8	1							1	1	1
IMI JU 9	1							1	1	1
IMI JU 10	1							1	1	1
IMI JU 11	7							7	7	4
IMI JU	11	0	0	0	0	0	0	11	11	8
IMI2 JU C1	1							1	1	
IMI2 JU C2	1							3	3	2
IMI2 JU C3	4						4	4	1	1
IMI2 JU C4										
IMI2 JU C5	5	1					5	6		
IMI2 JU C6	3	1			3			4		
IMI2 JU C7	6	1			6			7	1	1
IMI2 JU C8	4			3	1			4		
IMI2 JU C9	6			1	5			6	2	2
IMI2 JU C10	8			8				8	2	2
IMI2 JU C11	3			3				3	3	3
IMI2 JU C12	7		7					7		
IMI2 JU C13	13		13					13		
IMI2 JU C14	4		4					4		
IMI2 JU C15	7		7					7		
IMI2 JU C16	5		5					5		
IMI2 JU C17	3							0		
IMI2 JU C18*	6							0		
IMI2 JU C19	2							0		
IMI2 JU C21**	6									
IMI2 JU	94	3	36	15	15	9	4	82	9	11
Totals	105	3	36	15	15	9	15	93	16	19

* The estimated number of projects is based on the number of topics included in the ongoing IMI2 JU Calls.

** This is an estimated number of projects.

A key task will be to continue maximising efficiency, 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 Programme Office will work with consortia on helping to communicate on project progress and dissemination of achievements.

2.2.5 Monitoring and analysis of projects' results

93 project periodic reports will be submitted in 2020 (for ongoing projects and those finalised in 2019 see column 9 in the above table– 'Project periodic report due in 2020 – 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 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 2020, 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 2020, 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. In addition, IMI2 JU will organise one or more networking events and thematic workshops targeting specific stakeholders thereof (e.g. health care practitioners).

In addition, IMI2 JU will liaise closely with the EC to explore how the EU's strategic approach in certain areas such as pharmaceuticals in the environment can be addressed at the Programme level and also by the projects launched in 2020.

European Union Strategic Approach to Pharmaceuticals in the Environment:

https://ec.europa.eu/environment/water/water-dangersub/pdf/strategic_approach_pharmaceuticals_env.PDF.

Patient engagement

Building on the experience of patient engagement so far, the Programme Office will continue to work on developing an open and transparent system of meaningful patient engagement at all levels.

Having already put in place a new initiative, the IMI2 JU pool of patient experts, the Programme Office will continue to undertake significant efforts to facilitate and enhance patient participation in its activities. The involvement of patients/informal carers from the IMI2 JU pool of patient expert will enable IMI2 JU to identify, address and respond to patients' specific needs but also continuously improve, adapt and focus the patient engagement strategy priorities where necessary. Drawing from the IMI2 JU pool of patient experts, the Programme Office will invite patients/ informal carers to perform a variety of roles and tasks depending on the need and topics discussed. Their participation will contribute to shaping the IMI2 JU portfolio and improving the quality of IMI2 JU projects from the patient perspective.

In order to deploy the full potential of the IMI2 JU pool of patient experts, the Programme Office will provide training and support to all members, enabling their meaningful engagement and performance all across the spectre of its activities. Moreover, IMI2 JU will held targeted meetings covering specific disease areas which will optimise its approach to patient-centricity and enrich the discussions on future projects.

Additionally, IMI2 JU will lead efforts to ensure patient perspective 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 countries associated to Horizon 2020, IMI2 JU will remain engaged with SMEs and encourage their participation in IMI2 JU projects. In 2020, 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.

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 and it is critical to maximise the impact of research on innovative medicines. To ensure that the science generated by IMI-funded projects is translated into patient-centred healthcare, 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.

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 2020. 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 IMI2 JU 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.

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 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 IMI2 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 2020, IMI2 JU expects to receive 19 final project reports. Capturing the outcomes and impacts of these projects presents IMI2 JU with the opportunity of ensuring that project results are disseminated widely and taken up by researchers in the field and potential end user (e.g. healthcare professionals).

For the 19 projects, close-out meetings will be organised around the time of submission of the final report. 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 assessment

An important part of evaluating the performance of the IMI2 JU consists in assessing the socio-economic impact of the projects supported by the programme.

The efforts to assess this socio-economic impact will be continued using the previously developed methodology.

In 2020 IMI2 JU plans to release a follow-up of the Socio-economic Impact Assessment Expert Group Report that was initiated in 2016. At that time this assessment was conducted on a first set of projects as a pilot monitoring. The follow-up report will analyse an extended list of IMI2 JU projects which are finished to capture the impact of their innovations on society, on economy and on citizens, using the same methodology applied in 2016. The follow-up report will be published on IMI2 JU website in 2020.

IMI2 JU may also explore the opportunity and the feasibility of conducting an additional assessment employing a new methodology to track the socio-economic impact of its projects, remaining this in the context of a pilot evaluation.

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 2018-2020¹².

LIST OF COUNTRIES AND APPLICABLE RULES FOR FUNDING

By way of derogation¹³ 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 established¹⁴.

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.

STANDARD ELIGIBILITY CONDITIONS

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

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 condition¹⁵ applies:

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

TYPES OF ACTION: SPECIFIC PROVISIONS AND FUNDING RATES

Part D of the General Annexes to the Horizon 2020 Work Programme 2018-2020 shall apply *mutatis mutandis* for the actions covered by this 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, as follows:

Type of action	Excellence	Impact	Quality and efficiency of the implementation
	<i>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:</i>	<i>The following aspects will be taken into account:</i>	<i>The following aspects will be taken into account:</i>

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”

Type of action	<p>Excellence</p> <p><i>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:</i></p>	<p>Impact</p> <p><i>The following aspects will be taken into account:</i></p>	<p>Quality and efficiency of the implementation</p> <p><i>The following aspects will be taken into account:</i></p>
<p>RIA</p> <p>1st stage</p> <p>Evaluation of two-stage evaluation</p>	<ul style="list-style-type: none"> ▪ 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. 	<ul style="list-style-type: none"> ▪ 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: <ul style="list-style-type: none"> ▪ Disseminate, exploit and sustain the project results; ▪ Manage research data; ▪ Communicate the project activities to relevant target audiences. 	<ul style="list-style-type: none"> ▪ 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	<p>Excellence</p> <p><i>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:</i></p>	<p>Impact</p> <p><i>The following aspects will be taken into account:</i></p>	<p>Quality and efficiency of the implementation</p> <p><i>The following aspects will be taken into account:</i></p>
<p>RIA</p> <p>2nd stage of two-stage evaluation</p> <p>and</p> <p>Single stage evaluation</p>	<ul style="list-style-type: none"> ▪ 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. 	<ul style="list-style-type: none"> ▪ 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: <ul style="list-style-type: none"> ▪ Disseminate, exploit and sustain the project results; ▪ Manage research data; ▪ Communicate the project activities to relevant target audiences. 	<ul style="list-style-type: none"> ▪ 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 single-stage submission procedure, as well as in a two-stage submission procedure. At each evaluation stage of the two-stage submission procedure, the relevant evaluation criteria and threshold apply.

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

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.

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.

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.¹⁶

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 topic¹⁷ will be invited to discuss with the relevant industry consortium the feasibility of jointly developing a full proposal (second stage).

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

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

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

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

¹⁶ https://www.imi.europa.eu/sites/default/files/uploads/documents/apply-for-funding/call-documents/imi2/IMI2_ManualForSubmission_v1.7_November2018.pdf

¹⁷ 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.

Under the IMI2 JU Call 21, IMI2 JU will not organise hearings.

The 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.

IMI2 JU Call 21 - Public Health Emergency- Availability of research data

Beneficiaries in grants awarded under IMI2 JU Call 21 must make available their research data, at the latest within 30 days after it has been generated, through open access or, if agreed by the IMI2 JU or the European Commission, by giving access rights to those third parties that need the research data to address the Public Health Emergency. Therefore, the relevant option of Article 29.3 (option 1c) of the IMI2 JU Model Grant Agreement¹⁸ will apply. It is expected that quality-controlled data are shared in accordance with the FAIR principles. The use of harmonised protocols in collaboration with other actors is recommended for this purpose.

¹⁸ https://www.imi.europa.eu/sites/default/files/uploads/documents/reference-documents/h2020-mga-imi_en_v5.pdf

SUBMISSION TOOL

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

No other means of submission will be accepted.

OTHERS

For proposals including clinical trials/studies/investigations, a specific template to help applicants to provide essential information on clinical studies in a standardised format is available under: https://ec.europa.eu/research/participants/data/ref/h2020/other/legal/templ/h2020_tmpl-clinical-studies_2018-2020_en.pdf. In the first stage of a two-stage evaluation procedure, this template should not be submitted. However, applicants may integrate relevant aspects of this information in their short proposal (within the page limit). In the second stage of two-stage evaluation procedure involving clinical studies, the use of this template is mandatory in order to provide experts with the necessary information to evaluate the proposals. The template may be submitted as a separate document.

Ethical issues should be duly addressed in each submitted proposal to ensure that the proposed activities comply with ethical principles and relevant national, Union and international legislation. Any proposal that contravenes ethical principles or which does not fulfil the conditions set out in the H2020 Rules for Participation, or in the IMI2 JU Call for proposals shall not be selected.¹⁹

In order to ensure excellence in data and knowledge management consortia will be requested to disseminate scientific publications on the basis of open access²⁰ (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 documents²¹ (e.g. IMI2 JU model Grant Agreement).

¹⁹ Article 19 of Horizon 2020 Framework Programme and Articles 13 and 14 of the Horizon 2020 Rules for Participation.

²⁰ 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

²¹ <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 JU 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.

2020 being the last year of Horizon 2020 and the first year of a fully functional new European Parliament and new European Commission, IMI2 JU will cooperate closely with both institutions to increase awareness on the IMI2 JU activities.

2020 will also be the last year to commit research funds under IMI2 JU. There will be, therefore, a need to communicate on IMI2 JU calls with even more intensity, focussing on attracting the best researchers for an expected wide number of topics.

At the same time, the Communications team will remain alert to issues that could damage IMI2 JU's reputation and respond accordingly by providing timely feedback on stakeholders' views and reactions.

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 IMI2 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 (i) by promoting SME involvement through the SRG, regional contact points and 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 IMI2 JU website.

Further develop IMI success stories

IMI2 JU now holds close-out meetings with the representatives of projects that have finished, learning about what the projects have achieved and their legacy. 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 strong 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 2020, 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.

Communication channels

IMI2 JU will continue to develop content for the following channels with the aim of providing all interested stakeholders with access to relevant and specific information on the work of IMI:

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

In 2020, IMI2 JU might need to revise its corporate identity and update its communication tools accordingly. This will require the support of external contractors.

Key events in 2020

Events are a tool of central importance for engaging with the scientific community and reaching out to key stakeholders. The following events have been planned for 2020:

Event	Timeline
Promote IMI2 JU projects	Throughout year
IMI2 JU presence in the European Parliament (including joint JU's events)	Throughout year
IMI2 JU presence at relevant external events, e.g. BIO, BIO-Europe, ESOF, BioFIT	Throughout year
IMI2 JU Stakeholder Forum 2020	Q4
Promote IMI2 JU Calls for proposals (webinars, info days, website, etc.)	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.

IMI2 JU intends to launch an open call for tender for the conclusion of a service contract for corporate identity-related services for a total maximum value of EUR 200,000. It also foresees the launch of an open tender procedure for the signature of a service framework contract for event-related audio-visual services, for a total maximum value of EUR 150,000, designed to cover a four-year period.

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 2020.

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 2020 activities on three areas:

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

2.4.3.1 Business operations information systems

IMI2 JU's business operations makes use of the full suite of eGrants IT tools for the management of IMI2 JU calls, applications, evaluations and grants. The IT team will continue monitoring satisfactory functioning for all end-users, in close liaison with the European Commission services.

Since some IMI JU projects go on until at least 2024 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

The Programme Office has well established collaborative platforms to provide support to the governance bodies, namely the Governing Board, the Scientific Committee, the States Representatives Group and the Strategic Governing Groups. These platforms will be maintained and updated both from a content and operations point of view.

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 2020 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;
- renewal of wireless and wired network infrastructure in White Atrium building;
- renewal of conference audio visual equipment in Common meeting room 2 (subject of common JUs approval).

2.4.4 Human Resources

The 2020 objectives for Human Resources (HR) will be to ensure an efficient management of staff and an optimal working environment. To this end, HR will make sure to recruit, develop, assess, motivate and retain highly qualified staff with a view to ensure effective and efficient operation of the IMI2 JU, as well as equal opportunities. This objective will be implemented through the following four main themes:

Staff management and recruitment

In 2020 the total number of staff will remain the same 54 temporary and contract agents (of which 39 temporary agents and 15 contract agents), as well as two Seconded National Experts (SNEs).

Selection and recruitment processes will remain key areas of IMI2 JU HR, and it is expected that the Joint Undertaking will reach its complete staff establishment plan in 2020.

IMI2 JU will also foster its traineeship programme to provide young university graduates with the opportunity to gain hands-on professional experience in scientific fields related to IMI2 JU and to develop and strengthen their skills and competences. As the work of IMI2 JU will continue to increase, the Joint Undertaking might recruit interim staff to cope with peaks of work and guarantee business continuity.

In addition to the above, the HR team will deal with core functions such as: day-to-day management of administrative workflows and processes, salary, compensation and benefits, performance management, career development, reclassification, learning and development, safety and wellbeing at work; employees' motivation and communication. The daily management of HR activities will be facilitated by the full implementation of SYSPER II, which will also ensure alignment with the EC rules and procedures. In addition, in 2020 the HR team will start the preparatory work for the SYSPER Evaluation and Promotion module which should be effective as of 2021.

Legal Matters

IMI2 JU will continue working closely with DG HR and the Standing Working Party (group following the Staff Regulation and its implementing rules) to ensure the adoption of the implementing rules and to strengthen its legal framework also adopting internal guidelines.

The implementing rules giving effect to article 54 and article 87(3) of the Conditions of Employment of Other Servants of the European Union (CEOS) were implemented in 2017. In order to create a margin for reclassification, and to align the reclassification exercise to the average career equivalence and to recognise the performance of highly qualified staff, technical adaptations have been made to the Staff Establishment Plan. Those adaptations do not affect the total number of staff.

Organisation development

To help the development and the personal and professional growth of IMI2 JU staff, the human resources team will further develop the Learning and Development framework paying particular attention to the training needs of its staff and the organisation, and organising training activities to maintain staff knowledge up-to-date. The HR team will also continue advising management on means and actions to enhance operational efficiency and effectiveness. Tailor-made training courses and coaching programmes for managers will be organised to support and keep them abreast in their day-to-day management of staff and operational activities. Teambuilding activities will also be organised to strengthen the collaboration among staff members and to enhance the team spirit.

The Programme Office is committed to preserve a physically and psychologically healthy work environment where work is meaningful and people have conditions to contribute to their best. To this end, IMI2 JU is committed to a zero tolerance towards psychological and sexual harassment and disrespectful work environment, and it will further develop its well-being program providing tailor-made lunchtime workshops, conferences and training courses for its staff.

The HR team will keep overseeing duties and responsibilities assigned to staff in order to achieve the fulfilment of the IMI2 JU objectives and tasks.

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 2020, 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.

To enhance the selection process, a new selection tool may be implemented in 2020 following discussions with the other JUs. Cooperation with the others JUs will be further strengthen in other areas such as Learning and Development (e.g. organisation of standard and common training courses) and the management of the JUs network of confidential counsellors.

2.4.5 Administrative budget and finance

The budget 2020 for staff (Title 1) and infrastructure and operating expenditure (Title 2) has been defined in line with the planning of the year. The increase of 1.47% in 2020 compared to 2019, is mainly due to increase in staff related expenditures, rent and IT costs as well as costs of evaluations. For the first budget amendment of 2020, there is an increase of EUR 29.400, split 50% - 50% between EC and EFPIA. This is due to transfer from EC Health Programme and it has been allocated to chapter 21 'Information technology purchases', in line with operational needs. A comparison table of the financial years 2019 and 2020 is set out below.

	Heading	Financial year 2019	Financial year 2020	Evolution	Comments
Title Chapter		Budget EUR	Budget EUR		
1	Staff expenditure				
11	Staff in active employment	5,740,000	5,972,049	4.04%	Increase due to full implementation of Establishment Plan; standard annual reclassification rate and indexation set out in the EU Financial Regulation.
12	Staff recruitments - miscellaneous expenditure	20,000	19,538	-2.31%	
13	Missions and duty travels	190,000	185,608	-2.31%	
14	Socio-medical structure	360,000	207,100	-42.47%	The costs with interim staff have been moved to the newly introduced chapter 15.
15	External staff services		175,840		Newly introduced chapter to reflect the expenditure with interim staff.
17	Representation	20,000	19,538	-2.31%	
Total Title 1 (Staff expenditure)		6,330,000	6,579,673	3.94%	

	Heading	Financial year 2019	Financial year 2020	Evolution	Comments
Title Chapter		Budget EUR	Budget EUR		
2	Infrastructure expenditure				
20	Office building and associated costs	756,000	776,625	2.73%	Indexation and additional space.
21	Information technology purchases	779,000	815,794	4.72%	Additional recurrent licenses.
22	Office equipment (movable property and associated costs)	153,000	154,348	0.88%	Furniture for new staff and maintenance.
23	Current administrative expenditure	123,000	122,111	-0.72%	
24	Telecommunication and postal expenses	78,000	78,151	0.19%	Increase due to higher number of teleconferences.
25	Expenditure on formal meetings	158,000	156,302	-1.07%	
26	Running costs in connection with operational activities	388,154	388,801	0.17%	Increasing of operational activities.
27	External communication, information and publicity	625,000	610,555	-2.31%	
28	Service contracts	730,000	522,635	-28.41%	Reduction of costs for ex-post audits.
29	Expert contracts and cost of evaluations	900,000	976,887	8.54%	Based on number/costs of experts to be invited.
Total Title 2 (Infrastructure expenditure)		4,690,154	4,602,209	-1.88%	
Total Title 1+2 (Administrative expenditure)		11,020,154	11,181,882	1.47%	

The operational budget is covered under section 2.2.2. Scientific priorities for 2020.

Budget Plan 2020 – see Chapter 3.

Financial Management

During 2020, the Programme Office will implement the updated IMI2 JU Financial Rules in line with the Commission Delegated Regulation (EU) 2019/887 on the model financial regulation for public-private partnership bodies referred to in Article 71 of the 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 Regulation (EU) 2018/1725.

This will include raising awareness among IMI2 JU staff and stakeholders, liaising with the relevant services of the European Data Protection Supervisor and contributing to the activities of the inter-institutional data protection networks and working groups in which IMI2 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 line with the policy developed by the Programme Office. 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.

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 subsequent amendment(s) and on the scientific achievements to be described in the Annual Activity Report. Three meetings of the SC are planned for 2020. The Chair will participate in the Governing Board meetings as an observer. The term of the current Scientific Committee members will come to end in 2020, and a new Committee may be appointed in 2nd half of 2020. 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 2020. A change of chairpersonship is planned for the beginning of 2020 (the current mandates ending on 3 February 2020). 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 fourth 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, IMI2 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 **Strategic Governing Groups** (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 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.

In 2020 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 2020, facilitation of better cross-SGGs coordination will continue, notably through the dedicated IT platform, 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). 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.²²

²² 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 2020, the IMI2 JU will continue working to maintain an effective internal control framework that helps the Programme Office achieving its objectives and sustaining operational and financial performance, respecting the rules and regulations.

The overall target set by the IMI2 JU on internal control is to sustain operational and financial performance²³ in order to ensure the achievement of its objectives. Specific actions will aim at:

Keeping financial procedures effective and up to date;
Developing guidance materials on control and quality performance;
Ensuring prevention, detection and follow-up of irregularities in the framework of the Commission anti-fraud strategy.

2.6.1 Ex-ante and ex-post controls

Ex-ante controls

During 2020, the Programme Office will continue the implementation of its programme in line with H2020 legal framework in particular through 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 of 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 implementation of IMI Financial Circuits manual and a set of Standard Operating Procedures and checklists.

Specific attention will be placed on:

- implementation of the joint guidance on H2020 ex ante controls for interim and final payments;
- increased financial checks during the Grant Agreement Preparation (GAP) phase;
- raising the awareness of beneficiaries on financial and administrative aspects of H2020 rules and how to avoid errors in cost reporting.

Ex-post controls

For projects running under IMI JU (which was set up under the Seventh Framework Programme), the Programme Office will carry on with the implementation of its ex-post audit 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 rejection of any costs found to be in breach with the requirements of IMI JU Grant Agreement Rejection of systematic errors will continue to be extended to unaudited financial statements ('Form C') of the audited participants. Representative audits of participants will be launched on new cost claims received and validated by the Programme Office since the last audited period to reach the audit coverage ratio set in its ex-post audit strategy and if necessary risk based audits will be launched according to its risk based audit strategy.

²³ 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).

Systematic audits of accepted declarations of in-kind contributions by EFPIA companies will not be carried out in 2020 as the Work plan on ex post audits of EFPIA companies under IMI JU will have reached its end and almost the totality of the EFPIA companies' in-kind contributions will have been covered by audits. Risk-based audits may nevertheless be initiated should a specific need arise.

As regards IMI2 JU, ex-ante and ex-post controls of grants are both aligned with the harmonised strategies adopted for the entire H2020 Programme. The Programme Office will carry out the ex-ante checks as prescribed in the H2020 Control strategy. As for ex-post controls, the Commission Common Audit Service (CAS) will carry out the H2020 audits in accordance with the common H2020 audit strategy. The Programme Office contributes to the implementation of the H2020 audit strategy in close cooperation with the CAS and ensures that its ex-post audit strategy is complied with, including its audit coverage ratio. If necessary, risk based audits will be launched according to the risk based audit strategy approved by the Programme Office.

The harmonised legal framework will enable the Programme Office to draw an additional element of assurance from the extension of audit results on unaudited financial statements of common beneficiaries across the H2020 programme.

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

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, will follow up and assess 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 2020, the focus will be put on:

- The implementation of the IAS Strategic Internal Audit Plan for the period 2019-2021. IAS will audit H2020 Grant Agreement Implementation and Closing process within IMI2 JU. The objective of the audit is to assess the design and implementation of the management and control systems set up by IMI2 JU to support the grant agreement implementation and closing process, in terms of adequacy, efficiency and effectiveness.

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 2020 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 2019 and 2020 accounts;
- liaising an independent financial audit firm throughout the audit of accounts for financial year 2019 and 2020.

3 Budget 2020

The amended Budget 2020 reflects the following financial adjustments:

- The decrease of the European Union's financial contribution to IMI2 JU operational costs in 2020, due to a prioritization of and redeployment to climate related activities under Horizon 2020 in the voted 2020 budget. For IMI2 JU, the adopted budget was thus below the initial European Commission proposal, which was underlying the first IMI2 JU 2020 budget. It resulted in reduction of operational commitment appropriations (EUR -6,656,650) and operational payment appropriations (EUR -4,908,659).
- Transfer from the EC Health programme of EUR 14.700 to administrative expenditure, resulting a total increase of EUR 29,400 (50% EC - 50% EFPIA).
- Carry overs to 2020: IMI2 JU Call 19 unused appropriations, unused operational appropriations from 2019 to 2020, 50% unused administrative appropriations (see breakdown below for both commitment and payment appropriations).

An overview of the Budget 2020 per chapters is set out below.

STATEMENT OF REVENUE								
	Heading Revenue	Budget 2020.0		Budget 2020 Amendment 1		Amended Budget 2020.1		Comments
Chap		Commitment Appropriation (CA)	Payment Appropriation (PA)	Commitment Appropriation (CA)	Payment Appropriation (PA)	Commitment Appropriation (CA)	Payment Appropriation (PA)	
10	European Commission contribution (including EFTA contribution)	261,547,957	200,631,535	-6,641,950	-4,893,959	254,906,007	195,737,576	Commitment appropriations include EUR 5 590 941 (of which EUR 14 700 from non spent 2014 EU contribution) ²⁴ for administrative costs and EUR 249 315 066 for operational costs. Payment appropriations include administrative costs of EUR 5 590 941 and operational costs of EUR 190 146 635.
C2	Appropriations carried over	6,314,588		8,623,432	6,612,304	14,938,020	6,612,304	The amount carried over from previous year
EC contribution		267,862,545	200,631,535	1,981,482	1,718,345	269,844,027	202,349,880	

²⁴ European Commission contribution (including EFTA contribution): for administrative costs, on the E.U side, as year 2020 is the last year of H2020, the full remaining amount is committed (EUR 27 867 587). In 2020, EUR 5 590 941 will be paid to IMI2 JU, the remaining amount will be paid over the following years.

STATEMENT OF REVENUE								
	Heading Revenue	Budget 2020.0		Budget 2020 Amendment 1		Amended Budget 2020.1		Comments
Chap		Commitment Appropriation	Payment Appropriation	Commitment Appropriation	Payment Appropriation	Commitment Appropriation	Payment Appropriation	
20	EFPIA contribution	5,576,241	5,576,241	14,700	14,700	5,590,941	5,590,941	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			0	1,000,000	Four EFPIA companies contribution to operational payment appropriations
EFPIA and other Members contributions		5,576,241	6,576,241	14,700	14,700	5,590,941	6,590,941	
30	Associated Partners contributions		1,500,000			0	1,500,000	Bill and Melinda Gates Foundation contribution to operational payment appropriations
Associated Partners contributions			1,500,000	0	0	0	1,500,000	
Total revenues		273,438,786	208,707,776	1,996,182	1,733,045	275,434,968	210,440,821	

Breakdown of commitment appropriations amendment of **EUR -6,641,950**:

- Reduction of adopted budget by EUR -6,656,650 and transfer from EC Health Programme of EUR 14,700.

Breakdown of payment appropriations reduction of **EUR – 4,893,959**:

- Reduction of adopted budget by EUR -4,908,659 and transfer from EC Health Programme EUR 14,700.

Breakdown of commitment appropriations carry over to 2020, of **EUR 8,623,432**:

- 50% unused administrative expenditure 2019 carried over to operational budget 2020 for new IMI2 JU Calls of EUR 941,673.
- Unused operational appropriations 2019 carried over to operational budget 2020 for new IMI2 JU Calls of EUR 396,439.
- Unused appropriations IMI2 (H2020) Call 19 (2019) – to be re-activated in AWP 2020 for new IMI2 JU Calls to be launched in 2020, of EUR 7,285,320.

Breakdown of payment appropriations carry over to 2020, of **EUR 6,612,304**:

- Payment appropriations related to administrative commitments carried forward to 2020, of EUR 2,074,898.
- Unused operational payment appropriations 2019 to be carried over to 2020, of EUR 4,537,406.

STATEMENT OF EXPENDITURE

	Heading Title 1	Budget 2020.0		Budget 2020 Amendment 1		Amended Budget 2020.1		Comments
Title Chap		Commitment Appropriation (CA)	Payment Appropriation (CA)	Commitment Appropriation (CA)	Payment Appropriation (CA)	Commitment Appropriation (CA)	Payment Appropriation (CA)	
1	Staff expenditure							
11	Staff in active employment	5,972,049	5,972,049			5,972,049	5,972,049	Salaries and allowances of current staff (TAs and CAs), SNE, promotion and indexation
12	Staff recruitments - miscellaneous expenditure	19,538	19,538			19,538	19,538	Miscellaneous expenditure on staff recruitment: publication of vacancy call, medical visit to take up duties, services provided by the European Personnel Selection Office (EPSO)
13	Mission expenses	185,608	185,608		8,954	185,608	194,562	Mission expenses
14	Socio-medical structure	207,100	207,100		51,874	207,100	258,974	Other staff costs: EU school, medical check-up, trainings
15	External staff services	175,840	175,840		68,782	175,840	244,622	Interim staff expenses
17	Representation	19,538	19,538		1,853	19,538	21,391	Representation expenses
	Total Title 1 (Staff expenditure)	6,579,673	6,579,673	0	131,463	6,579,673	6,711,136	

	Heading Title 2	Budget 2020.0		Budget 2020 Amendment 1		Amended Budget 2020.1		Comments
Title Chap		Commitment Appropriation (CA)	Payment Appropriation (CA)	Commitment Appropriation (CA)	Payment Appropriation (CA)	Commitment Appropriation (CA)	Payment Appropriation (CA)	
2	Infrastructure expenditure							
20	Rent and related expenditures	776,625	776,625		166,990	776,625	943,615	Building related expenditure: rent, works, charges, maintenance, repairs, security and surveillance
21	Information technology (hardware and software)	786,394	786,394	29,400	688,656	815,794	1,475,050	IT purchases, software licences, software development
22	Office equipment	154,348	154,348			154,348	154,348	Purchases and rental of office equipment, maintenance and repair
23	Current administrative expenditure	122,111	122,111		93,683	122,111	215,794	Office supply, newspaper subscriptions, translation services, bank charges and miscellaneous office expenditure
24	Telecommunica tion and postal expenses	78,151	78,151		28,378	78,151	106,529	Data communication such as telephone, video and audio conferences and postal services
25	Formal meetings	156,302	156,302		50,761	156,302	207,063	Official meetings such as States Representative Group, Scientific committee, Governing Board and working groups created by the Governing Board
26	Administrative expenditure in connection with operational activities	388,801	388,801		115,520	388,801	504,321	Administrative expenditure in connection with research activities and objectives of IMI (workshops, meetings and events targeting IMI projects)

	Heading Title 2	Budget 2020.0		Budget 2020 Amendment 1		Amended Budget 2020.1		Comments
Title		Commitment	Payment	Commitment	Payment	Commitment	Payment	
27	External communication, information and publicity	610,555	610,555		2,720	610,555	613,275	External communication and events such as Info Days, stakeholder forums
28	Service contracts	522,635	522,635		517,072	522,635	1,039,707	Ex-post audits, studies, audits, accounting services
29	Expert contracts and cost of evaluations	976,887	976,887		309,055	976,887	1,285,942	Costs linked to evaluations, expert contracts
Total Title 2 (Infrastructure expenditure)		4,572,809	4,572,809	29,400	1,972,835	4,602,209	6,545,644	
Total Title 1 + 2 (administrative expenditure)		11,152,482	11,152,482	29,400	2,104,298	11,181,882	13,256,780	

	Heading	Budget 2020.0		Budget 2020 Amendment 1		Amended Budget 2020.1		Comments
Title Chap		Commitment Appropriation (CA)	Payment Appropriation (CA)	Commitment Appropriation (CA)	Payment Appropriation (CA)	Commitment Appropriation (CA)	Payment Appropriation (CA)	
3	Operational expenditure							
30	Implementing the research agenda of IMI2 JU	255,971,716	197,555,294	-6,656,650	-4,908,659	249,315,066	192,646,635	Calls, Grant agreements - Payments
C2	Implementing the research agenda of IMI2 JU	6,314,588		8,623,432	4,537,406	14,938,020	4,537,406	Appropriations carried over from 2019
Total Title 3 (Operational expenditure)		262,286,304	197,555,294	1,966,782	-371,253	264,253,086	197,184,041	
Total expenditure		273,438,786	208,707,776	1,996,182	1,733,045	275,434,968	210,440,821	

An overview of the 2020 Budget and structure per budget lines is set out in the table below:

Budget line Chapter	Description	Commitment Appropriations (CA)	Payment Appropriations (PA)	C2 - Payment Appropriations (PA)
A01100	Staff in active employment and costs linked to employment	3,847,049	3,847,049	
A01101	Family Allowances	374,000	374,000	
A01102	Transfer and expatriation allowance	405,000	405,000	
A01110	Contract Agents	800,000	800,000	
A01111	Seconded National Experts	120,000	120,000	
A01130	Insurance against sickness	103,000	103,000	
A01131	Insurance against accidents and occupational diseases	15,000	15,000	
A01132	Unemployment insurance for temporary staff	40,000	40,000	
A01133	Pension	0	0	
A01140	Birth and death allowance	9,000	9,000	
A01141	Annual travel costs from the place of employment to place of origins	62,000	62,000	
A01144	Fixed local travel allowances	0	0	
A01149	Other allowances	0	0	
A01172	Cost of organising traineeships within IMI2 JU	17,000	17,000	
A01175	Translation and typing services and work to be contracted	0	0	
A01177	Other services rendered	60,000	60,000	
A01178	PMO fees	60,000	60,000	
A01180	Sundry recruitment expenses	0	0	
A01181	Travelling expenses (including taking up duty)	0	0	
A01182	Installation allowance	43,000	43,000	
A01183	Moving expenses	0	0	
A01184	Temporary daily allowance	13,000	13,000	
A01190	Weightings (correction coefficient)	4,000	4,000	
A01191	Salaries adaptation	0	0	
11	Staff in active employment	5,972,049	5,972,049	
A01200	Miscellaneous expenditure on staff recruitment	19,538	19,538	

Budget line Chapter	Description	Commitment Appropriations (CA)	Payment Appropriations (PA)	C2 - Payment Appropriations (PA)
12	Staff recruitments - miscellaneous expenditure	19,538	19,538	
A01300	Mission expenses	185,608	185,608	8,954
13	Missions and duty travels	185,608	185,608	8,954
A01401	Socio-medical structure, EU school	80,000	80,000	
A01410	Other trainings	76,100	76,100	39,818
A01430	Medical service	20,000	20,000	
A01440	Trainings covered by the SLA	31,000	31,000	9,800
A01490	Other interventions	0	0	2256.62
14	Socio-medical structure	207,100	207,100	51,874
A01500	External staff expenditures	175,840	175,840	68,782
15	External staff services	175,840	175,840	68,782
A01700	Representation expenses	19,538	19,538	1,853
17	Representation	19,538	19,538	1,853
Total Title 1 (Staff expenditure)		6,579,673	6,579,673	131,463

Budget line Chapter	Description	Commitment Appropriations (CA)	Payment Appropriations (PA)	C2 - Payment Appropriations (PA)
A02000	Rentals office building	566,625	566,625	
A02001	Guarantees	0	0	
A02002	Contributions	0	0	
A02010	Insurance	0	0	
A02020	Charges (water, gas, electricity)	161,000	161,000	125,543
A02030	Cleaning and maintenance	10,000	10,000	
A02040	Furnishing of premises (works)	10,000	10,000	41,448
A02050	Security and surveillance	29,000	29,000	
A02090	Other expenditure on buildings	0	0	
20	Office building and associated costs	776,625	776,625	166,990
A02101	Hardware, infrastructure and related services	284,400	284,400	268,686
A02102	Software development, licenses and related services	531,394	531,394	390,570

Budget line Chapter	Description	Commitment Appropriations (CA)	Payment Appropriations (PA)	C2 - Payment Appropriations (PA)
A02103	Other expenses maintenance and repair	0	0	
21	Information technology purchases	815,794	815,794	659,256
A02200	Purchase office equipment	124,348	124,348	
A02201	Rentals office equipment	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)	154,348	154,348	
A02300	Stationery and office supply	40,000	40,000	2,200
A02320	Bank charges	0	0	
A02321	Exchange rate losses	0	0	
A02329	Other financial charges	0	0	
A02330	Legal expenses	20,000	20,000	25,000
A02350	Other operating expenditure	13,000	13,000	32,624
A02351	Petty expenses	0	0	
A02360	Library stocks purchase of books and subscriptions	44,000	44,000	29,358
A02370	Translation interpretation	5,111	5,111	4,502
23	Current administrative expenditure	122,111	122,111	93,683
A02400	Correspondence and communication expenses	78,151	78,151	28,378
24	Telecommunication and postal expenses	78,151	78,151	28,378
A02500	Formal meetings	156,302	156,302	50,761
25	Expenditure on formal meetings	156,302	156,302	50,761
A02600	Administrative costs in connection with operational activities	47,801	47801	6000
A02601	Events targeting IMI projects	10,000	10,000	
A02602	Workshops	325,000	325,000	101,520
A02603	Knowledge Management	6,000	6,000	8,000
26	Administrative costs in connection with operational activities	388,801	388,801	115,520
A02700	External communication	210,555	210,555	

Budget line Chapter	Description	Commitment Appropriations (CA)	Payment Appropriations (PA)	C2 - Payment Appropriations (PA)
A02701	Events external communication	300,000	300,000	
A02702	Material	100,000	100,000	2,720
27	External communication, information and publicity	610,555	610,555	2,720
A02800	Ex-post Audits	250,000	250,000	226,572
A02801	Studies, consultancy	177,635	177,635	268,020
A02802	Audit services	60,000	60,000	22,480
A02803	Accounting services	35,000	35,000	
28	Service contracts	522,635	522,635	517,072
A02900	Evaluation Experts meetings	956,887	956,887	297,227
A02901	Evaluation Facilities	20,000	20,000	11,829
A02902	Evaluations ENSO	0	0	
29	Expert contracts and cost of evaluations	976,887	976,887	309,055
Total Title 2 (Infrastructure expenditure)		4,602,209	4,602,209	1,943,435

Budget line Chapter	Description	Commitment Appropriations (CA)	Payment Appropriations (PA)	C2 - Payment Appropriations (PA)
B03000	Implementing the research agenda of IMI JU			
B03001	IMI JU Call 1			
B03002	IMI JU Call 2			
B03003	IMI JU Call 3		2,138,864	
B03004	IMI JU Call 4			
B03005	IMI JU Call 5			
B03006	IMI JU Call 6		7,000,000	
B03007	IMI JU Call 7		437,288	
B03008	IMI JU Call 8		7,500,000	
B03009	IMI JU Call 9		4,000,000	
B03010	IMI JU Call 10		500,000	
B03011	IMI JU Call 11		13,832,011	
B03012	ENSO 2012			
B03013	ENSO 2013			
B03020	Implementing the research agenda of IMI2 JU		10,000,000	
B03021	IMI2 JU Call 1		3,756,354	
B03022	IMI2 JU Call 2		2,008,348	
B03023	IMI2 JU Call 3		7,008,000	
B03024	IMI2 JU Call 4			
B03025	IMI2 JU Call 5		8,054,728	
B03026	IMI2 JU Call 6		9,600,000	
B03027	IMI2 JU Call 7		2,750,000	
B03028	IMI2 JU Call 8		3,985,767	
B03029	IMI2 JU Call 9		9,146,732	
B03030	IMI2 JU Call 10		18,306,489	
B03031	IMI2 JU Call 11		291,875	
B03032	IMI2 JU Call 12		7,124,448	
B03033	IMI2 JU Call 13		10,422,145	
B03034	IMI2 JU Call 14			

Budget line Chapter	Description	Commitment Appropriations (CA)	Payment Appropriations (PA)	C2 - Payment Appropriations (PA)
B03035	IMI2 JU Call 15		10,000,000	
B03036	IMI2 JU Call 16		3,256,921	
B03037	IMI2 JU Call 17		10,604,360	
B03038	IMI2 JU Call 18		18,212,957	
B03039	IMI2 JU Call 19		7,709,348	
B03040	IMI2 JU Call 20	126,694,412		
B03041	IMI2 JU Call 21	45,000,000	15,000,000	
B03042	IMI2 JU Call 22	20,000,000		
B03043	IMI2 JU Call 23	57,620,654		
B03999	Recovery Ex-post audit			
30-C1	Implementing the research agenda of IMI2 JU	249,315,066	192,646,635	
B03040 – C2	IMI2 JU Call 20	6,314,588		
B03043 – C2	IMI2 JU Call 23	8,596,444		
B03030 – C2	IMI2 JU Call 10			4,510,418
B03000 – C2	Implementing the research agenda of IMI JU	26,988		26,988
Total Title 3 (Operational expenditure)		264,253,086	192,646,635	4,537,406
Total expenditure		275,434,968	203,828,517	6,612,304

3.1 Staff Establishment Plan 2020

Grade	Posts filled on 31/12/2018	Establishment Plan 2019		Year 2020														
				Posts evolution						Organisational evolution			Establishment Plan 2020					
				Promotion / Career advancement			Turn-over (departures/ arrivals)			New posts (per grade)			Requested (Budget)					
				TEMP	PERM	TEMP	TOTAL	Offi- cials	TA - LT	TA - ST	Offi- cials	TA - LT	TA - ST	Perm	TA - LT	TA - ST	PERM	TA
AD16																		
AD15																		
AD14	1		1	1												1	1	
AD13																		
AD12	1		2	2												2	2	
AD11	2		2	2												2	2	
AD10						+1										1	1	
AD9	3		6	6		+1										7	7	
AD8	6		7	7		- 1										6	6	
AD7	6		3	3		- 1										2	2	
AD6	2		4	4		+ 4										8	8	
AD5	10		8	8		- 4										4	4	
Total AD	31		33	33												33	33	
AST11																		
AST10																		
AST9																		
AST8	1		1	1												1	1	
AST7																		
AST6																		
AST5																		
AST4	2		4	4												4	4	
AST3	2																	
AST2						+1										1	1	
AST 1	1		1	1		- 1												
Total AST	6		6	6												6	6	
SC6																		
SC5																		
SC4																		
SC3																		
SC2																		
SC1																		
Total SC	0		0	0												0	0	
Overall Total	37		39	39												39	39	

Contract Agents Grade	Posts filled on 31/12/2018	Establishment plan 2019	Establishment plan 2020
FG IV	1	2	3
FG III	8	12	11
FG II	1	1	1
FG I	0	0	0
Total CA	10	15	15

Seconded National Experts	Posts filled on 31/12/2018	Establishment plan 2019	Establishment plan 2020
	1	2	2

Annex I - IMI2 JU Call 20 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 created²⁵ 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 World²⁶.

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 companies²⁷, 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 JU Strategic Research Agenda (SRA)²⁸ is the main reference for the implementation of research priorities for IMI2 JU. The scientific priorities for 2020 for IMI2 JU have been prepared based on the SRA.

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

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

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

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

Applicant consortia shall ensure that where relevant their proposals are in compliance with the General Data Protection Regulation (EU) 2016/679²⁹ and Clinical Trial Regulation (EU) 536/2014³⁰ (and/or Directive 2001/20/EC³¹) and any relevant legislation³².

Before submitting a proposal, applicant consortia should familiarise themselves with all Call documents such as the IMI2 JU Manual for submission, evaluation and grant award³³, and the IMI2 JU evaluation criteria. Applicants should refer to the specific templates and evaluation procedures associated with the topic type Research and Innovation Actions (RIA).

Please note that topics under this call for proposals may provide financial support to third parties according to Part K of the General Annex of the H2020 Work Programme.

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: Early diagnosis, prediction of radiographic outcomes and development of rational, personalised treatment strategies to improve long-term outcomes in psoriatic arthritis

Topic details

Topic code	IMI2-2020-20-01
Action type	Research and Innovation Action (RIA)
Submission and evaluation process	2 stages
IMI2 JU Strategic Research Agenda - Axis of Research	Target validation and biomarker research (efficacy and safety)
IMI2 JU Strategic Research Agenda - Health Priority	Immune-mediated diseases

Specific challenges to be addressed by public-private collaborative research

Psoriatic arthritis (PsA) is a chronic immune-mediated disease involving axial and peripheral joints, nails, skin and enthesitis. Cutaneous manifestations often precede articular symptoms and it has been estimated that about 20-30 % of psoriatic patients develop arthritis or enthesitis over time [1]. In fact, the precedence of cutaneous symptoms may give as much as about 7 years to predict, detect and potentially treat PsA [2].

Although still a matter of debate, the pathogenesis of PsA is multifactorial and includes genetic and environmental triggers, like dysbiosis, infections or a mechanic stress, which could induce and maintain the aberrant activation of the innate and adaptive immune system.

Current therapeutic approaches aim to cover the entire clinical spectrum of PsA, from nail and skin involvement to joint, tendon and enthesitis damage and inflammation. The newest discoveries in PsA pathogenesis have promoted the development of several drugs with different mechanisms of action targeting molecules involved in both musculoskeletal and cutaneous manifestations. The choice of the best treatment for PsA patients should rely on a global evaluation, including the predominant clinical manifestations, comorbidities or contraindications to the therapy [3].

There are still a large number of patients suffering from PsA that are diagnosed after several years of signs and symptoms (late diagnosis) and fail to respond to current standard of care treatments, or quickly relapse on, or following treatment. Currently, it is felt that the earlier PsA can be diagnosed, the better the chances that treatment could influence the disease. It also seems that the physiopathology of PsA evolves with the “age” of the disease, and this may provide opportunities to discover new targets in early PsA patients.

The Group for Research and Assessment of Psoriasis and Psoriatic Arthritis (GRAPPA) identified the following major unmet medical needs:

- Early diagnosis of PsA either in psoriasis (PsO) patients or in patients without initial psoriasis skin manifestations. Significant delay in diagnosis contributes to poor clinical and radiographic outcome;
- Early identification of patients at risk of progression to PsA. Defining the predictors of progression to PsA in patients with skin PsO will enable earlier intervention and possibly even prevent development of PsA;
- Definition of the clinical, genetic, immune factors or protein biomarkers that predict disease progression in PsA patients at time of diagnosis;

- Better prediction, at diagnosis, for prognosis and stratification by therapeutic needs.

The focus of this topic is a multifactorial disease represented by its different forms through a wide patient population. It goes beyond the more homogeneous patients enrolled in clinical trials for the registration of new drugs. A broad spectrum of expertise is required for this challenge to be adequately addressed. In this context, collaborative efforts among pharmaceutical industries, academia, small and medium-sized enterprises (SMEs) and patient organisations in a public-private partnership are most likely to harness all the skills and expertise required. Lastly, the involvement of representatives of health and regulatory authorities will ensure the necessary regulatory guidance paving the way towards the regulatory acceptance of “early PsA” diagnostic methods and personalised treatments. A synergy is expected from industry and other stakeholders joining forces in this particular area of medicines innovation.

Scope

The overall scope of this topic is to provide patients and physicians with new tools including clinical data patterns, biomarker profile patterns and imaging analysis for a better control of PsA. The aim of this topic is to characterise the natural history of PsA from psoriasis to “early” PsA to “full-fledged” PsA, as diagnosed by the Classification Criteria for Psoriatic Arthritis (CASPAR). This characterisation will be based on discovering new biomarkers and endotypes, constructed on genetic, epigenetic, transcriptomic, proteomic and/or clinical markers. To identify those endotypes, artificial intelligence (AI) and machine learning (ML) processes will be needed.

In particular, the topic aims to achieve the following specific objectives:

- to enable rheumatologists, dermatologists and general practitioners to make an early diagnosis of PsA in patients with PsO and other rheumatic disorders;
- to identify early patients at risk of progression to PsA in order to enable earlier interventions and possibly prevent PsA development;
- to define the factors that predict disease progression in PsA patients, including early prediction of bone/joint damages, leading to the development of more adapted treatment strategies;
- to develop rational and personalised treatment strategies (e.g. select the optimal first line or second line treatment based on patient characteristics) with optimised outcomes in PsA patients and reduce the disease burden.

Expected key deliverables

- Early diagnosis of PsA in PsO patients:
 - identification of predictors of disease progression, e.g. genetic, epigenetic, transcriptomic, proteomic and/or clinical biomarkers assessed through longitudinal follow-up until evidence of CASPAR;
 - identification and characterisation of biomarkers to predict, diagnose and monitor PsA in patients with PsO and to assess treatment response;
 - biomarkers of tissue damage, predicting disease progression among PsA patients;
 - ML/AI tools to identify novel biomarker signatures;
 - digital tool(s) developed for use by physicians and/or patients.
- Early prediction of bone/joint damages in PsA patients:
 - identification of poor radiographic outcomes;
 - biomarker assay(s) to identify patients that may rapidly develop bone or joint damages, indicating that these patients need strict control of PsA.
- Prediction of best treatment for patients at diagnosis:
 - biomarker assay(s) to assess response/non-response for various treatments of PsA;
 - development of a PsA specific algorithm to estimate the expected response to treatments.

- Creation of a tissue library, accessible by all involved parties, comprising skin, synovial tissue, synovial fluid and/or peripheral blood cells (including CD4+ and/or CD8+ T cells and/or other lymphocytes, monocytes) for analysis. This tissue library will have to be organised by the consortium with a perspective of sustainability incorporated in its foundation documents. Existing libraries will also be considered and be contacted for possible sustainable collaboration;
- Development and implementation of new techniques for diagnostic use e.g. peptide immunoaffinity enrichment with targeted mass spectrometry (immuno-multiple reaction monitoring, iMRM), mass cytometry (e.g. CyTOF), (single cell) investigation of autoantibodies / DNA methylation (e.g. as marks for tissue damage), and other techniques for single cell analysis to support detailed investigation of signalling cross-talk within and between relevant cell populations;
- Novel methods for data mining and AI-driven information extraction;
- Letter of support from regulatory bodies (e.g. the European Medicines Agency, EMA and/or Food and Drug Administration FDA) on the potential for qualification/validation of the biomarker(s) and their clinical applications (context of use) in PsA.

It is expected that applicants should propose a coherent, strategic plan to cover how they plan to address the key deliverables (identification of predictors of disease progression e.g. genetic, epigenetic, transcriptomic, proteomic and/or clinical biomarkers assessed through longitudinal follow-up until evidence of CASPAR; identification and characterisation of biomarkers to predict, diagnose and monitor PsA in patients with PsO and to assess treatment response).

Expected impact

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

- “Early PsA” diagnosis and earlier personalised treatments for patients would impact the disease progression and ultimately prevent PsA development. AI would help identifying endotypes which could take into account the clinical and biological heterogeneities of PsA.
- Development of objective and sensitive functional measures would enable the early diagnosis of PsA in PsO patients and the early prediction of bone/joint damages in PsA patients, yielding long-lived reduction in disease and improvement of patients’ quality of life.
- Improved rates of treatment successes through better understanding of the relation between molecular characteristics of PsA and treatment responses would reduce costs to patients (side effects) and society (economics).

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

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

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

- Manage research data including use of data standards;³⁴

³⁴ 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

- Disseminate, exploit, and sustain the project results. This may involve engaging with suitable biological and medical sciences research infrastructures;³⁵
- Communicate the project's activities to relevant target audiences.

Potential synergies with existing consortia

Synergies and complementarities should be considered with relevant national, European and non-European initiatives (including suitable biological and medical sciences research infrastructures³⁶) in order to incorporate past achievements, available data and lessons learnt where possible, thus avoiding unnecessary overlap, and duplication of efforts and funding.

Industry consortium

The industry consortium is composed of the following EFPIA partner(s):

- Novartis (lead)
- UCB (co-lead)
- BMS
- Pfizer.

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

- translational medicine expert: leading role from a strategic, scientific, organisational and project management perspective;
- data manager: support to organise and control database systems within the project generated from this topic and interoperability with other relevant IMI-funded or open public projects;
- biomarker expert: scientific adviser to make sure that the selected biomarkers are relevant or sufficiently innovative;
- bioinformatics expert: analysis of large datasets (big data) to find predictive signatures of disease and response to therapy;
- statistical expert: scientific adviser to make sure that the statistical approaches are relevant or sufficiently innovative;
- pharmacometric expert: scientific adviser to make sure that the pharmacometric approaches are relevant or sufficiently innovative;
- regulatory affairs expert: regulatory adviser to make sure that the selected biomarkers or new tools (e.g. questionnaire) are relevant.

During the funded action, members of the industry consortium plan to contribute scientifically relevant activities for generating data / collecting samples in prospective activities that are part of broader industry clinical studies. The relevant activities will be included in the project's Description of the Action and are necessary for achieving its objectives. The introduction of the data constitutes an in-kind contribution which entails access rights to these project results in line with IMI2 JU intellectual property (IP) rules. The estimated in kind contribution for the prospective activities to generate these data and samples is EUR 9 880 000.

³⁶ <http://www.corbel-project.eu/about-corbel/research-infrastructures.html>

The data and samples collected are planned to come from the prospective studies described below, and consist of the following data/samples types & volume:

Company	Study description	Data/sample description	Estimated number of involved patients
Novartis	Phase 3, 2 arm study in PsA	Placebo arm only, 16 week treatment duration	190
UCB	Phase 3 or 3B PsA study	Baseline data	300
BMS	Ph3 PsA subset of PBO	Data only (no samples)	200

These data and samples are essential for achieving the objectives of the project. Disclaimer: the final quantitative contribution in the form of data and samples is contingent on successful study readouts. The industry consortium partners will team up to address any unexpected changes in the above so that the estimated total in-kind contribution remains at its planned level.

The industry consortium may contribute additional prospective cohorts of patients, including PsO patients, as they become available.

In addition, retrospective industry historical data may be contributed as background as relevant.

Indicative duration of the action

The indicative duration of the action is 60 months.

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

Indicative budget

The financial contribution from IMI2 JU is a maximum of EUR 10 211 000.

The indicative in-kind contribution from EFPIA partners is EUR 13 880 000.

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

Expertise and resources expected from applicants at stage 1

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

The stage 1 submitted short proposals should include suggestions for creating a full proposal architecture.

This may require mobilising, as appropriate the following expertise:

- SMEs & academia / research and technology organisations (RTOs) with past and present experience on genetic, epigenetic, transcriptomic, proteomic, biomarkers, AI/ML techniques and “big data” management techniques. Experience and capacity to manage large volumes of various data (clinical, biological, genetic, imaging) to potentially identify endotypes by using AI and ML systems;
- Patient associations and/or patient advocacy groups in PsO/PsA to ensure access to data and information;

- Regulatory agencies and/or HTA agencies and/or health authorities interested in innovative PsO/PsA assessments and new diagnostic tools to build a strategy for regulatory qualification/acceptance of project outputs;
- Academics, physicians (both rheumatologists and dermatologists) and/or clinical trial centres experienced in PsO/PsA clinical, biological and imaging assessments; capable of justifying (1) their expertise in recruiting PsO & PsA patients; and (2) the number they envisage to support a valid statistical conclusion; capable of organising prospective longitudinal assessments of PsO patients;
- Strong data management experience in managing and coordinating a multi-centre, multi-node clinical research data generation activity of comparable scope. This must include the ability to design and execute an effective and feasible scientific work plan and related robust processes to deliver objectives and deliverables on time. Essential experience should also cover the legal and ethical challenges associated with integrating multi-centre, patient-derived data, as well as physical data processing/data management practices (privacy, security);
- Demonstrated ability to deliver analytical platforms for a range of scientific/medical and analytical communities;
- Expertise in a) clinical characterisation and patient access/recruitment (incl. samples and/or data from ongoing prospective collections/trials for PsO and/or PsA); b) biological specimen-based profiling; and c) advanced informatics;
- Expertise in access to and use of medical record-based information. Other publicly available data or cohorts could be incorporated into the action generated by this topic;
- Skills in molecular epidemiology, clinical science, and the integration of biological profiling with relevant datasets;
- Proven expertise in rigorous programme management of large and complex multi-stakeholder projects, including expertise in risk management and sustainability of results.

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

- Access to clinical cohorts and corresponding datasets of PsO and PsA patients, particularly longitudinal timed assessments. For a successful project, samples and data will need to be accessible to the whole consortium. Since access to clinical information and specimens is critical to the overall success of defining endotypes and the project goals, applicants should demonstrate their capacity (e.g. patient consent or waiver to consent) and the process by which they can provide access to these. Applicants may involve academics, medical centres with existing materials, biobanks, or organisations planning or actively participating in clinical trials and able to obtain consent. Access to large numbers of patients is essential to ensuring the statistical power for definition of endotypes. Value is seen in both cross-sectional and longitudinal approaches but longitudinal data (e.g. patients before and after therapy) is of higher value.

Partners providing medical record-based information as project background must be mindful that they, as background contributor, should have sufficient title to the said background to authorise its use within the project pursuant to the IMI2 JU IP and legal framework.

Considerations for the outline of project work plan

In their stage 1 proposal, applicants should:

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

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

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

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

Data management

In their stage 2 proposal, applicants should give due visibility to data management including use of data standards. A full 'data management plan' (DMP) as a distinct deliverable must be delivered within the first 6 months of the project. The DMP needs to be kept up to date with the needs of the project and as such be updated as necessary during its lifetime.³⁷

Dissemination, exploitation and sustainability of results

In their stage 2 proposal, applicants must provide a draft plan for dissemination and exploitation, including sustainability of results. A full plan as a distinct deliverable must be delivered within the first 6 months of the project³⁸, and updated during the project lifetime and could include identification of:

- different types of exploitable results;
- potential end users of the results;
- results that may need sustainability and proposed sustainability roadmap solutions.

From its creation, the consortium will dedicate a group of participants to think of a process for sustainability.

Sufficient resources should be foreseen for activities related to dissemination and exploitation, including the plan for the sustainability of the project results. This may involve engaging with suitable biological and medical sciences research infrastructures (RIs).³⁹ Alternatively, if a sustainable organisation can be implemented as a follow-up to some activities generated by this topic consortium, and possibly in coordination with other related projects (e.g. BIOMAP (www.biomap-imi.eu/)), this will be investigated.

Communication

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

³⁷ 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

³⁸ As an additional dissemination obligation under Article 29.1 of the IMI2 Grant Agreement will apply

³⁹ <http://www.corbel-project.eu/about-corbel/research-infrastructures.html>

References

- [1] Mease PJ. Psoriatic arthritis assessment and treatment update. *Curr Opin Rheumatol.* 2009;21(4):348-55. doi: 10.1097/BOR.0b013e32832c7832.
- [2] Scher, JU, Ogdie A, Merola JF and Ritchlin C. Preventing psoriatic arthritis: focusing on patients with psoriasis at increased risk of transition. *Nat Rev Rheum,* 2019, 15;153-166. doi: 10.1038/s41584-019-0175-0.
- [3] Talotta R, Atzeni F, Sarzi-Puttini P. Psoriatic arthritis: from pathogenesis to pharmacologic management. *Pharmacol Res.* 2019 Sep 7:104394. doi: 10.1016/j.phrs.2019.104394.

Topic 2: Innovations to accelerate vaccine development and manufacture

Topic details

Topic code	IMI2-2020-20-02
Action type	Research and Innovation Action (RIA)
Submission and evaluation process	2 stages
IMI2 JU Strategic Research Agenda - Axis of Research	Innovative medicines
IMI2 JU Strategic Research Agenda - Health Priority	Vaccines

Specific challenges to be addressed by public-private collaborative research

Vaccination is one of the greatest achievements in healthcare. However, developing a vaccine remains costly, time consuming, and risky (approximately EUR 800 million, 11 years in clinical development with <10% chance of entering the market) [1]-[3].

Advances in immunology, disease modelling, in silico modelling, including the analysis of big data and the application of machine learning (ML) artificial intelligence (AI), provide opportunities to innovate, de-risk and accelerate the vaccine-development process. Many of these advances have occurred in the academic sector.

These advances can be harnessed to tackle scientific bottlenecks in vaccine development and to nurture and expand a vaccines innovation ecosystem by bringing together academics, small and medium-sized enterprises (SMEs) and industry to collaborate in four areas:

- In silico platform for knowledge management and mathematical modelling of the immune system;
- Novel controlled human infection models (CHIMs);
- Next-generation human in vitro systems and assays; and
- Mathematical modelling platforms for vaccine substance and product attributes in biomanufacturing.

Currently, computational models have been applied to immunology data, but these models are limited to particular aspects [4]-[11]. There is the potential for these models to become more sophisticated and to predict how responses to pathogens and vaccines are affected by pre-disposing factors [12][13]. In biomanufacturing, in silico modelling could be applied to predicting optimal conditions for maintaining vaccine attributes with changes to processes or in the cold chain, thus replacing more expensive and time-consuming empirical methods.

CHIMs are especially helpful for the development of vaccines and can provide early evidence of clinical efficacy and samples for cutting-edge immunological research [14]-[22]. In particular, suitable CHIMs are needed for the development of universal or broadly protective vaccines against influenza, respiratory syncytial virus (RSV) and *Clostridium difficile* [23]-[29].

Next-generation in vitro systems (i.e. organoids and other self-organised in vitro-derived tissue culture systems that exhibit human organ functionality) and assays related to them, have the potential to model and evaluate host-pathogen interactions in the mucosa; the tissue in which the majority of pathogens enter the human body [30]- [47]. Some of these in vitro systems utilise human-induced pluripotent stem (iPS) cells,

allowing the potential to evaluate human pathogens with consideration to particular pre-disposing factors in the donor [30]-[41]. Also, in vitro systems and assays are needed to phase out animal models[48].

A consortium of academics, SMEs and industry will provide the opportunity to gather the best experts to address these challenges. Academia is at the forefront of scientific and technological advances; SMEs are adept at providing services and innovating those services; and industry has broad overlapping expertise in vaccine development and manufacture. Although the topic covers distinct scientific domains, there are numerous synergies among them. Hence, to address the challenges and to maximise these synergies, collaborations within the sector and with other sectors are needed, and therefore investment in a public-private partnership can provide the impetus to bring academics and SMEs into an alliance with industry partners.

Scope

The overall objective is to accelerate and de-risk the development of new vaccines by incorporating scientific and technological advances from the academic and biotech sectors into industry, and to develop more predictive biological and mathematical models of vaccine performance. The topic is composed of four subtopics, which constitute the four respective challenges described above. Subtopics 1 and 4 are centred on developing in silico model platforms for the immune system and biomanufacturing, respectively, which should be sustainable after the completion of the project; and subtopics 2 and 3 seek to widen the use of CHIMs and next-generation in vitro models and assays in vaccine development.

All subtopics in the programme relate to the use of novel modelling technologies (biological or mathematical) to accelerate the development of vaccines. Hence, by bringing together stakeholders from all areas of vaccine R&D (preclinical, clinical and manufacturing), the programme offers a unique opportunity to explore and open up an interdisciplinary dialogue on the future use, acceptance and further co-ordinated development of these technologies.

For each of the subtopics the specific objectives are as follows:

Subtopic 1: Systems-immunology platform for model development

To develop an open-data/open-source in silico platform focussed on immunobiological processes, and not on a given disease or vaccine indication, for the prediction of:

- immune responses to vaccines and pathogens and how those responses are affected by pre-disposing factors, using a combination of data sets to predict vaccination response of individuals (e.g. multi-layer omics and immunophenotyping);
- antigen and pathogen features most likely to induce protective immunity, and the anticipated immune responses to those features;
- emerging medical needs (via AI systems) such as infectious disease outbreaks, and the associated required investment in vaccination development and implementation.

Subtopic 2: CHIMs

To develop improved or novel CHIMs for influenza, RSV and *C. difficile*, in order to facilitate the generation of early efficacy data for vaccine candidates. This will include the:

- identification, characterisation and manufacture of pathogen strains;
- identification of key parameters for CHIM standardisation, generalised adoption, and ultimately, regulatory acceptance.

Subtopic 3: State-of-art innovations in human in vitro mucosa models and assays

(i) To develop prototype next-generation in vitro systems (self-organised in vitro tissue-culture systems derived from human stem cells or human primary tissue that exhibit organ-like functionality) for antigen identification/validation and drug substance and drug product characterisation/validation.

(ii) To develop associated functional immune assays (e.g. miniaturised, medium to high throughput) for clinically-relevant (surrogate) endpoints.

- At least one in vitro model should be included for each of the following mucosae: gastro-intestinal, respiratory and urovaginal;
- Pathogens of interest are those relevant for global health, such as those with pandemic potential (influenza), or those for which vaccines are not yet available, including RSV, *C. difficile*, *Bordetella pertussis*, *Moraxella catarrhalis*, nontypeable *Haemophilus influenzae*, *Chlamydia trachomatis*, *Neisseria gonorrhoeae*, herpes simplex virus, norovirus, *Pseudomonas aeruginosa*, ExPEC (extra-intestinal pathogenic *Escherichia coli*) and cytomegalovirus.⁴⁰

Subtopic 4: Biomanufacturing platforms using mathematical modelling

To develop an open data/open source in silico biomanufacturing platform incorporating models for predicting:

- Vaccine-product stability (drug substance/product);
- The parameters to maintain process robustness for unit-operation scale up or scale down, and for process transfer.

This will also include:

- Defining the new approach to working which integrates these models in the biomanufacturing regime;
- Initiating a dialogue with relevant regulatory authorities, that paves the way for future use of predictive stability and process scale-up modelling in chemistry, manufacturing, and control (CMC) dossiers for new and improved vaccines.

Subtopics and the Call process

The Call process has two stages.

At stage 1, applicant consortia should submit short proposals to one of the four subtopics (1–4). An applicant consortium can submit a short proposal for more than one subtopic, on condition that a separate short proposal is submitted for each subtopic.

To achieve the project objectives, maximise cross-learning and enable data sharing, it is envisaged that a single full proposal should be submitted at stage 2. This full proposal will include activities covering all four subtopics and their specific work packages (Figure 1). Thus, at stage 2, the full proposal will be submitted by the consortium composed by the successful applicant subconsortia of all four subtopics and the industry consortium.

An overall coordinator, selected from the winning consortium of Subtopic 3 (State-of-art innovations in human in vitro mucosa models and assays), and an overall project leader from the industry consortium, will be nominated by the consortium at the start of the preparation of the full proposal.

⁴⁰Pathogens not of interest include: fungi, parasites, syphilis, *Acinetobacter*, *Enterococcus*, *Klebsiella pneumoniae*, *Mycoplasma pneumoniae*, *legionella*, enteroviruses, coxsackieviruses, adenovirus, bocavirus, Chikungunya/Zika, hantavirus, hepatitis viruses C and E, HIV-1, human herpesvirus 6 (HHV-6), MERS/SARS, parvovirus B19, and West-Nile virus

In the event that no short proposal is over the threshold for one or two subtopics, stage 2 of the Call will still be initiated by the merger of the remaining consortia and the industry consortium. The overall IMI2 JU maximum financial contribution and the EFPIA in-kind contributions will be adapted accordingly, based upon the allocation provided under the section 'Indicative budget'.

If no short proposal is selected for Subtopic 3, activities related to the overall coordination and project management (proposed work package [WP] 1), as well as the overall communication and dissemination activities (proposed WP6), will be preferentially transferred to the Subtopic 2 leader, together with the amount of the relevant financial contribution identified for these activities under section 'Indicative budget'.

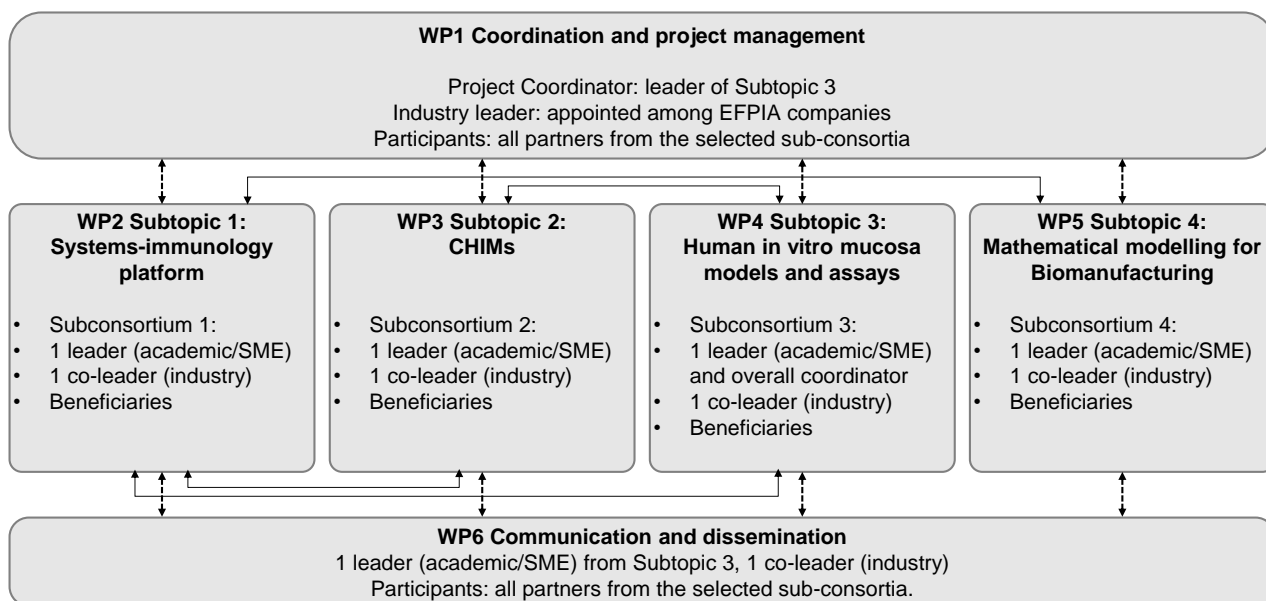


Figure 1: Consortia composition and interactions between suggested work packages (WPs), where each of the four subtopics will constitute distinct work packages.

Expected key deliverables

Based on the objectives of the topic, the following key deliverables have been identified.

All subtopics (under the direction of the coordinator)

- Data-management and data-sharing procedures, tools and infrastructures to support collaborations between subtopics;
- Sustainability plan for datasets and data management;
- Joint subtopic workshops to identify/develop/ratify collaborations between subtopics;
- Scientific publications.

Subtopic 1

- Sustainable open-access and cloud-based in silico platform incorporating knowledge management tools with links to databases of existing knowledge, omics data and validated computational knowledge-driven models and data-driven models, including data from related disease fields.

Subtopic 2

- New CHIMs that can accelerate the development of vaccines against, influenza, RSV and *C. difficile*;

- Definition of clinical and laboratory (molecular, immunological and microbiological) endpoints for efficacy and/or safety, for use in larger field trials;
- Improved or new comprehensive pre-screening methodologies that capture relevant pre-disposing factors, e.g. deep immunophenotyping and multi-layer omics;
- Clear definitions of rescue therapy including appropriate infection control and contingency plans, and for using CHIMs in at-risk populations that could be included in the contemplated CHIMs studies;
- Identification of key parameters for CHIM standardisation, generalised adoption, and ultimately, regulatory acceptance.

Subtopic 3

- Prototype next-generation in vitro models (as defined above) and assays for clinically-relevant (surrogate) endpoints with guidelines for good laboratory practice (GLP) implementation including robust biostatistical plans for:
 - evaluating the interactions between pathogens or their antigens with human gastro-intestinal, respiratory and urovaginal mucosae, ideally including interfaces with immune-system components such as innate-immune cells, antibodies or T cells;
 - addressing immunological mechanisms during convalescence from naturally-acquired infection or disease;
 - addressing heterogeneity within a particular human population;
 - evaluating human samples from biobanks, including serum, stool, vomitus, or mucosal secretions from vaccine recipients or individuals infected with a relevant human pathogen.

Scientific validation of selected prototype model(s) could be performed in a clinically-relevant setting, e.g. in parallel with a CHIM.

Subtopic 4

- Sustainable cloud-based in silico platform for:
 - vaccine substance and product stability for different types of vaccines (e.g. subunit, virus, conjugates, etc.);
 - biomanufacturing process robustness (applicable to unit operation scale up or scale down, and process transfer).

Expected impact

The overall expected impacts are: a greater success rate in bringing vaccine candidates through clinical development; increased efficiencies in the transitioning of biomanufacturing processes during vaccine development; and a more vibrant ecosystem of vaccine innovation in Europe. This impact will be demonstrated by more extensive alliances between academia, SMEs and industry through sustainable in silico platforms, CHIMs, CHIM-challenge strains and next-generation in vitro systems and assays, as potential services and products, and case-study based guidance for the use of CHIMs and next-generation in vitro systems and assays. This should also result in the increased probability of successful phase 3 efficacy trials and the acceleration of vaccine development, leading to benefits for trial participants and ultimately those with the medical need for the vaccine.

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

All subtopics

- The extent of the collaborative engagement of multiple partners across academia, SMEs and industry in developing and potentially sustaining the outcomes of the project.

Subtopic 1

- Better understanding of the immune response to disease, host-pathogen interactions, vaccine mechanisms of action and the associated contribution of genetic/epigenetic/environmental factors on immunobiology.

Subtopic 2

- The likelihood of the CHIMs being incorporated into vaccine-development programmes on a wider scale, and how their associated guidelines for use will support this incorporation.

Subtopic 3

- The likelihood of the next-generation in vitro models and assays being incorporated into vaccine-development programmes on a wider scale, and how their potential versatilities and associated guidelines for use will support this incorporation;
- The potential for the next-generation in vitro models and assays to replace the use of animal testing in research, licensure and release of vaccines (with regulatory agency approval) in the future.

Subtopic 4

- Better understanding of how scale-up and scale-down transitions affect vaccine manufacturing, and can be modulated to ensure vaccine quality and stability/shelf-life;
- More efficient vaccine-manufacturing processes that could also allow affordable vaccine development for small or restricted target populations, personalised vaccines, or sustainable vaccine development for diseases in low-to-middle income countries.

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

In addition, all applicants should describe how their specific subtopic will impact competitiveness and growth of companies including SMEs;

In their proposals, all applicants should outline how their specific subtopic will:

- manage research data, including use of data standards;⁴¹
- disseminate, exploit, and sustain the project results. This may involve engaging with suitable biological and medical sciences Research Infrastructures;⁴²
- communicate the project activities to relevant target audiences.

In addition, the following additional exploitation⁴³/dissemination⁴⁴ obligations must be considered to maximise impact:

- The in silico immune-systems platform and biomanufacturing platform should be open-access cloud-based resources.

⁴¹ 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

⁴² <http://www.corbel-project.eu/about-corbel/research-infrastructures.html>

⁴³ Article 28.1 (Additional exploitation obligations) of the IMI2 Grant Agreement will apply

⁴⁴ Article 29.1 (Additional dissemination obligations) of the IMI2 Grant Agreement will apply

Potential synergies with existing Consortia

Synergies and complementarities should be considered with relevant national, European and non-European initiatives (including suitable biological and medical sciences research infrastructures³⁹ to incorporate, whenever possible, past achievements, available data and lessons learnt, thus avoiding unnecessary overlap, and duplication of efforts and funding.

Industry consortium

The industry consortium is composed of the following EFPIA partners:

- GSK (Lead) - contribution to Subtopics 1, 2, 3 and 4;
- Sanofi Pasteur (Co-lead) - contribution to Subtopics 1, 2, 3 and 4;
- Takeda - contribution to Subtopic 3;
- CureVac AG - contribution to Subtopic 3.

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

All subtopics:

- Expertise in vaccine development, manufacturing processes and global regulatory affairs;
- Industry leadership in IMI projects;
- Establishing links with other major existing initiatives (e.g. Human Vaccines Project, HIC-Vac in the United Kingdom, IMI2-Periscope, IMI2-VITAL, IMI2-FLUCOP, IMI2-RESCEU, IMI2-iConsensus, etc.), and where possible, obtaining access to relevant databases or datasets.

Subtopic 1

- Expertise:
 - Mathematical modelling, knowledge-management system for data integration;
 - Immunology.
- Assets:
 - Data from non-clinical and clinical studies. This may include suitable datasets, adapted experiments or analytical experiments (e.g. in vitro data from ongoing or past research projects) to support the project. The specific nature of contribution may be refined at stage 2 of the application process to be more appropriately aligned with the project proposed by the applicant consortium.

Subtopic 2

- Expertise:
 - Clinical and translational research, virology, immunology, biostatistics, bioinformatics, quantitative mathematics;
 - Good-manufacturing-practice (GMP) production of material and/or viral and bacterial strains for CHIM development;
 - Phenotypic and genetic characterisation of microbial strains.
- Contributions to clinical studies:
 - GSK intends to cover the cost of characterisation and GMP manufacturing of relevant challenge strains;

- Sanofi Pasteur intends to contribute to the production of GMP RSV stocks;
- Sanofi Pasteur also intends to contribute data on experimental human infection with RSV, obtained via in-house study (or studies) to be conducted within 24 months of the start of the project. These data are expected to be used to inform and refine the design of RSV CHIM studies in the project.

Subtopic 3

- Expertise:
 - Translational preclinical models and in vitro infection models, including organoids;
 - Biomarkers of vaccine safety, reactogenicity, immunogenicity and efficacy, and infectious disease outcomes;
 - Assay miniaturization;
 - Phenotypic and genetic characterization of microbial strains.
- Assets:
 - Samples/data from non-clinical and clinical studies conducted with the pathogens of choice to help define how findings in the models developed by the consortium relate to natural/controlled infection in humans and how they concord with data from preclinical in vivo studies used historically to predict the behaviour of vaccines in humans.
- Contributions to studies for the development of next generation in vitro systems:
 - Pending the final choice of pathogens for the in vitro models and assay development, GSK may contribute by providing relevant materials (antigens, antibodies, preclinical or clinical samples);
 - Takeda intends to provide an in-cash contribution for the development and evaluation of in vitro gastro-intestinal models of infection and/or immunity.
- Contributions to services:
 - Sanofi Pasteur intends to provide a contribution for investigating the use of next-generation in vitro systems in evaluating vaccine safety.

Subtopic 4

- Expertise:
 - Process modelling support and revision;
 - Knowledge-management system for data integration.
- Assets:
 - To help build the in silico models, EFPIA companies will provide retrospective data on stability of drug substance and/or process intermediaries and on bioprocess scale-up/scale-down, collected for different classes of vaccines (e.g. native and recombinant proteins, viruses, conjugated protein-polysaccharide, and others);
 - EFPIA companies will conduct prospective empirical studies to support qualification/validation of the resulting in-silico models (i.e. proof-of-concept studies) for both stability and process development. These will be designed in consultation with the consortium partners to best suit the project objectives.

Indicative duration of the action

The indicative duration of the action is 66 months.

- Within each subtopic, it is expected that scientific activities should be completed within 60 months after project start;

- Activities related to communication, dissemination, exploitation and management (reporting) should continue for an additional 6-months (i.e. up to Month 66) to focus on communication of the results, including publications, and implementation of the sustainability plan.

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

Indicative budget

Overall budget

The financial contribution from IMI2 JU is a maximum of EUR 18 600 000 for the four subtopics and open calls listed below.

The indicative in-kind and financial contribution from EFPIA partners is EUR 19 870 000 for the four subtopics and open calls listed below. The total financial contribution available from the EFPIA partners for activities in relation to the objectives of this action is EUR 2 000 000.

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

Subtopic 1 budget

The financial contribution from IMI2 JU is a maximum of EUR 2 100 000.

The indicative in-kind contribution from EFPIA partners is EUR 4 100 000.

Therefore, at stage 1, the applicant consortium may allocate up to EUR 2 100 000 (IMI2 JU financial contribution) in the budget of their stage 1 proposal.

Subtopic 2 budget

The financial contribution from IMI2 JU is a maximum of EUR 9 825 000.

The indicative in-kind contribution from EFPIA partners is EUR 7 210 000.

Therefore, at stage 1, the applicant consortium may allocate up to EUR 9 825 000 (IMI2 JU financial contribution) in the budget of their stage 1 proposal.

Subtopic 3 budget

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

The indicative in-kind and financial contribution from EFPIA partners is EUR 5 385 000. The total financial contribution available from the EFPIA partners for activities in relation to objectives of this subtopics (i.e. the conduct of pre-clinical studies) is EUR 1 000 000.

At stage 1, the applicant consortium may allocate up to EUR 5 000 000 in the budget of their stage 1 proposal. This amount is subdivided in the following categories:

- Scientific activities:
 - EUR 4 000 000 of which EUR 1 000 000 for the conduct of pre-clinical studies (development and evaluation of gastro-intestinal models of infection and/or immunity)
- Coordination and management activities (for entire project, not a specific subtopic):
 - EUR 1 000 000 for the management, communication and dissemination activities for the whole consortium and to the data management and sustainability plan for the whole consortium

Subtopic 4 budget

The financial contribution from IMI2 JU is a maximum of EUR 2 175 000.

The indicative in-kind contribution from EFPIA partners is EUR 2 175 000.

Therefore, at stage 1, the applicant consortium may allocate up to EUR 2 175 000 (IMI2 JU financial contribution) in the budget of their stage 1 proposal.

Financial contribution for open calls for proposals

To ensure access to state-of-the-art technologies that may become available after the start of the project and could support the development of new platforms and tools (e.g. CHIMs and organoids, algorithms), the consortium may consider enrolling additional participants, after year 2, to fulfil the tasks identified by the consortium. The need for enrolling additional participants will be based on the identification of objectives that could be better addressed by those new technologies, and should be endorsed by the independent panel of experts during the interim project review conducted by IMI2 JU.

This will be achieved by launching at least two open calls: one call per year, the first one being planned after year 2. These open calls (which will specify the needs, type of technologies, selection criteria, etc.) will constitute project activities. Each open call will be prepared by a dedicated working group and endorsed by the entire consortium. In principle, new beneficiaries identified by means of the open calls will join the consortium for carrying out activities additional to those already planned. The detailed mechanism and procedure for conducting these calls will be established in the full proposal.

A maximum financial contribution of EUR 1 500 000 (composed by financial contributions of EUR 500 000 from IMI2 JU and EUR 1 000 000 from EFPIA) will be allocated for the implementation of the open calls. This amount has not been included in any of the subtopic budgets at stage 1, as it will be allocated in the budget of the stage 2 proposal by the full consortium. This financial contribution is a fixed amount and will not be modified in the event that no short proposals are not selected under one or two subtopics at stage 1.

Expertise and resources expected from applicants at stage 1

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

The stage 1 submitted short proposals should include suggestions for creating a full-proposal architecture for the subtopic, which could be in line with the suggested architecture described below, though this architecture is only a suggestion. It should also recognise potential inter-subtopic interactions within the project.

This project may require mobilising, as appropriate the following expertise:

Subtopic 1

- Expertise in computational and mathematical modelling, and immunology;
- Front-end and back-end in silico platform development;
- Knowledge-management systems for data integration;
- Evaluation/curation of open-source data and knowledge that can be utilised for mathematical modelling;
- Project management skills (subtopic coordination);
- Communication and dissemination skills;
- Business sustainability plans.

Subtopic 2

- Expertise in microbiology, virology, microbial genetics;
- Clinical expertise in ethics, immunology, big data analyses and establishment of large databases, regulatory science;
- Project management skills (subtopic coordination);
- Communication and dissemination skills.

It may also require mobilising, as appropriate, the following resources: clinical infrastructures for inpatients, data on previous CHIM activities with specific pathogens, and existing ethical and regulatory frameworks (ethical aspects and guidance will have to be considered).

Subtopic 3

- Expertise in next-generation in vitro systems (organ on chip, 3D tissue models, organoids etc.);
- Advanced biostatistics and data analysis;
- Novel immunological assays;
- Novel reagents for interrogating immune responses to complex epitopes on pathogens;
- Expertise in association of peripheral immune responses to mucosal pathogens to potentially protective mucosal immune responses;
- Expertise in prospective clinical cohort studies and in the identification of immune correlates of protection;
- Given that the project coordinator will be appointed from Subtopic 3, strong expertise and track record in EU project management of large consortia, including reporting, legal and financial aspects, is required;
- Communication and dissemination skills: development and implementation of communication, dissemination and use plan.

In light of the scope of the project and its four aspects, the applicant consortium for Subtopic 3 should have a global vision and a profound understanding of the challenges and activities to ensure good oversight.

Subtopic 4

- Bio pharmaceutical process knowledge;
- Process Modelling expertise;
- Front-end and back-end platform development;
- Knowledge-management system for data integration;
- Evaluation/curation of open-source data and knowledge that can be utilized for the modelling;
- Project management skills (subtopic coordination);
- Communication and dissemination skills;
- Business sustainability plans.

SMEs

Suitable SMEs could be considered in the four subtopics for the following activities:

- Back-end and front-end IT infrastructure construction for in silico platforms.
- Manufacture (and associated optimisation) of challenge pathogens for CHIMs.
- Design/production of monitoring devices for biomanufacturing.
- Project management activities.

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

Considerations for the outline of project work plan (for all subtopics)

In their stage-1 proposals applicants should:

- Give due visibility to data management; dissemination, exploitation and sustainability; and communication activities. This should be described by each submitting applicant consortium, and should include the elements necessary to ensure the proper functioning of each subtopic as well as sufficient resources for these tasks, bearing in mind that some modifications will be necessary at the stage 2 full proposal and several activities will be shared among all participants of the full consortium to ensure integration and avoid redundancy;
- Consider including a strategy for ensuring the translation of the project results to drug development, regulatory/health technology assessment (HTA) settings (e.g. through scientific advice/qualification advice/opinion, etc.), clinical and healthcare practices and/or decision-making processes.

Suggested architecture

The architecture of the proposed project is described in Figure 2.

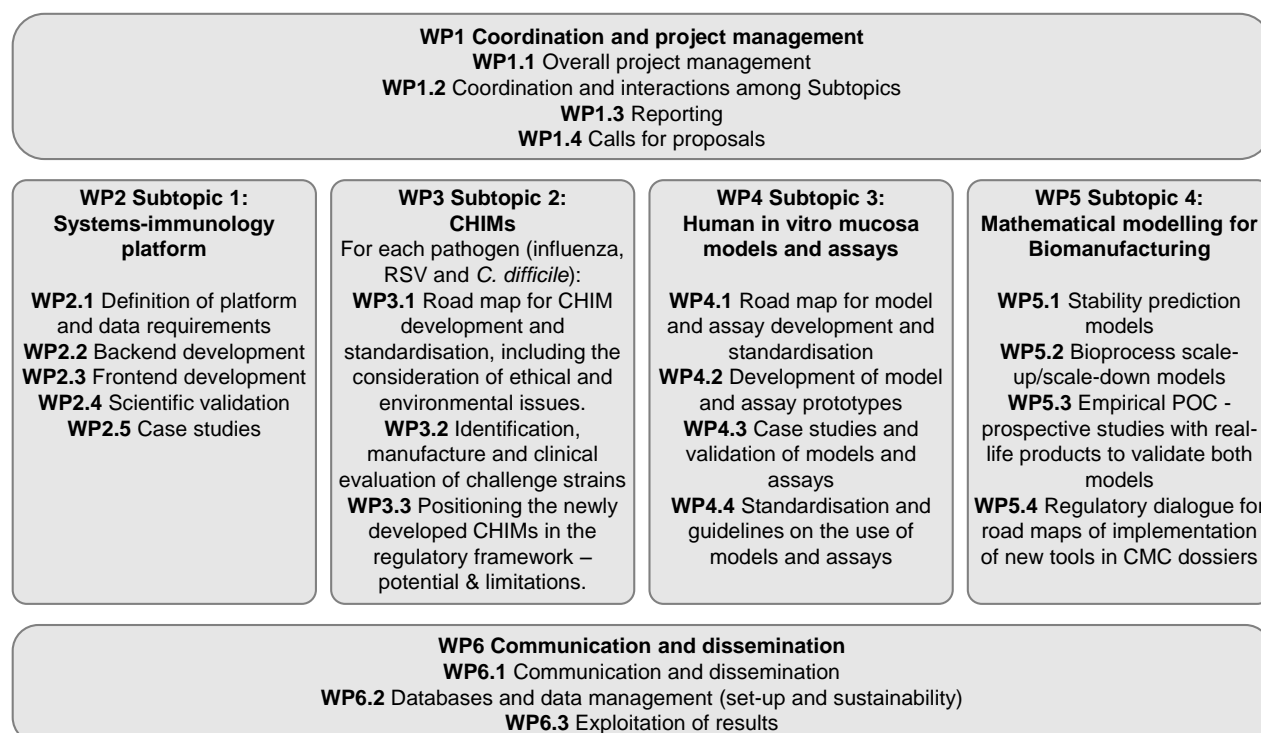


Figure 2: The project could be composed of two horizontal work packages (WPs) for project management and communication and four subtopics, each comprising several work streams.

The governance structure should reflect the specific setting of this topic, i.e. the inclusion of four subconsortia into one single consortium managed under a single grant agreement and a single consortium agreement.

Within Subtopic 4, it is proposed that scientific activities would be completed within 48 months after project start to be in coordination with internal activities of EFPIA members. Dissemination and exploitation activities within this subtopic (specifically for data exchange with other subtopics) and some new activities (arising from open calls for proposals) could be extended until the end of the project (Month 66).

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

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.

In consideration of the nature of the consortium (potentially large with the merger of four subconsortia into one single consortium), all beneficiaries should be prepared to start discussing the main terms of the consortium agreement (i.e. governance, liabilities, intellectual property, publication, data protection, financial management) during the preparation of the full proposal.

Data Management

In their stage 2 proposal, applicants should give due visibility to data management including use of data standards. A full 'data management plan' (DMP) as a distinct deliverable must be delivered within the first 6 months of the project. The DMP needs to be kept up to date with the needs of the project and as such be updated as necessary during its lifetime.⁴⁵

Dissemination, exploitation and sustainability of results

In their stage 2 proposal, applicants must provide a draft plan for dissemination and the exploitation, including sustainability of results. A full plan as a distinct deliverable must be delivered within the first 6 months of the project⁴⁶, and updated during the project lifetime and could include identification of:

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

Sufficient resources should be foreseen for activities related to dissemination and exploitation, including the plan for the sustainability of the project results. This may involve engaging with suitable biological and medical sciences Research Infrastructures (RIs).⁴⁷

Communication

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

⁴⁵ 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

⁴⁶ As an additional dissemination obligation under Article 29.1 of the IMI2 Grant Agreement will apply

⁴⁷ <http://www.corbel-project.eu/about-corbel/research-infrastructures.html>

References

- [1] Rappuoli R, Hanon E. Sustainable vaccine development: a vaccine manufacturer's perspective. *Curr Opin Immunol* 2018; 53:111-118.
- [2] Pronker ES, Weenen TC, Commandeur H, Claassen EH, Osterhaus AD. Risk in vaccine research and development quantified. *PLoS One* 2013; 8:e57755.
- [3] Plotkin S, Robinson JM, Cunningham G, Iqbal R, Larsen S. The complexity and cost of vaccine manufacturing - An overview. *Vaccine* 2017; 35:4064-4071.
- [4] Chakraborty AK. A Perspective on the Role of Computational Models in Immunology. *Annu Rev Immunol* 2017; 35:403-439.
- [5] Goodswen SJ, Kennedy PJ, Ellis JT. Discovering a vaccine against neosporosis using computers: is it feasible? *Trends Parasitol* 2014; 30:401-411.
- [6] Robert PA, Rastogi A, Binder SC, Meyer-Hermann M. How to Simulate a Germinal Center. *Methods Mol Biol* 2017; 1623:303-334.
- [7] Schneidman-Duhovny D, Khuri N, Dong GQ, Winter MB, Shifrut E, Friedman N, Craik CS, Pratt KP, Paz P, Aswad F, et al. Predicting CD4 T-cell epitopes based on antigen cleavage, MHCII presentation, and TCR recognition. *PLoS One* 2018; 13:e0206654.
- [8] Sanchez-Trincado JL, Gomez-Perosanz M, Reche PA. Fundamentals and Methods for T- and B-Cell Epitope Prediction. *J Immunol Res* 2017; 2017:2680160.
- [9] Mustafa AS. In silico analysis and experimental validation of Mycobacterium tuberculosis -specific proteins and peptides of Mycobacterium tuberculosis for immunological diagnosis and vaccine development. *Med Princ Pract* 2013; 22 Suppl 1:43-51.
- [10] Castelli M, Cappelletti F, Diotti RA, Sautto G, Criscuolo E, Dal Peraro M, Clementi N. Peptide-based vaccinology: experimental and computational approaches to target hypervariable viruses through the fine characterization of protective epitopes recognized by monoclonal antibodies and the identification of T-cell-activating peptides. *Clin Dev Immunol* 2013; 2013:521231.
- [11] Pappalardo F, Flower D, Russo G, Pennisi M, Motta S. Computational modelling approaches to vaccinology. *Pharmacol Res* 2015; 92:40-45.
- [12] Arvaniti E, Claassen M. Sensitive detection of rare disease-associated cell subsets via representation learning. *Nat Commun* 2017; 8:14825.
- [13] Strickland J, Zang Q, Paris M, Lehmann DM, Allen D, Choksi N, Matheson J, Jacobs A, Casey W, Kleinstreuer N. Multivariate models for prediction of human skin sensitization hazard. *J Appl Toxicol* 2017; 37:347-360.
- [14] Tacket CO, Losonsky G, Nataro JP, Cryz SJ, Edelman R, Kaper JB, Levine MM. Onset and duration of protective immunity in challenged volunteers after vaccination with live oral cholera vaccine CVD 103-HgR. *J Infect Dis* 1992; 166:837-841.
- [15] Jin C, Gibani MM, Moore M, Juel HB, Jones E, Meiring J, Harris V, Gardner J, Nebykova A, Kerridge SA, et al. Efficacy and immunogenicity of a Vi-tetanus toxoid conjugate vaccine in the prevention of typhoid fever using a controlled human infection model of Salmonella Typhi: a randomised controlled, phase 2b trial. *Lancet* 2017; 390:2472-2480.
- [16] Darton TC, Blohmke CJ, Moorthy VS, Altmann DM, Hayden FG, Clutterbuck EA, Levine MM, Hill AV, Pollard AJ. Design, recruitment, and microbiological considerations in human challenge studies. *Lancet Infect Dis* 2015; 15:840-851.
- [17] de Graaf H, Gbesemete D, Gorringe AR, Diavatopoulos DA, Kester KE, Faust SN, Read RC. Investigating *Bordetella pertussis* colonisation and immunity: protocol for an inpatient controlled human infection model. *BMJ Open* 2017; 7:e018594.
- [18] Merkel TJ, Halperin SA. Nonhuman primate and human challenge models of pertussis. *J Infect Dis* 2014; 209 Suppl 1:S20-23.
- [19] Roestenberg M, Hoogerwerf MA, Ferreira DM, Mordmuller B, Yazdanbakhsh M. Experimental infection of human volunteers. *Lancet Infect Dis* 2018; 18:e312-e322.

- [20] Spring M, Polhemus M, Ockenhouse C. Controlled human malaria infection. *J Infect Dis* 2014; 209 Suppl 2:S40-45.
- [21] Levine MM, Chen WH, Kaper JB, Lock M, Danzig L, Gurwith M. PaxVax CVD 103-HgR single-dose live oral cholera vaccine. *Expert Rev Vaccines* 2017; 16:197-213.
- [22] Roestenberg M, Kamerling IMC, de Visser SJ. Controlled Human Infections As a Tool to Reduce Uncertainty in Clinical Vaccine Development. *Front Med (Lausanne)* 2018; 5:297.
- [23] Sherman AC, Mehta A, Dickert NW, Anderson EJ, Roupheal N. The Future of Flu: A Review of the Human Challenge Model and Systems Biology for Advancement of Influenza Vaccinology. *Front Cell Infect Microbiol* 2019; 9:107.
- [24] Innis BL, Berlanda Scorza F, Blum JS, Jain VK, Older Aguilar A, Post DJ, Roberts PC, Wairagkar N, White J, Bresee J. Meeting report: Convening on the influenza human viral challenge model for universal influenza vaccines, Part 1: Value; challenge virus selection; regulatory, industry and ethical considerations; increasing standardization, access and capacity. *Vaccine* 2019; 37:4823-4829.
- [25] Innis BL, Scorza FB, Blum JS, Jain VK, Aguilar AO, Post DJ, Roberts PC, Wairagkar N, White J, Bresee J. Convening on the influenza human viral challenge model for universal influenza vaccines, Part 2: Methodologic considerations. *Vaccine* 2019; 37:4830-4834.
- [26] Habibi MS, Chiu C. Controlled human infection with RSV: The opportunities of experimental challenge. *Vaccine* 2017; 35:489-495.
- [27] Pandya MC, Callahan SM, Savchenko KG, Stobart CC. A Contemporary View of Respiratory Syncytial Virus (RSV) Biology and Strain-Specific Differences. *Pathogens* 2019; 8.
- [28] Guery B, Galperine T, Barbut F. Clostridioides difficile: diagnosis and treatments. *BMJ* 2019; 366:l4609.
- [29] Bruxelle JF, Pechine S, Collignon A. Immunization Strategies Against Clostridium difficile. *Adv Exp Med Biol* 2018; 1050:197-225.
- [30] Dedhia PH, Bertaux-Skeirik N, Zavros Y, Spence JR. Organoid Models of Human Gastrointestinal Development and Disease. *Gastroenterology* 2016; 150:1098-1112.
- [31] Chen YW, Huang SX, de Carvalho A, Ho SH, Islam MN, Volpi S, Notarangelo LD, Ciancanelli M, Casanova JL, Bhattacharya J, et al. A three-dimensional model of human lung development and disease from pluripotent stem cells. *Nat Cell Biol* 2017; 19:542-549.
- [32] Wilkinson DC, Alva-Ornelas JA, Sucre JM, Vijayaraj P, Durra A, Richardson W, Jonas SJ, Paul MK, Karumbayaram S, Dunn B, et al. Development of a Three-Dimensional Bioengineering Technology to Generate Lung Tissue for Personalized Disease Modeling. *Stem Cells Transl Med* 2017; 6:622-633.
- [33] Workman MJ, Mahe MM, Trisno S, Poling HM, Watson CL, Sundaram N, Chang CF, Schiesser J, Aubert P, Stanley EG, et al. Engineered human pluripotent-stem-cell-derived intestinal tissues with a functional enteric nervous system. *Nat Med* 2017; 23:49-59.
- [34] Sachs N, Papaspyropoulos A, Zomer-van Ommen DD, Heo I, Bottinger L, Klay D, Weeber F, Huelsz-Prince G, Iakobachvili N, Amatngalim GD, et al. Long-term expanding human airway organoids for disease modeling. *EMBO J* 2019; 38.
- [35] Iakobachvili N, Peters PJ. Humans in a Dish: The Potential of Organoids in Modeling Immunity and Infectious Diseases. *Front Microbiol* 2017; 8:2402.
- [36] Drummond CG, Bolock AM, Ma C, Luke CJ, Good M, Coyne CB. Enteroviruses infect human enteroids and induce antiviral signaling in a cell lineage-specific manner. *Proc Natl Acad Sci U S A* 2017; 114:1672-1677.
- [37] Dang J, Tiwari SK, Lichinchi G, Qin Y, Patil VS, Eroshkin AM, Rana TM. Zika Virus Depletes Neural Progenitors in Human Cerebral Organoids through Activation of the Innate Immune Receptor TLR3. *Cell Stem Cell* 2016; 19:258-265.
- [38] Ganesan VK, Duan B, Reid SP. Chikungunya Virus: Pathophysiology, Mechanism, and Modeling. *Viruses* 2017; 9.
- [39] Porotto M, Ferren M, Chen YW, Siu Y, Makhsous N, Rima B, Briese T, Greninger AL, Snoeck HW, Moscona A. Authentic Modeling of Human Respiratory Virus Infection in Human Pluripotent Stem Cell-Derived Lung Organoids. *MBio* 2019; 10.

- [40] Ramani S, Crawford SE, Blutt SE, Estes MK. Human organoid cultures: transformative new tools for human virus studies. *Curr Opin Virol* 2018; 29:79-86.
- [41] Fonseca KL, Rodrigues PNS, Olsson IAS, Saraiva M. Experimental study of tuberculosis: From animal models to complex cell systems and organoids. *PLoS Pathog* 2017; 13:e1006421.
- [42] Takahashi Y, Sato S, Kurashima Y, Yamamoto T, Kurokawa S, Yuki Y, Takemura N, Uematsu S, Lai CY, Otsu M, et al. A Refined Culture System for Human Induced Pluripotent Stem Cell-Derived Intestinal Epithelial Organoids. *Stem Cell Reports* 2018; 10:314-328.
- [43] Nadkarni RR, Abed S, Cox BJ, Bhatia S, Lau JT, Surette MG, Draper JS. Functional Enterospheres Derived In Vitro from Human Pluripotent Stem Cells. *Stem Cell Reports* 2017; 9:897-912.
- [44] Zhou J, Li C, Sachs N, Chiu MC, Wong BH, Chu H, Poon VK, Wang D, Zhao X, Wen L, et al. Differentiated human airway organoids to assess infectivity of emerging influenza virus. *Proc Natl Acad Sci U S A* 2018; 115:6822-6827.
- [45] Hui KPY, Ching RHH, Chan SKH, Nicholls JM, Sachs N, Clevers H, Peiris JSM, Chan MCW. Tropism, replication competence, and innate immune responses of influenza virus: an analysis of human airway organoids and ex-vivo bronchus cultures. *Lancet Respir Med* 2018; 6:846-854.
- [46] Rossi G, Manfrin A, Lutolf MP. Progress and potential in organoid research. *Nat Rev Genet* 2018; 19:671-687.
- [47] Barrila J, Crabbe A, Yang J, Franco K, Nydam SD, Forsyth RJ, Davis RR, Gangaraju S, Ott CM, Coyne CB, et al. Modeling Host-Pathogen Interactions in the Context of the Microenvironment: Three-Dimensional Cell Culture Comes of Age. *Infect Immun* 2018; 86.
- [48] Netherlands National Committee for the protection of animals used for scientific purposes (NCad). Transition to non-animal research. 2016. Available: <https://www.ncadierproevenbeleid.nl/documenten/rapport/2016/12/15/ncad-opinion-transition-to-non-animal-research>.

Introduction to the IMI2 Antimicrobial Resistance (AMR) Accelerator programme

Background and problem statement

The discovery and development of new preventions and treatments to address antimicrobial resistance (AMR) is an undisputed European and global challenge. The challenge is compounded by a low return on investment (RoI) for the pharmaceutical sector driven largely by the lack of established reimbursement models and standard methods to express the true societal value for new technologies addressing AMR. This has subsequently led to a reduction in resources applied across the pharmaceutical industry and a decline in scientific discoveries. Overall, this situation has compromised the delivery of new options to treat and prevent resistant infections. This was highlighted in the European One Health Action Plan against Antimicrobial Resistance (for more info please visit the following link:

https://ec.europa.eu/health/amr/sites/amr/files/amr_action_plan_2017_en.pdf). Beyond Europe, it is of note that AMR is one of four public health concerns that has been raised to the level of discussion at the UN General Assembly (September 2016), putting it on par with subjects such as HIV and Ebola. Additionally, drug resistant tuberculosis (TB) is the largest single contributor to AMR health, mortality, and economic impact.

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

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

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

Overall objectives of the AMR Accelerator

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

The AMR Accelerator will provide, under one operational structure, a wide-ranging series of projects that will address many of the scientific challenges in AMR. The scientific scope will be broad, including prevention (vaccines, monoclonal antibodies (mAbs), immunoprophylaxis, other means) and treatment (new antibiotics, non-antibiotic alternatives, and combinations). For clarity, the term 'AMR' should be interpreted to include Gram-positive and Gram-negative bacteria, tuberculosis (TB) and non-tubercular mycobacteria (NTM). Within this broad scope, projects in the Accelerator will develop new pre-clinical tools and methods, validate alternative or 'non-traditional' approaches, and progress potential new treatments through phase 1-3 clinical

trials. They will also analyse data from EFPIA-funded clinical trials to assist in the translation of preclinical data to clinical results of novel anti-infective agents and vaccines. The Accelerator will also potentially generate new clinical/regulatory phase 2-3 pathways. Over the past years, IMI's New Drugs for Bad Bugs (ND4BB) programme has created a vibrant drug discovery and development network in AMR, and met important milestones. The AMR Accelerator will complement and augment the capabilities of the IMI ND4BB programme.

Progression of successful assets beyond the scope of the Accelerator (pillar-dependent, see below) may occur, as appropriate, by other mechanisms. Such mechanisms might include EU funding programmes within Horizon 2020 (including SME instruments) or future framework programmes, InnovFin instruments, structural funds, venture capitals, other internal R&D funding mechanisms, etc. In addition, the applicable principles from the Davos Declaration on Antimicrobial Resistance (January 2016) or the Industry Roadmap for Progress on Combatting Antimicrobial Resistance (September 2016: <https://www.ifpma.org/wp-content/uploads/2016/09/Roadmap-for-Progress-on-AMR-FINAL.pdf>⁴⁸) should be taken into account.

The Accelerator will contribute to one of the three pillars of the European One Health Action Plan against Antimicrobial Resistance 'Boosting research and development and innovation in AMR' (June 2017: https://ec.europa.eu/health/amr/sites/amr/files/amr_action_plan_2017_en.pdf). The Accelerator will also directly address the IMI2 JU objective to 'develop new therapies for diseases for which there is a high unmet need, such as Alzheimer's disease and limited market incentives, such as antimicrobial resistance' (Article 2(b)(iii) of the Council Regulation establishing IMI2 JU: <http://eur-lex.europa.eu/legal-content/EN/TXT/?uri=celex%3A32014R0557>)

AMR Accelerator programme structure

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

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

The overall IMI2 JU financial contribution to the AMR Accelerator topics under Pillars A, B and C will be a maximum of EUR 237 230 000.

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

The two-stage IMI2 JU Call 20 includes one topic (topic 3) under Pillar B to complement the actions funded under IMI2 JU Call 15 and IMI2 JU Call 16.

Future calls for proposals could be launched at a later stage to select under each pillar additional research projects or networks depending on developing scientific needs and objectives in AMR research.

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

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

The initial action in the CBN resulting from topic 7 in IMI2 JU Call 15 will implement a coordination and support group that will support operations of all projects in the AMR Accelerator with effective management, communication, and data capture capabilities. The initial CBN action also will focus on the collection, sharing,

⁴⁸ For example, points 3 and 4 from the 'Roadmap for Progress'.

and analysis of vaccine and/or antibacterial clinical trial data and the optimisation of animal infection models for bacterial infections.

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

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

The platform will be self-sustained and independent from other similar activities (Integrated Research Platform (IRP), TB Drug Accelerator (TBDA)). It is anticipated that there will be linkages with the TBDA (for more info on TBDA, please visit: <http://partnerships.ifpma.org/partnership/tb-drug-accelerator-program>). It will provide ready-to-use services for rapid progression of available (1st line) new and innovative candidates. The platform will be partly supported by the coordination and support group from Pillar A but will include management resources to self-sustain its scientific and financial reporting as well as innovation management procedures.

Topic 8 of IMI2 JU Call 15 will result in the creation of a group to profile and progress anti-TB compounds from advanced lead through phase 1 and to collect, share, and analyse TB clinical trial data. Additionally, it will address the development of new alternative anti-tubercular drugs (for example, host-defence or virulence approaches).

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

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

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

Consortia selected under this pillar may have a limited number of partners, and will require the participation of an EFPIA partner (e.g. 1 EFPIA partner + 1 SME/academic partner)⁴⁹. IMI2 JU Call 16, the first call under Pillar C, is divided in several topics, each dedicated to specific individual asset or research area. Additional single-stage calls, one or two per year, may be launched in the future pending budget availability. A total of at least 8-10 grant agreements are anticipated in the PBN (indicative number only).

⁴⁹ See 'Applicant consortium' section of IMI2 JU Call 16 topic text (Pillar C, "Portfolio Building Networks").

Collaboration agreements

To ensure smooth operation of the projects in the AMR Accelerator, the grant agreement of the first CBN action (COMBINE- 853967 selected under Pillar A from IMI2 JU Call 15 topic 7, and containing the coordination and support group⁵⁰) is complementary to all the grant agreements of actions selected under Pillars B and C (via IMI2 JU Call 15 topic 8, IMI2 JU Call 16 topics, IMI2 JU Call 20 topic 3 and potential future additional calls for proposals), as well as probable future grant agreements from actions selected under Pillar A. In addition, all grant agreements of actions under pillar B will be complementary between them. The respective options of Article 2, Article 31.6 and Article 41.4 of the IMI2 JU Model Grant Agreement⁵¹ will be applied. Accordingly, the consortia selected under Pillars A, B, and C will conclude collaboration agreements with the COMBINE- 853967 consortium selected from IMI2 JU Call 15 topic 7. These collaboration agreements will provide the framework for COMBINE- 853967 to provide day-to-day support of projects in the Accelerator, and will ensure exchange of relevant information, exploration of synergies, collaboration where appropriate, and avoid duplication of efforts.

Furthermore, a memorandum of understanding (MoU) will be pursued between the Pillar B TBDDN actions (IMI2 JU Call 15 topic 8 and Call 20 topic 3) and the Integrated Research Platforms (IRP) action of IMI2 JU Call 15 topic 1 (EU-PEARL 853966) to cover collaboration and sharing of information on TB-related activities. The MoU should constitute one deliverable in each action resulting from topic 8 of IMI2 JU Call 15 and topic 3 of IMI2 JU Call 20. Similarly, when reasonable, a MoU should be pursued between potential TB-focused actions under Pillar C of the Accelerator (resulting from IMI2 JU Call 16) and TBDDN actions, as well as the IRP action of IMI2 JU Call 15 topic 1 (EU-PEARL 853966), with appropriate provisions to protect confidentiality of the interactions between the consortia and their intellectual property rights.

Need and opportunity for public-private collaborative research

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

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

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

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

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

⁵⁰ For additional details see the topic 7 “Capability Building Network” of IMI2 JU Call 15.

⁵¹ See: https://www.imi.europa.eu/sites/default/files/uploads/documents/reference-documents/h2020-mga-imi_en_v5.pdf

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

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

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

Topic 3: Academia and industry united innovation and treatment for tuberculosis (UNITE4TB)

Topic details

Topic code	IMI2-2020-20-03
Action type	Research and Innovation Action (RIA)
Submission and evaluation process	2 stages
IMI2 JU Strategic Research Agenda - Axis of Research	Innovative medicines
IMI2 JU Strategic Research Agenda - Health Priority	Antimicrobial resistance

Specific challenges to be addressed by public-private collaborative research

Tuberculosis (TB) is the leading infectious cause of death worldwide [1]. To achieve the target of TB elimination by 2035, the WHO estimates that there is a funding shortfall of over USD1 billion per year in TB research. The treatment of drug-sensitive TB is an onerous regimen of four drugs for two months followed by two drugs for four months (six-months total), and multidrug-resistant TB may require treatment for up to two years. Many patients find adherence difficult, and the current drugs are associated with significant tolerability issues. Shorter and safer treatment regimens are urgently needed. Tuberculosis has a low or negative expected return on investment and therefore fails to attract funding: this call addresses this acute unmet medical and public health need.

Currently, TB drug development involves 14-day monotherapy trials for early bactericidal activity (EBA) to identify the maximally efficacious dose for a new chemical entity (NCE). The standard trial design contains no option to change doses or de-escalate in-stream in response to emerging Pharmacokinetic-pharmacodynamic (PKPD) or safety data, resulting in a flat dose-response [2]. In Phase 2B, the efficacy of treatment combinations is then studied in eight weeks of dosing, with time-to-sputum-culture-conversion as the primary endpoint. This paradigm has multiple weaknesses: inadequate exploration of dose response; lack of innovative study designs to empirically determine optimal duration of therapy, as well as inability to study multiple regimens in parallel. Moreover, there is a lack of Phase 2 biomarkers that adequately predict phase 3 outcome (relapse-free cure) [3][4][5].

Therefore, there is a critical need for innovative trial designs in TB. Efficient adaptive trial designs would accelerate clinical development in Phase 2, but cannot currently be implemented due to the lack of in-stream biomarkers for sterilising cure/relapse. Several RNA expression, cytokine, bacterial and radiological biomarkers have been proposed in the literature, but to date there has been neither comparison nor prospective validation of these biomarkers. A biomarker that predicts relapse at an individual level may further create opportunities for individualised medicine, or even permit creation/validation of trial simulations. These trial simulations could help optimise trial design, and facilitate in-stream decision-making in adaptive trials.

Private and public investment has been made in the discovery of NCEs but there is at present no mechanism for clinical exploration of these NCEs in innovative combinations. The collaboration of industry academics, clinicians and SME partners pooling resources and NCE's, developing adaptive trial designs alongside implementation of biomarkers, diagnostics and digital technology will make this a unique partnership. It will accelerate the development of combination regimens for the treatment of the world's biggest cause of mortality in infectious disease, aligned with the World Health Organisation's sustainable development goals.

Scope

The objectives of this Call Topic are to develop and implement innovative, state of the art adaptive clinical trial designs for the field of TB regimen development able to define the therapeutic dose for existing experimental New Chemical Entities (NCE's) within treatment combinations. The funded action will define the duration and composition of novel treatment combinations that will shorten or simplify the standard of care, for drug resistant TB as well as prospectively validating biomarkers against the relapse endpoint. In addition, the funded action is expected to develop clinical trial simulations, evaluate new technologies to monitor and enhance treatment adherence, and develop an understanding of population pharmacogenomics in all forms of active TB.

The funded action will develop a portfolio of ten NCEs that have completed first-in-human studies from a pool of existing NCE's supplied by EFPIA/Associated partners, and carry out Phase 2A (EBA) studies followed by Phase 2B/C efficacy and relapse assessment. The funded action will also study high-quality NCEs that are either owned or controlled by (with the right to further develop) EFPIA, academics or SMEs that wish to perform TB Phase 2 studies performed by the consortium on their compounds (in monotherapy (Phase 2a) or combination (Phase 2b/c)). It is expected that minimum requirements for compounds entering the consortium would include lack of pre-existence resistance in the field (focus on drug-resistant tuberculosis), a suitable safety and efficacy profile alongside suitable supplies of formulated product. Only molecules with a novel mechanism of action, not already existing within the portfolio, or with proof of a substantial improvement over existing compounds, would be accepted for Phase 2A EBA studies (please refer to EFPIA/AP contribution for pipeline current target classes under **NCEs portfolio**). Acceptance of suitable molecules will be subject to due diligence by the governing bodies of the consortium. These NCEs will be studied alone in early clinical efficacy EBA studies and in combinations for relapse studies, including with recently approved drugs in innovative Phase 2 trials designed to accelerate drug development and maximise the chance of success in Phase 3. These trials may include innovative ways of combining drugs and new formulations in different phases of a regimen.

The funded action will develop innovative trial designs able to define optimal treatment duration against endpoints that better predict the current Phase 3 endpoint of relapse and will improve efficiency by comparing multiple regimens in parallel within the same study [6][7]. Early interims will stop failing/futile arms, resulting in even greater efficiencies.

The funded action should also prospectively validate biomarkers against a relapse endpoint. The primary objectives of the biomarker work is to validate i) biomarkers able to accurately prioritise regimens for evaluation in phase 3, ii) biomarkers that are able to predict sterilising cure/relapse at the individual patient level, and iii) a third, more ambitious objective to identify biomarkers that permit the building of a clinical trial simulation platform.

A combination of biomarkers that predicts relapse and guides treatment duration alongside innovative adaptive trials, would greatly accelerate drug development in TB by enabling in-stream adaptation of a clinical trial to prioritise evaluation of the most promising regimens. The simulation platform should embrace and validate data-driven technologies such as artificial intelligence/ machine learning (AI/ML) to set criteria for stopping arms and to determine treatment duration.

Clinical data generated in one population are not always applicable to other populations. The understanding of how host genetics influence TB outcomes are critical, but are often missing in early-stage development. This can result in failures when therapies which have been validated in one population are then implemented in other populations. The applicant consortium is expected to study the influence of host genomic factors on drug factors, such as drug exposures and clearance in the patient, and to match these against a relapse endpoint. This would permit the selection of drugs and doses that are appropriate to particular populations or even to specific patients. It is anticipated that a proportion of the data generated in the funded action will be generated outside of Europe and this pharmacogenomic activity will therefore be critical to ensuring the applicability of that data to a European population.

Adherence is critical for the efficacy of a treatment regimen. The proposed activities should exploit innovative technologies (including biomarkers and diagnostics) to facilitate and monitor adherence in resource-poor settings, while generating evidence that shorter regimens improve adherence.

The consortium will develop and execute innovative adaptive trial designs to evaluate approximately ten NCEs and approximately ten combination regimens. To complete recruitment within relevant timeframes, the trial network should be able to enrol about one thousand TB patients annually. To achieve this level of recruitment, a proportion of patients may have to be recruited from highly endemic countries outside Europe. The consortium should propose a mechanism for the allocation of financial resources matched to actual patient recruitment costs per site which ensures objectives are met. A significant proportion of funding for sites should be linked to the actual number of study participants recruited.

Collaboration agreement(s)

The action funded under this call topic will be the second one launched under 'Pillar B TBDDN (Tuberculosis Drug Development Network),' of the AMR accelerator. Please refer to Call 15 and 16 topic texts regarding 'collaboration agreements', and 'Questions and answers'⁵² associated with both calls. This topic will be complimentary to the actions funded under Pillar A and B of the AMR accelerator:

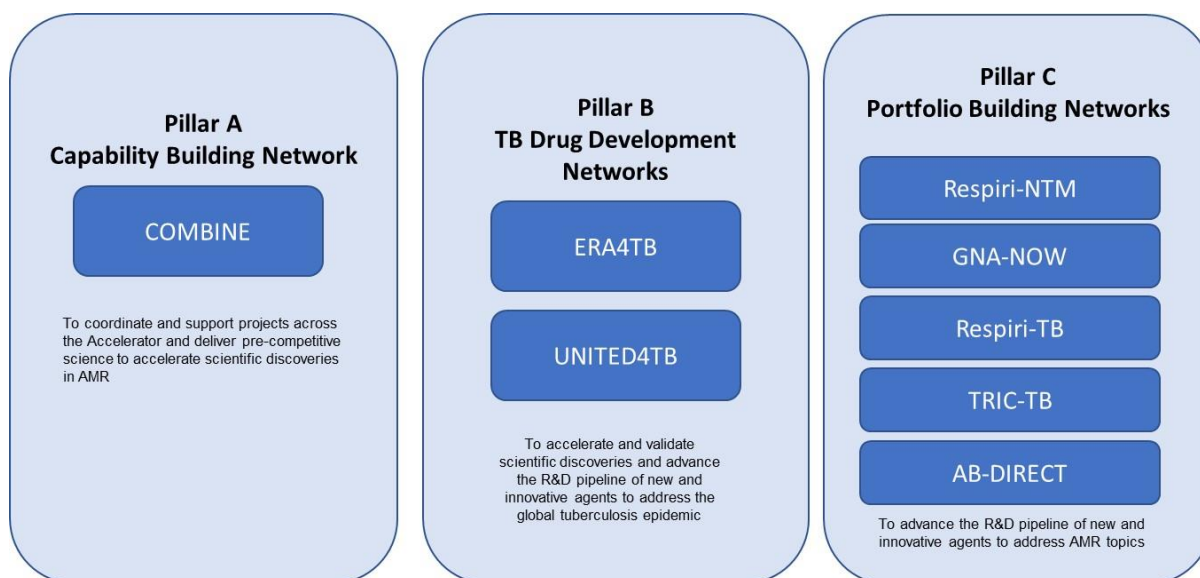


Figure 1 The structure of the AMR accelerator

- IMI2 JU Call 15 topic 8 – (ERA4TB), for using the generated pre-clinical regimen prioritisation to guide regimen selection for Phase 2B/C studies;
- IMI2 JU Call 15 topic 7 AMR Pillar A (COMBINE) on selection of biomarkers for validation, standardisation and quality control of assays that are common to AMR consortia.

The options regarding 'complementary grants' of the IMI2 JU Model Grant Agreement and the provisions therein (Articles 2, 31.6 and 41.4) will be enabled in the corresponding IMI2 JU grant agreements for all the concerned AMR accelerator projects.

Moreover, this action will seek cooperation through memoranda of understanding (MoU) with the actions that are funded under the following topic:

- **IMI2 JU Call 15 topic 1 - EU-PEARL**, the proposed phase 2 trial designs will be presented to the EMA and FDA for scientific advice and the proposed biomarker development framework will be presented to the EMA and FDA for biomarker qualification advice in co-ordination with **EU-PEARL** and TB Drug Translational Development Collaboration (TDTDC) as necessary;

⁵² https://www.imi.europa.eu/sites/default/files/uploads/documents/apply-for-funding/open-calls/Questions_and_answers_on_the_AMR_accelerator_programme.pdf

- Individual-level patient data will be made publicly available through a sustainable data-sharing platform developed in co-ordination with **COMBINE (Call 15 topic 7)**, **ERA4TB (Call 15 topic 8)** and **EU-PEARL (Call 15 topic 1)**.

Additionally, where reasonable, a MoU should be pursued between potential TB-focused actions under Pillar C of the Accelerator (resulting from IMI2 JU Call 16) and TBDDN actions (i.e. Call 15 topic 8, and Call 20 topic 3) with appropriate provisions to protect confidentiality of the interactions between the consortia and their intellectual property rights.

Expected key deliverables

The proposed activities will be expected to achieve the following deliverables for the implementation of innovative state-of-the-art adaptive clinical trials, the development of biomarkers and the development of Artificial Intelligence:

- Innovative, adaptive clinical trials
 - To develop strategies for adaptive dosing (escalation/de-escalation) and trial-stopping criteria based on in-stream pharmacokinetic, efficacy and safety read-outs while building a pharmacokinetic-pharmacodynamic model, as appropriate;
 - Successful submission of documents to EMA and FDA for scientific advice on proposed innovative trial designs by the end of the first year, and for innovative trials with novel endpoints, designs and analysis plans prior to study start as required;
 - An approved plan for quality assurance (clinical data collection and analysis; laboratory assays and standardisation across a global study) and compliance with ICH GCP, European Clinical Trial Regulations, EMA and FDA clinical trial guidelines. The proposed plan should include provisions for independent study monitoring and audit; and for laboratory quality assurance;
 - A strategy for the standardisation of sample collection, laboratory assays, imaging protocols, radiation safety for subjects across a global study. This should include a plan for collaborating with **IMI2 JU Call 15 topic 7 AMR Pillar A**;
 - Established clinical trial capacity with the ability to recruit approximately 1 000 patients per year, spanning at least two WHO regions able to deliver regulatory trials in TB by the end of the first year;
 - An established Target Product Profile (TPP), Target Regimen Profile (TRP), aligned with that described by WHO, and due diligence criteria for the progression of assets within the consortium;
 - The consortium should publish a Phase 2A (EBA) design that permits in-stream adaptation of dosing in response to pharmacokinetic and pharmacodynamic readouts, so as to permit the full characterisation of the dose-response curve;
 - The consortium should publish a Phase 2B/C design that evaluates multiple regimens in parallel against novel endpoints related to the current Phase 3 endpoint (relapse and poor outcome), an ability to determine the optimal duration for a regimen, and interim(s) for futility that permit efficiency to increase as arms are dropped;
 - Establish a plan for quality assurance (clinical data collection and analysis; laboratory assays and standardisation across a global study) and compliance with ICH GCP, European Clinical Trial Regulations, EMA and FDA clinical trial guidelines. The proposed plan should include provisions for independent study monitoring and audit; and for laboratory quality assurance.
 - Completed clinical trial data: Dose selection criteria for the UNITE4TB portfolio of Innovative NCEs based on completion and results from Phase 2A EBA, and Phase 2B/C combination studies. Identification of at least one viable regimen for Phase 3 clinical trials, or a ranked list of viable treatment regimens (maximum four NCEs each), capable of shortening therapy and/or with a safety/tolerability/accessibility profile better than the current standard-of-care, and which are ready to enter Phase 3;
 - An established data sharing platform where individual level patient data are FAIR (Findable, accessible, Interoperable and Recoverable) and publicly available beyond the life of the consortium;
 - Reporting outcomes in compliance with the European Clinical Trial Directive. The applicant consortia must present a publication strategy that does not delay the external availability of individual level patient data beyond the lifetime of the consortium;

- Innovative biomarkers
 - A strategy for how published biomarkers will be prioritised and selected for evaluation and validation and subsequently implemented within ongoing trials. For the avoidance of doubt, novel biomarker development is outside the scope of this action;
 - A strategy for early scientific engagement with the EMA and FDA, prior to clinical study start, to obtain regulatory buy-in for the proposed biomarker validation framework;
 - A methodological framework to prospectively validate biomarkers to be used in adaptive trial designs to shorten drug development and expand clinical trial capacity, and ideally used as a surrogate marker of sputum culture conversion and sterilising cure;
 - Data package of prospectively validated model/panel of biomarkers to be used in clinical trials to shorten TB drug/regimen development duration, and ready for submission to the EMA and FDA for regulatory qualification.
- Pharmacogenomics
 - Pharmacogenomics strategy for exploring how host genetic variation may influence drug absorption, target exposure, clearance, and patient outcomes resulting in pharmacogenomic PKPD models for individual NCEs.
- Clinical trial simulation tool
 - Developed clinical trial simulation tool(s) incorporating AI/ML to inform trial design, facilitate in-trial adaptation and, possibly, phase 2 trial waiver.
- Digital health technologies
 - A strategy for the evaluation of the impact of these technologies on adherence, and the impact of varying treatment durations on adherence in the field
 - Technology to evaluate the impact of treatment duration on adherence. Implement and validate digital health technologies to improve adherence to TB regimens within the currently proposed studies.
- Artificial Intelligence/Machine Learning
 - A strategy for regulatory agency advice and alignment with proposed AI/ML-based models;
 - Establish models that describe the role of individual biomarkers suitable for regulatory acceptance.
- Biobank.
 - Establish a sustainable biobank to make samples with linked de-identified clinical data collected from the consortium clinical trials publicly available beyond the life of the consortium.
 - Human biological samples collected as part of the clinical studies should be banked and made available to external researchers beyond the lifetime of the consortium. Samples provided to researchers should be linked to de-identified demographic and clinical study data in a manner compliant with GDPR;
 - The applicant consortia should provide a strategy for human biological sample tracking, access and management that is compliant with relevant European legislation;
 - A strategy for granting access to samples should also be presented (e.g., an independent panel for evaluation of proposed research plans).

Expected impact

The objectives, deliverables and impact of the resulting action are well aligned with the mission and goals of IMI2 JU to deliver increased success rate of biomarkers and priority medicines in innovative clinical trials. The expected impact of the funded action will also help attain 2030 UN Sustainable Development Goals and WHO 2035 End TB Targets by:

- providing new tools and understanding on how to progress TB science for the discovery and development of new clinical candidates and combinations thereof across the TB R&D landscape, with special emphasis on innovative clinical trial design and development of novel biomarkers;
- contributing to the EU's ambition of being a 'best practice region' for addressing AMR, and profit from its medical capacity to individualise and implement into medical practice combination therapies addressing MDR/XDR;
- developing new knowledge and tools, innovative clinical trial designs, imaging technology, biomarkers and pharmacogenomics diagnostics and exploiting artificial intelligence for the development of new clinical candidates and combinations;
- enabling the progression of potential new, safe, efficacious, shorter and affordable treatment solutions for TB patients worldwide, with the intent to improve the quality of life and life expectancy of TB patients;
- contributing to the development of a vibrant TB research environment in the EU, fostering private-public collaboration across EFPIA, academia, NGO's and SME's and strengthening the competitiveness and industrial leadership of Europe;
- providing a legal frame and agreement on IP terms and exploitation, as a paradigm of public and private international collaboration in the development of combination regimes;
- implementing agreement with other consortia facilitating prompt data sharing and data exploitation to accelerate TB drug regimen development.

In addition, the following additional exploitation⁵³/dissemination⁵⁴ obligations must be considered to maximise impact: the applicant consortium is expected to have a strategy on the translation of the relevant project outputs into regulatory, clinical and healthcare practice. These strategies aim to ensure fast access and uptake in high TB burden countries to secure maximum impact on the TB epidemic.

A plan for interactions with regulatory agencies/health technology assessment bodies with relevant milestones and resources allocated should be proposed to ensure, for example, qualification advice on the proposed methods for novel methodologies for drug development.

The major outputs of the proposed activities, such as innovative clinical trial designs, biomarker evaluation and the evaluation of novel technologies to monitor and enhance adherence must be disseminated in peer-reviewed open access journals. Any clinical trial simulation created must be made available via an open access platform to external researchers beyond the lifetime of the funded action.

Clinical samples must be made available to researchers outside the consortium and beyond the lifetime of the consortium through a sustainable biobank.

In their proposals, applicants should outline how the proposed activities will:

- manage research data including use of data standards and a fully developed strategy for FAIR storage and access to data and models beyond the lifetime of the consortium;⁵⁵
- disseminate, exploit, and sustain the project results. This may involve engaging with suitable biological and medical sciences research infrastructures;⁵⁶
- communicate the project activities to relevant target audiences.

⁵³ Article 28.1 (Additional exploitation obligations) of the IMI2 Grant Agreement will apply

⁵⁴ Article 29.1 (Additional dissemination obligations) of the IMI2 Grant Agreement will apply

⁵⁵ Guidance on data management is available at http://ec.europa.eu/research/participants/docs/h2020-funding-guide/cross-cutting-issues/open-access-data-management/data-management_en.htm

⁵⁶ <http://www.corbel-project.eu/about-corbel/research-infrastructure.html>

Potential synergies with existing consortia

Synergies and complementarities should be considered with relevant national, European and non-European initiatives (including suitable biological and medical sciences research infrastructures⁵⁷) in order to incorporate past achievements, available data and lessons learnt where possible, thus avoiding unnecessary overlap, and duplication of efforts and funding. Applicants should specifically consider synergies with partnerships that have existing TB clinical trial networks, TB drug discovery consortia, or with relevant not-for-profit organisations in the field.

The funded project is also expected to seek collaboration and establish a data-sharing framework agreement with the TB Drug Translational Development Collaboration (**TDTDC**) to ensure complementarity and sharing of results particularly with regards to efficacy, safety and experimental biomarkers.

Industry consortium

The industry consortium is composed of the following EFPIA partner(s):

- GlaxoSmithKline Investigación y Desarrollo S L (co-lead)
- BioMérieux
- Janssen Pharmaceutical
- Otsuka Pharmaceutical Europe Ltd.

In addition, the industry consortium includes the following IMI2 JU Associated Partner(s)

- Deutsches Zentrum für Infektionsforschung (DZIF) (co-lead)
- Klinikum of the Ludwig-Maximilians-Universität München (KUM)

The industry consortium (EFPIA and Associated Partners) plan to contribute the following expertise and assets:

- **NCEs portfolio.** To ensure a working portfolio of ten assets, it is anticipated that EFPIA and Associated Partners will contribute a substantial number of assets to the pipeline to mitigate potential compound attrition. It is expected that in the region of eight NCEs will be made available to the consortium in the first year, consisting of ATPsynthase inhibitors, Nitroimidazoles, Decaprenylphosphoryl- β -d-ribose 2'-epimerase (Dpre1) inhibitors, b-lactams, Leucyl-tRNA synthetase (LeuRS) inhibitors and cholesterol catabolism inhibitors. Approximately seven additional NCE's may be included the years that follow, with at least four additional mechanisms of action including novel oxazolidinones, protein synthesis inhibitors, transcriptional repressors affecting the metabolism of medicines and new generation ATP synthase inhibitors. Molecules may become available via EFPIA members and/or IMI2 JU Associated Partners, (i.e. TB Alliance, Gates MRI) in other AMR Accelerator projects, e.g. ERA4TB, or through other initiatives. Selection of molecules will be subject to due diligence by the governance bodies of the consortium. For further information on the existing portfolio of TB assets please refer to the working group on new TB drugs (www.newtbdrugs.org).
- The Sponsor for each clinical trial within the consortium will be chosen from among the asset owners contributing NCEs to a study and will assume all legal and regulatory Sponsor accountabilities. In this capacity Sponsors will retain full responsibility only for the investigation and reporting of SUSARs and serious GCP breaches occurring within a trial. Other pharmacovigilance responsibilities will be agreed at the second stage of application.

⁵⁷ <http://www.corbel-project.eu/about-corbel/research-infrastructures.html>

- EFPIA members and Associated Partners will provide expertise and advice on core clinical trial activities and minimum standards expected as outlined in relevant regulatory guidelines which will be the responsibility of the applicant consortium including, but not limited to:
 - Clinical: protocols and informed consents, for data collection and quality management, privacy, reporting and disclosure. Minimum standards for monitoring and audit plans;
 - Statistical analysis plans and quality control processes;
 - Provision of regulatory documents such as investigator brochures and IMPD will be provided by asset owners. Asset owners will also be responsible for the creation of annual regulatory reporting for each asset (INDSR, DSUR, PSRI) using data provided by the applicant consortium. Asset owners will provide guidance on the construction of regulatory packages;
 - Pharmacovigilance: requirements for safety reporting within trials;
 - Laboratory and imaging: requirements for assay standardisation/imaging protocol standardisation, results reporting and quality control and assurance. Legal obligations for tracking of human biological samples;
 - Clinical pharmacology: standards for model building, quality assurance and reporting;
 - Sample collection and banking protocol and standards for biomarkers and diagnostics. Assay protocol, reagents and equipment standardisation. Collaboration with applicants regarding selection of biomarkers and their validation/approval from regulatory agencies
 - Investigational product: requirements for storage, transport, tracking and destruction of investigational product (both NCEs and licensed medicines);
 - Agreements and contracting: requirements for transfer of Sponsor responsibilities, and compliance with relevant European regulations and legislation when contracting third parties or vendors.

Contribution of Data by industry and associated partners as “in-kind”

During the funded action, members of the industry consortium plan to contribute scientifically relevant activities for generating data/collecting samples in prospective activities that are part of broader clinical studies initiated independently of the Action. Certain of these studies activities, relevant to the Action and necessary for achieving its objectives, will be included in the project’s Description of the Action but solely carried out by the contributing member of the industry consortium. The introduction of the data constitutes an in-kind contribution which entails access rights to these project results in line with IMI2 JU IP rules. The estimated in-kind contribution for the prospective activities to generate these data and samples will constitute a substantial proportion of the EFPIA-based in-kind contribution.

The prospective data and samples are planned to include preclinical and clinical studies with assets from the EFPIA partners that will be carried out to prepare assets to be potentially included as part of the UNITE4TB asset pipeline. These data and samples are essential for achieving all the objectives of the project as they will provide a basis for inclusion of compounds within the studies and access to data on the disease per se. Significant scientific contributions are also being delivered in the other pillars of the AMR accelerator and outputs from these activities are transferable to this project.

Indicative duration of the action

The indicative duration of the action is 84 months.

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

Indicative budget

The financial contribution from IMI2 JU is a maximum of EUR 92 500 000.

The indicative in-kind from EFPIA partners and IMI2 JU Associated Partner(s) is EUR 92 500 000.

This contribution comprises an indicative EFPIA in-kind contribution of EUR 62 500 000 and an indicative IMI2 JU Associated Partner(s) in-kind contribution EUR 30 000 000.

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

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

Expertise and resources expected from applicants at stage 1

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

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

Applicant consortia wishing to include their own NCE(s) will be subject to the same governance and acceptance criteria as other assets in the existing portfolio as determined by the decision-making bodies within the consortium. Any NCE brought into the consortium must be novel and clearly differentiated from any asset existing in the funded action pipeline according to guidelines proposed by the governing bodies. Applicants consortia may refer to the expected NCEs portfolio under industry contribution,

- **Innovative clinical trials.** Applicant consortia should include experienced TB investigators and sites with proven trial capacity (the number of sites should be limited to a reasonable number to facilitate management and coordination), capitalising on sites from previously established European networks, or from sites within endemic countries outside of Europe. The consortium should not attempt to set up a trial network *de novo* nor attempt to build capacity at sites with no previous TB clinical trial experience. Quality of data generated by the trials must be adequate for inclusion in a regulatory file, delivered in a timely fashion, and with appropriate cost efficiencies. The consortium may subcontract specific activities to CROs to seek for efficiency or additional expertise. Applicant consortia must have the expertise needed to execute and collect and analyse efficacy and safety data from an EBA study and for the analysis of data from phase 2B/C efficacy and relapse studies;
- **Innovative Biomarkers.** Expertise in the implementation of previously-identified biomarkers and regulatory buy-in for the proposed biomarker validation framework;
- **Clinical trial simulation.** Experience in building clinical trial simulations and regulatory qualification. Understanding of regulatory requirements for model specification and interrogation, with a specific understanding of the issues around black-box versus white-box approaches. Any AI/ML algorithms deployed to prioritise regimens and/or to predict sterilising cure should be complementary to existing mechanistic models;
- **Artificial Intelligence/Machine Learning (AI/ML)** The applicant consortia should have access to AI/ML expertise and its application in drug development/clinical trials;
- **Digital Health Technologies** The applicant consortia should have knowledge of digital health tools/technologies and expertise in deployment in resource-poor settings;
- **Pharmacogenomics** The applicant consortia should have expertise in pharmacogenomic techniques, collection, assay and analysis techniques.

This may require mobilising, as appropriate the following expertise:

- Experience in running clinical trials of a standard sufficient to support inclusion in a regulatory file in the field of TB. Including a deep understanding of relevant clinical trial guidelines, regulations and legislation and previous experience of engagement with the EMA and FDA;
- Expertise in analysis and interpretation of relevant biomarker modalities, including, but not limited to, the host response, bacterial antigens and radiology;

- Operational expertise in the transport and management of clinical trial supplies and human biological samples;
- Understanding of scientific and regulatory requirements for biomarker validation and qualification, appropriate to build a plausible validation/qualification strategy acceptable to the EMA and FDA, including an awareness of the scientific and regulatory issues relating to clinical trial simulations;
- Expertise in digital health technologies relevant to treatment adherence;
- Pharmacogenomic expertise in the collection of host DNA, and the ability to sequence and identify relevant pharmacogenomic variations in different populations. Ability to de-identify data and to store it in compliance with relevant guidelines and legislation. Ability to analyse genomic data and correlate this to drug PK and trial endpoints;
- GCP, GDPR, ethics, legal and data privacy expertise.

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

- Access to historical data archived by Critical Path to TB Drug Regimens (CPTR).

Considerations for the outline of project work plan

In their stage 1 proposals applicants should

- give due visibility to data management; dissemination, exploitation and sustainability; and communication activities. This should include the allocation of sufficient resources for these tasks which will be further developed in the stage 2 proposal;
- present a strategy for ensuring the translation of the project results to drug development: a key deliverable will be qualification advice from the EMA and FDA for the biomarker validation strategy.

Suggested architecture

The applicant consortium is expected to have a structure that address the following areas:

Administration. In view of the complexity and size of the action, the applicant consortium should make provisions for project management, general administration (including project co-ordination, communication strategy for consortium partners and between consortia, meeting management), compliance with IMI requirements (reporting and financial audit), including a suitable mechanism to adjust funding for clinical sites based on successful recruitment strategies. Applicants should refer to reflection paper EMA/121340/2011 [8].

Compliance and quality control. Compliance with relevant guidelines and regulations (ICH GCP, European Clinical Trial Directive, GDPR, human biological sample tracking and other sponsor obligations), selection of trial Sponsor, pharmacovigilance and safety reporting, mechanisms for oversight, clinical data quality, laboratory/radiological assay standardisation and internal and external quality control strategy, management of clinical trial supplies/investigational product. Applicants should refer to reflection paper EMA/121340/2011[8].

Clinical trial design. Co-ordination of regulatory activities and designs with **IMI2 JU Call 15 topic 1: EU-PEARL**, protocol development, statistical analysis and quality plans, publication plans.

Clinical operations. Implementation of consortium strategies for compliance and quality assurance, site selection (including provisions for flexible allocation of resources by recruitment rate) and set-up, logistics plans (transport of samples and consumables), equipment purchase, preparation of regulatory and ethics packages, annual regulatory and ethics reports, training of monitors and sites, creation of site files, creation/review of clinical and laboratory SOPs, and evaluation of innovative technologies for adherence.

Biomarkers. Create biomarker validation strategy, create infrastructure for transfer of samples and data between consortium partners, validate biomarkers against relapse endpoint and report results, create clinical trial simulation, prepare package for FDA/EMA biomarker qualification.

In addition, applicants should consider a suitable structure that incorporates all of the other Innovative key deliverables.

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

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

Decision-making. Following the first stage of the IMI2 JU Call process and selection of partners to receive IMI2 JU funding, it is expected that the consortium preparing the full proposal for the second stage of the IMI2 JU Call process will agree on a robust decision-making process (including escalation procedures) for progression of different NCEs, combination regimens and biomarkers. Overall plans and go/no-go milestones will be established during the stage 2 application that will assist in the decision-making process to help ensure that the overall portfolio remains dynamic and work on NCEs is appropriately prioritised across the portfolio. For the avoidance of doubt, any decisions directly affecting an existing NCE shall always require the consent of the NCE owner.

Such decisions will be made by a committee that includes representatives from all project partners. The composition of this committee will be detailed and agreed by all partners in the Consortium Agreement. A fair and efficient decision-making process will be presented in the full proposal at the second stage of the IMI2 JU Call process. This committee will track the progress of the project against its own internal milestones and will be empowered (to be outlined in the Consortium Agreement) to make progression/termination decisions based on pre-agreed go/no go milestones in a regular, streamlined, single-meeting process. The decision-making process by the committee may result, in case of a 'no-go' decision, in the recommendation from the committee/consortium to IMI2 JU for terminating the grant based on Art. 50.3.1 (h) of the IMI2 JU MGA. The final decision on project continuation or termination will be taken by IMI2 JU in line with the provisions of the Grant Agreement. However, the JU may also make such a decision without prejudice to any decision-making process at the level of the consortium, that is, even without the aforementioned recommendation.

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/Associated Partners, 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 EFPIA co-project leader from among EFPIA beneficiaries/Associated Partners shall facilitate an efficient negotiation of the required legal consortium agreement. Project content and science shall jointly be facilitated by both co-project leaders.

All beneficiaries are encouraged to discuss the project architecture and governance and the weighting of responsibilities and priorities therein.

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

Dissemination, exploitation and sustainability of results

In their stage 2 proposal, applicants must provide a draft plan for dissemination and exploitation, including sustainability of results. A full plan as a distinct deliverable must be delivered within the first 6 months of the project.⁵⁸, and updated during the project lifetime. It could include identification of:

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

⁵⁸ As an additional dissemination obligation under Article 29.1 of the IMI2 Grant Agreement will apply

Sufficient resources should be foreseen for activities related to dissemination and exploitation, including the plan for the sustainability of the project results. This may involve engaging with suitable biological and medical sciences Research Infrastructures (RIs).⁵⁹

Communication

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

References

- [1] World Health Organization. *Global Tuberculosis Report 2018*. Geneva; World Health Organization (2018). <http://apps.who.int/iris>
- [2] A. H. Diacon, R. Dawson, et al. Randomized dose-ranging study of the 14-day early bactericidal activity of bedaquiline (TMC207) in patients with sputum. *Antimicrobial Agents and Chemotherapy* Volume 57, Issue 5, Pages 2199–2203 (2013). <https://doi.org/10.1128/AAC.02243-12>
- [3] S. H. Gillespie, A. M. Crook, et al. Four-month moxifloxacin-based regimens for drug-sensitive tuberculosis. *New England Journal of Medicine* Volume 371, Issue 17, Pages 1577–1587 (2014). <https://doi.org/10.1056/NEJMoa1407426>
- [4] A. Jindani, T. S. Harrison, et al. High-dose rifapentine with moxifloxacin for pulmonary tuberculosis. *New England Journal of Medicine* Volume 371, Issue 17, Pages 1599–1608 (2014). <https://doi.org/10.1056/NEJMoa1314210>
- [5] F. von Groote-Bidingmaier, R. Patientia R, et al. Efficacy and safety of delamanid in combination with an optimised background regimen for treatment of multidrug-resistant tuberculosis: a multicentre, randomised, double-blind, placebo-controlled, parallel group phase 3 trial. *Lancet Respiratory Medicine* Volume 7, Issue 3, Pages 249–259 (2019)
- [6] P. P. J. Phillips, K. E. Dooley, et al. A new trial design to accelerate tuberculosis drug development: The Phase IIC Selection Trial with Extended Posttreatment follow-up (STEP). *BMC Medicine* Volume 14, Issue 1, Pages 1–11 (2016). <https://doi.org/10.1186/s12916-016-0597-3>
- [7] M. Quartagno, A. S. Walker, et al. Rethinking non-inferiority: a practical trial design for optimising treatment duration. *Clinical Trials* Volume 15, Issue 5, Pages 477–488 (2018). <https://doi.org/10.1177/1740774518778027>
- [8] European Medicines Agency. Reflection paper on ethical and GCP aspects of clinical trials of medicinal projects for human use conducted outside of the EU/EEA and submitted in marketing authorisation applications to the EU Regulatory Authorities

⁵⁹ <http://www.corbel-project.eu/about-corbel/research-infrastructures.html>

Topic 4: Tumour plasticity

Topic details

Topic code	IMI2-2020-20-04
Action type	Research and Innovation Action (RIA)
Submission and evaluation process	2 stages
IMI2 JU Strategic Research Agenda - Axis of Research	Innovative medicines
IMI2 JU Strategic Research Agenda - Health Priority	Cancer

Specific challenges to be addressed by public-private collaborative research

The last decade has seen tremendous advances in the development of effective targeted therapies as well as in immuno-oncology to more effectively treat cancer. Despite this, cures are still rare in the metastatic setting. In most cases, an initial response to treatment is followed by the eventual emergence of **drug resistance** [1]. Drug resistance in cancer is one of the greatest causes of mortality, and despite increasing success with targeted therapies in the clinic (including immunotherapy), the mechanisms by which cancer cells evade cell death are still not well understood. Drug combinations are likely to be critical to overcoming drug resistance but are dependent on identifying the cellular programmes that cancer cells use to resist therapeutic agents.

In tumours that initially respond to treatment, rare cancer cells can survive and withstand therapy (**'drug tolerant persister' cells, DTPs**) and can act as a reservoir for the eventual emergence of drug resistance (**Figure 1**) [2]. Furthermore, these studies have shown that these cells are able to survive drug treatment by altering the transcriptional state of specific signalling pathways, and that in the early stages such changes are plastic and reversible, but that over time these changes become stable and fixed.

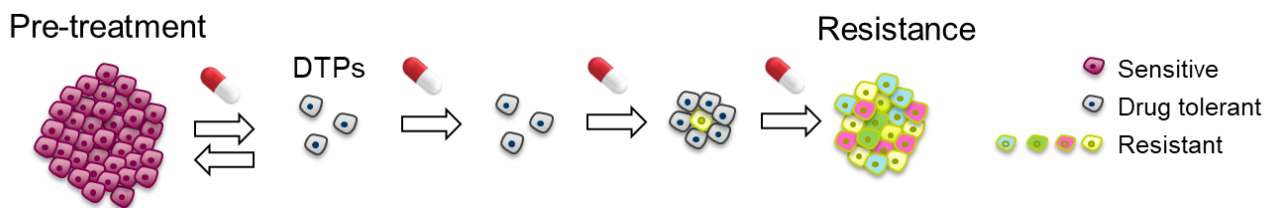


Figure 1. Diagram showing how drug tolerant persister cells (DTPs) arise from the bulk tumour following successful treatment, and ultimately contribute to the emergence of drug resistance.

Recent technological advances in **single-cell sequencing** have revolutionised the study of individual cells within cancer populations and, importantly, would allow the characterisation of DTPs, something previously impossible with bulk sequencing technologies [3]. Single-cell sequencing provides information that is not confounded by genotypic or phenotypic heterogeneity of bulk samples. Importantly, it has confirmed the existence of DTPs in patients following treatment response and, more importantly, the characterisation of the transcriptionally altered pathways in DTPs [2][4]. Characterising the transcriptionally altered pathways in persister cells, the biological processes they regulate and their druggability will be critical to **future drug combination strategies**, with the goal of preventing or significantly delaying the development of drug resistance.

There are numerous challenges in applying single cell sequencing to drug resistance- arguably one of the most important barriers to curing cancer today, and specifically:

- defining best sequencing protocols – single-cell RNA-sequencing (scRNA-seq) is a fast-moving field with a recent benchmarking paper comparing 13 different methods [5];
- computational approaches to big data – as with sequencing methods, the analysis framework is constantly evolving and there are challenges in integrating data across studies and platforms;
- standardisation of data formats;
- best practice single cell collection from *in vitro* and *in vivo* model systems;
- application of single-cell sequencing to clinical samples;
- spatial imaging technologies;
- biological interpretation of data, including novel target identification.

This topic proposes to apply state-of-the-art single-cell sequencing technologies to characterise cancer cell populations pre-treatment, at minimal residual disease (for DTPs), and upon the acquisition of drug resistance and from a variety of pre-clinical human and mouse models as well as clinical samples.

Scientific advances in single-cell sequencing, use of patient-derived xenografts (PDX) and patient-derived organoids (PDO), and clinical tissue imaging have come together to create the perfect environment to address one of the most important challenges in cancer biology today: **drug resistance**. Each of these areas is a rapidly advancing field and, importantly, no single sector has complete expertise in all these areas. Additionally, the collection and sorting of cells in a standardised way is well-aligned with the capabilities of industry partners and is an activity that academic groups are typically not well set up to deliver at scale. Conversely, the techniques for evaluating single cells and the computational methods for interpretation of data are under constant development (mainly in academic labs). Finally, industry partners are ideally placed to interrogate different drug mechanisms against common tumour backgrounds (or vice versa). Taken together, these factors provide a compelling opportunity for private-public collaboration.

Therefore, to address such a wide range of complex issues, there is a need for strong cooperation amongst industry, biotechnology companies, academia, and patient organisations, bringing their diverse expertise in the following fields:

- acquisition of single-cells from pre-clinical and clinical models;
- adoption of best single-cell sequencing practice;
- standardisation of analytical methods, including data integration across studies;
- application of scRNA-seq to characterise non-malignant cells in the tumour microenvironment;
- spatial transcriptomics and imaging techniques;
- development of protocols for clinical single-cell sequencing.

This Call topic is an ideal opportunity to systematically address how viewing a patient's cancer not as a single homogeneous entity but rather as a population (containing diverse subpopulations with different behaviours) might ultimately alter the paradigm of drug resistance.

The strategic relationship between leading scientists and key opinion leaders in industry, small and medium-sized enterprises (SMEs) and academia will enable a better understanding of drug development post-novel target identification, and increase the likelihood of spin-off projects based on the better understanding of DTP biology.

Scope

The overall objective of the Call topic is to use state-of-the-art single-cell sequencing to understand and overcome drug resistance in cancer by **characterising the biology of drug tolerant persister cells**, building the capability for such studies across Europe.

The call topic will address primarily adult tumours, with the provision to include childhood tumours where appropriate models are available at a later stage of the programme. To optimise our ability to determine the role of tissue lineage on the biological processes observed in single-cells, we propose that the majority (>80 %) of the single cells should be provided from drug treatments in 3 adult cancers:

- non-small cell lung cancer (NSCLC);
- breast cancer;
- colorectal cancer.

Each industry partner will nominate five tumour types/drug treatments aligned to the tumour areas summarised above and it is expected that nomination of study systems will be in consultation with academic consortium partners. Upwards of 20 % of the studies can be proposed in tumour types in addition to these 3 core cancers, including childhood cancers.

We anticipate that most of the single cells from the models described above will be provided by the industry partners, while the academic consortium will provide expertise in single-cell sequencing and data analysis.

To facilitate data integration across studies, it is preferable to use a small number of sequencing technologies that are complementary, well supported and widely used, and which are able to analyse large numbers of single cells versus smaller number of cells at greater depth of coverage. For these reasons, the Chromium (10X Genomics) [6] and Smart-Seq2 [7] platforms are preferred as the main complementary single-cell sequencing technologies used for the implementation of the proposed activities. These are mature, commonly used protocols that have been extensively benchmarked.

The goals of the Call topic are:

- To characterise the biology of Drug Tolerant Persister cells - defining the signalling pathways and cellular processes that enable DTPs to survive drug treatment and thereby identify novel drug targets to overcome this – using state-of-the-art single-cell sequencing and spatial transcriptomics in a range of cancer models.
- To better understand the tumour microenvironment – to avoid solely focusing on cell intrinsic drug resistance programmes, a key element of the work packages should be to use spatial imaging techniques to explore the interaction between cancer cells and the microenvironment.
- Generation of single cell RNAseq data from adult and childhood cancers – although the pre-clinical models used to explore the biology of drug treatment in cancer are predominantly based on adult cancers, drug resistance is equally a major problem in childhood tumours. The applicants should anticipate that from year 3 of the funded project, specific childhood cancers (up to 20 % of the total studies proposed) could be considered for inclusion where the appropriate models are accessible and where there is a hypothesis relationship with drugs or tumours being investigated by the consortium. To develop best practice in clinical validation and single-cell sequencing – clinical validation will be key to translation of any findings and a change in clinical practice. To include informed patient consent forms that cover all intended uses, including clinical outcome data and sharing of data inside the consortium and with 3rd parties. General Data Protection Regulation (GDPR) compliant tracking of patient data, samples and PDXs.
- To create gold standard protocols for single cell collection – across a range of models and to include differing methods for isolating single cells from human (organoids, clinical biopsies) and mouse (PDX, genetically engineered mouse models (GEMM) and syngeneic mice) model systems.

- To develop core analytical methods – use pre-treatment, on treatment and post-treatment single-cell sequencing data to develop novel computational approaches to identify the different subtypes of cancer cells present, and the biological processes that are complicit in maintaining their survival following drug treatment.
- To build EU capability in single-cell sequencing – in the process of developing the protocols for single cell collection, sequencing and analysis, the funded project will put in place infrastructure to enable other groups in the EU to carry out similar single-cell sequencing studies in both cancer and non-cancer models.

Importantly, despite the fact that over the five years of the funded project we expect to adopt new technologies as and when they are developed and where they demonstrate significant advantages over current protocols, the goal of this Call topic is not the explicit development of such new methods and technologies *per se*. Additionally, we do not expect all of the drug-tumour combinations for study to be fixed at the outset. This will emerge as the industry partners identify agents and systems for study and will be managed by a consortium portfolio review process.

Expected key deliverables

The expected key deliverables should include the following:

Deliverable 1: Benchmarked and standardised protocols for single cell identification and collection from PDX/PDO models.

Deliverable 2: Gold standard methods for tissue-based spatial imaging. To include pre-clinical models as well as clinical samples for validation in relevant patient populations.

Deliverable 3: Multi-omics methods for characterising single cells. Incorporate new technologies such as CITE-seq (single-cell RNA sequencing and cell surface antibody expression), combined ATAC-seq/scRNA-seq and single-cell metabolomics protocols.

Deliverable 4: DTPs and metadata/annotation from human and mouse models. Provision of single cells from various time points (pre-treatment, on treatment and tumour progression) in (typically) 3-6 models per cancer type, and including pre-clinical (PDO, PDX, GEMM and syngeneic models) and clinical samples. Additional models from non-industry partners will also be permitted.

Deliverable 5: State-of-the-art analysis methods of single-cell sequencing. Define regulatory networks from transcriptional data as well as druggability of relevant targets and identify novel drug combinations to prevent the emergence of DTPs following treatment in the relevant cancers.

Deliverable 6: Single-cell measurement data combined with treatment and outcome data / clinical outcome data.

Deliverable 7: Gold standard methods for the validation of key transcriptional changes. To validate transcript(s) implicated in DTP biology using spatial imaging techniques applied to treated patient samples and combining CRISPR screens with scRNA-sequencing.

Deliverable 8: Tools to allow cross-study analyses of single-sequencing data. Develop novel methods and software packages to combine data across multiple studies for enhanced power and to detect novel biology not otherwise revealed by single study analyses.

Deliverable 9: A raw data repository with access for all consortium partners. A repository for data (measurement raw data, preclinical treatment and outcome data and clinical treatment and outcome data) with granular access rights that supports quality control and data queries in line with access and intellectual property (IP) rights according to the IMI2 JU Grant Agreement rules and as specified in the consortium agreement. The proposal should outline how sustainability of data access will be ensured. Where patient data is generated or used, this will be integrated across studies in a legally and ethically compliant way, including any GDPR requirements.

Deliverable 10: White paper on single-cell sequencing to characterise DTP biology.

Expected impact

A comprehensive effort to prevent drug resistance in cancer is generally lacking at the present time. This topic proposes the use of state-of-the-art single-cell sequencing technologies to address this challenge across a number of the most prevalent cancer types, in both adult and childhood cancers.

A comprehensive database, profiling DTPs across a range of cancers and therapies would enable a deeper understanding of the biology of DTPs and allow cross-tumour studies.

Impact for patients:

- identification of novel drug targets in DTPs and resulting drug combinations that delay or prevent the emergence of drug resistance in cancer;
- better understanding of the contribution of tumour heterogeneity and plasticity to disease outcome, progression and relapse.

Impact for academia and SMEs:

- harmonisation of protocols for single cell experiments;
- enhanced infrastructure in the EU for single cell sequencing;
- development of gold standards for the analysis of single-cell sequencing data;
- access to comparative data on different pre-clinical and clinical models and better understanding of the biology of DTPs in cancer with a high likelihood of spin-off projects;
- improvements in single cell sequencing and spatial imaging with potential for commercial development;
- better understanding of drug development post-novel target identification.

Impact for industry:

- access to a data source for further functional studies (e.g. knock-out, knock-in, target perturbation) that will lead to opportunities for identification of novel targets in the DTP space - pointing to new targets or rational drug combinations that alter the drug resistance paradigm;
- access to single cell measurement data combined with outcome data (models) and clinical outcome data;
- development of expertise in the analysis of single-cell sequencing data;
- gold standard methods for the delivery of single cell projects.

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

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

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

- manage research data including use of data standards⁶⁰;
- disseminate, exploit, and sustain the project results; this may involve engaging with suitable biological and medical sciences research infrastructures⁶¹;
- communicate the project activities to relevant target audiences.

In addition, the following additional exploitation⁶²/dissemination⁶³ obligations must be considered to maximise impact:

- Quality control (QC), standardisation data and the agreed standardised operating procedures will be made publicly available as soon as possible;
- A mechanism needs to be proposed to ensure that input data and results generated by an industry partner working together with an academic partner are kept confidential until the dataset and experiment is complete. A process for release to the rest of the consortium will also be agreed;
- A mechanism needs to be proposed to enable third party access to results at the end of the action. A plan for aspects related to sustainability should be proposed, especially ensuring that the database remains accessible and facilitating its population with additional clinical outcome data. This can include a proposal for options transferring the open access database into an existing structure and should include realistic ideas for long-term financial and operational sustainability of the database;
- Any publications arising from the action need to link to an open access area of the consortium database to coincide with publication.

Potential synergies with existing consortia

Synergies and complementarities should be considered with relevant national, European and non-European initiatives (including suitable biological and medical sciences research infrastructures⁶⁴) in order to incorporate past achievements, available data and lessons learnt where possible, thus avoiding unnecessary overlap, and duplication of efforts and funding.

Key synergies with existing consortia that could be considered are:

- International programmes using single-cell sequencing to create reference maps of human cells (e.g. Cell Atlas programmes). In particular, dialogue with pre-existing working groups to develop standards in the generation and analysis of single-cell sequence data will be advantageous;
- Programmes that allow the inclusion of specific pre-clinical models would add value. Programmes directed towards developing an expanded range of adult and childhood cancer PDX models are particularly relevant;
- If aligned with the goals of the Call topic, programmes already collecting clinical samples for single-cell sequencing would be valuable as some of this data could be considered for integration.

⁶⁰ 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

⁶¹ <http://www.corbel-project.eu/about-corbel/research-infrastructure.html>

⁶² Article 28.1 (Additional exploitation obligations) of the IMI2 Grant Agreement will apply

⁶³ Article 29.1 (Additional dissemination obligations) of the IMI2 Grant Agreement will apply

⁶⁴ <http://www.corbel-project.eu/about-corbel/research-infrastructure.html>

Industry consortium

The industry consortium is composed of the following EFPIA partners:

- AstraZeneca (lead)
- Bayer
- Eli Lilly
- Transgene SA
- Merck KG
- Charles River

The industry consortium anticipates contributing the following expertise and assets:

- work package co-leadership;
- contribution to database / IT solutions and bioinformatic analyses;
- contribution to samples, metadata and curation and models.

In particular, industry partners will **contribute single cell samples from the relevant human and mouse tumour models** and therapies as well as access to the relevant clinical samples. It is anticipated that nearly all of these will be in-kind, rather than background contributions. (In-kind samples will be the results of studies specifically designed for this programme and carried out during in the frame and duration of the project; if background contributions are introduced, they could include validation sets of cells collected prior to this action commencing).

During the funded action, members of the industry consortium plan to contribute scientifically relevant activities for generating data on single cells or collecting and sorting single cells in prospective activities that are part of broader industry clinical studies. The relevant activities will be included in the project's Description of the Action and are necessary for achieving its objectives. The introduction of the data constitutes an in-kind contribution which entails access rights to these project results in line with IMI2 JU IP rules. The single-cell samples will be collected from drug treatment studies in pre-clinical mouse or human tumour models (PDO, GEMM or PDX samples). The industry partners will provide samples corresponding to approximately 80 drug/tumour combinations in total. Each study will aim to collect cells at three time points. A small proportion (<20 %) of study samples will be provided for spatial and multi-omic analysis. Submitting these samples to scRNAseq analysis is an essential activity of the project and the data derived will drive better understanding of the origin of DTPs.

Optionally, prospective data will be provided by industry partners, derived from scRNAseq analysis of PDO or PDX samples and subjected to the same bioinformatic analysis as above.

In addition to project leadership, industry partners' staff efforts are expected to be largely spent on work packages 1-4 and 7 (please refer to the suggested architecture).

Indicative duration of the action

The indicative duration of the action is 60 months.

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

Indicative budget

The financial contribution from IMI2 JU is a maximum of EUR 7 058 000.

The indicative in-kind contribution from EFPIA partners is EUR 8 500 000.

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

Expertise and resources expected from applicants at stage 1

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

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

This may require mobilising, as appropriate the following expertise:

Relevant technology companies, in particular SMEs, along with academic centres that have expertise in single-cell sequencing and analysis of sequencing data, as well as spatial transcriptomics, should be part of the successful consortium.

The size and budget allocation of the applicant consortia should reflect the expertise needed to achieve the proposed objectives within the indicated budget while ensuring the 'manageability' of the consortium as well as efficient and effective teamwork. Therefore, the number of members of the applicant consortium needs to be thoroughly justified in the proposal and all partners involved should make a significant contribution to the proposed work.

Specifically, the applicant consortium should be able to demonstrate (through publications, consortia leadership, local capability development, grants):

- the technical expertise to carry out single-cell sequencing using technology platforms that are mature, well-supported and widely used, as well as technical expertise in spatial transcriptomics techniques;
- expertise in the development of new versions of single cell technology, plus a demonstrated ability to evaluate and rapidly internalise new single cell techniques;

- expertise in parallel single-cell sequencing technologies that capture epigenome-transcriptome interactions e.g. scNMT-seq (chromatin accessibility, methylation and transcription sequencing) [8];
- expertise in the bioinformatics analysis of single-cell sequencing data, spatial transcriptomics, gene regulatory network reconstruction, and computational approaches to novel target identification;
- expertise in the data integration of single-cell RNA-seq datasets across multiple platforms, individuals, and centres [9];
- to support standardisation of data, adherence to the FAIR principles ('findable, accessible, interoperable and reusable') [10];
- where there is a proposal for the applicant consortium to provide single-cells for sequencing, it should demonstrate the ability to deliver single cells from the relevant human (clinical, PDO) and mouse (PDX, GEMM, syngeneic) tumour models and from pre-treatment and treated models, with fixation/storage as specified in the consortium SOPs. Applicants should demonstrate the feasibility of collecting the outlined number of samples based on selected cancer types/therapies (see Deliverables);
- ability to coordinate a large research initiative and to create a scientific network.

The applicant consortium is expected to set up a governance structure that includes the necessary project management skills suitable for the consortium and activities. This could be ensured by one of the publicly funded partners, who in this case would need to have significant project management and coordination skills as well as the necessary experience in supporting complex – per size and composition – consortia in IMI/EU funded projects.

Considerations for the outline of project work plan

In their stage 1 proposals applicants should:

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

Suggested architecture

The public partners are expected to carry out most of the sequencing work whereas industry partners contribute in kind in the form of single cells (collected specifically for this programme) so that work can be carried out centrally with clear streamlined processes. Both industry and public partners will collaborate in the analysis of the data. Steering of the individual work packages and content decisions will be done jointly by the public and private partners.

For clarity, there will also be an opportunity for non-industry consortium partners to provide samples from up to 20 drug/tumour combinations, assuming that the models are appropriate with a hypothesis relationship with drugs or tumours being investigated by the consortium as agreed by the portfolio management process.

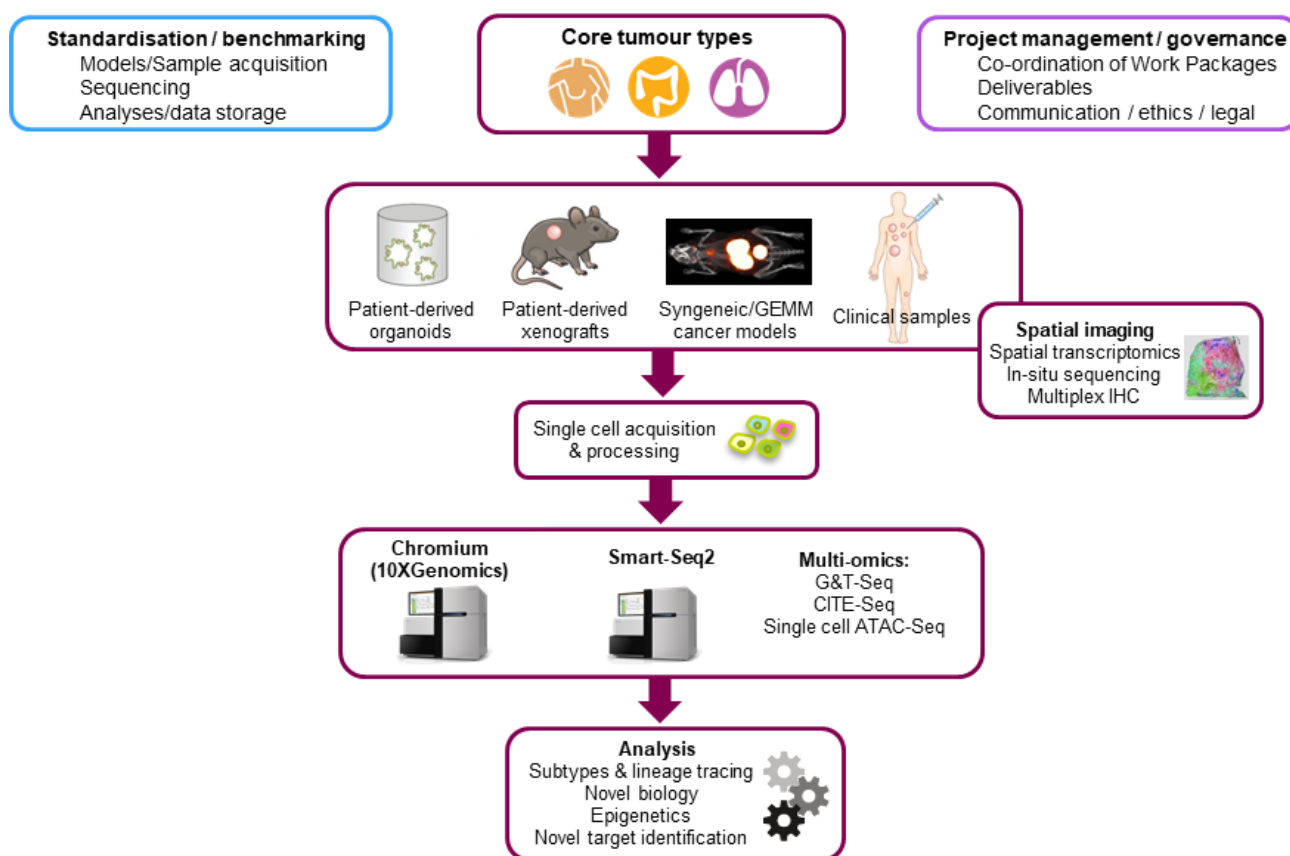


Figure 2. Work flow of the project. The various activities captured here form the basis for the 7 Work Packages detailed below.

Work Package 1 – Project management, coordination 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 the appropriate dissemination of the project progress and outcomes.

Industry contribution: Project leader, coordination across different work packages (including overall scientific and strategic oversight).

Expected applicant consortium contribution: Project coordinator, project management expertise.

Work Package 2 – Portfolio management, coordination and prioritisation

Description: To direct and support optimal project delivery across tumour types, ensuring sufficient overlap that results are interpretable without wasteful duplication. To provide a mechanism for the identification and integration of bespoke test systems so that they have maximal impact.

- **Proposed objectives:**

- set up a review and selection process for models to resolve duplication between tumour type/drug treatments and ensure quality and technical standards (as defined in WP3) are met;
- provide additional models– PDO, PDX, GEMMs or patient samples – complementary to the EFPIA set.

Industry contribution: Portfolio leader, technical advice on the quality of studies that are proposed. Portfolio management expertise. Allocation and prioritisation of studies in a transparent way. Allocation of time and resources for appropriate technical development.

Expected applicant consortium contribution: Portfolio coordinator, technical advice on the quality of studies that are proposed. Allocation and phasing/timing of studies.

Work Package 3 – Standardisation and benchmarking of standard operating procedures

Description: To ensure the standardisation and benchmarking of protocols, raw and meta-data used across the consortium, both for sequencing technologies and analytics.

Industry contribution: Knowledge of PDO, PDX, GEMM and syngeneic models.

Expected applicant consortium contribution: Expertise in single-cell sequencing protocols and current gold standard analysis techniques, including data integration across platforms and studies.

Work Package 4 – Single cell acquisition from models of tumour plasticity

Description: The acquisition of high-quality single cells from the relevant tumour models that are suitable for single-cell sequencing.

Industry contribution: Expertise in the use of biological models for single cell provision (PDO, PDX, GEMM, Syngeneic). Drug treatment regimes *in vivo*. Industry will be the source of most of the single cells for study.

Expected applicant consortium contribution: Knowledge of best practice for processing single cells. Methods to avoid batch effects in collection and processing. Provision of single cells from additional pre-clinical and clinical models where appropriate.

Work package 5 – Single-cell sequencing

Description: The generation of high quality single-cell sequencing data from single cells acquired from each study

- **Proposed objectives should include:**

- high quality single-cell sequencing data in a format suitable for data Integration across studies (see work package below), using complementary technology platforms that are mature, well-supported and widely used;
- specific single-cell sequencing technologies that address aspects of the epigenetic landscape of single cells (e.g. scATAC-seq) or cell surface protein expression (e.g. CITE-seq);
- evaluation and internalisation/uptake of new and emerging single cell techniques.

Industry contribution: Single-cell sequence data from internal platforms where available. Data upload and annotation from scRNAseq experiments.

Expected applicant consortium contribution: Expertise in single-cell sequencing, including alternate non-transcriptomic platforms (e.g. scATAC-seq, CITE-seq, G&T-seq) that are nominated to be included in specific studies. Expertise in evaluating new techniques and platforms. Data upload and annotation from scRNAseq experiments.

Work package 6 – Spatial imaging technologies

Description: To add spatial context to single-cell sequence data using a variety of spatial imaging technologies in order to validate the observed transcriptional changes from the single-cell sequencing studies, and to understand the value of adding spatial orientation to these single cell observations. Apply to clinical samples as well as relevant pre-clinical models.

Industry contribution: Collection and curation of material from pre-clinical models as well as clinically relevant patient samples for analysis.

Expected applicant consortium contribution: Expert labs in spatial imaging of protein and transcript expression at single cell resolution.

Work package 7 – Analytical methods & integration of single cell datasets

Description:

- a) To optimise/develop analytical methods and define the gold standard practice of single-cell sequencing data.
- b) The integration of single-cell RNA-sequencing data and metadata/annotation across multiple platforms (including epigenetic), individuals, and studies and in addition to transfer information between datasets and spatial methods. Ultimately, to enable a more comprehensive comparison of cell populations in complex biological systems.

- **Proposed objectives:**

- characterise the specific biological programs operative in Drug Tolerant Persister cells using single-cell sequencing datasets;
- integrate single-cell sequencing data across studies and technologies to capture common biological processes;
- identify novel drug targets.

Industry contribution: Pharma experience in novel target identification ligand affinity and druggability. IT expertise to support the data platform and analytics tools and ensure compatibility with industry requirements (e.g. FAIR requirements).

Expected applicant consortium contribution: Analysis expertise in single-cell sequencing data, both scRNA-seq as well as protocols addressing the epigenome. Expertise in data integration techniques, data storage solutions that allow interoperability. Academic experience in novel target ID.

Work package 8 – Communication/dissemination and ethics

Description:

- a) to ensure effective communication and dissemination both within the consortium during the action, as well as external communication as appropriate with external synergy partners and stakeholders;
- b) public engagement;
- c) where clinical samples are to be used, appropriate planning and execution of correctly consented studies with corresponding ethical oversight and approval.

We anticipate that both industry and academic consortium partners will need to take full ownership and participation in this work package.

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

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

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

Data management

In their stage 2 proposal, applicants should give due visibility to data management including use of data standards. A full 'data management plan' (DMP) as a distinct deliverable must be delivered within the first 6 months of the project. The DMP needs to be kept up to date with the needs of the project and as such be updated as necessary during its lifetime.⁶⁵

Dissemination, exploitation and sustainability of results

In their stage 2 proposal, applicants must provide a draft plan for dissemination and exploitation, including sustainability of results. A full plan as a distinct deliverable must be delivered within the first 6 months of the project⁶⁶, and updated during the project lifetime. It could include identification of:

- different types of exploitable results;
- potential end-users of the results;
- results that may need sustainability and proposed sustainability roadmap solutions.

Sufficient resources should be foreseen for activities related to dissemination and exploitation, including the plan for the sustainability of the project results. This may involve engaging with suitable biological and medical sciences research infrastructures (RIs).⁶⁷

Communication

⁶⁵ 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

⁶⁶ As an additional dissemination obligation under Article 29.1 of the IMI2 Grant Agreement will apply

⁶⁷ <http://www.corbel-project.eu/about-corbel/research-infrastructures.html>

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

References

- [1] Konieczkowski, D.J., Johannessen, C.M., and Garraway, L.A. (2018). A Convergence-Based Framework for Cancer Drug Resistance. *Cancer Cell* 33, 801-815.
- [2] Rambow, F., Rogiers, A., Marin-Bejar, O., Aibar, S., Femel, J., Dewaele, M., Karras, P., Brown, D., Chang, Y.H., Debiec-Rychter, M., *et al.* (2018). Toward Minimal Residual Disease-Directed Therapy in Melanoma. *Cell* 174, 843-855 e819.
- [3] Stuart, T., and Satija, R. (2019). Integrative single-cell analysis. *Nat Rev Genet.* <https://doi.org/10.1038/s41576-019-0093-7>
- [4] Shaffer, S.M., Dunagin, M.C., Torborg, S.R., Torre, E.A., Emert, B., Krepler, C., Beqiri, M., Sproesser, K., Brafford, P.A., Xiao, M., *et al.* (2017). Rare cell variability and drug-induced reprogramming as a mode of cancer drug resistance. *Nature* 546, 431-435.
- [5] Mereu, E., Lafzi, A., Moutinho, C., Ziegenhain, C., MacCarthy, D.J., Alvarez, A., Battle, E., Sagar, Grün, D., Lau, J.K., *et al.* (2019). Benchmarking Single-Cell RNA Sequencing Protocols for Cell Atlas Projects. bioRxiv <https://www.biorxiv.org/content/10.1101/630087v1>
- [6] Zheng, G.X., Terry, J.M., Belgrader, P., Ryvkin, P., Bent, Z.W., Wilson, R., Ziraldo, S.B., Wheeler, T.D., McDermott, G.P., Zhu, J., *et al.* (2017). Massively parallel digital transcriptional profiling of single cells. *Nat Commun* 8, 14049.
- [7] Picelli, S., Faridani, O.R., Bjorklund, A.K., Winberg, G., Sagasser, S., and Sandberg, R. (2014). Full-length RNA-seq from single cells using Smart-seq2. *Nat Protoc* 9, 171-181.
- [8] Clark, S.J., Argelaguet, R., Kapourani, C.A., Stubbs, T.M., Lee, H.J., Alda-Catalinas, C., Krueger, F., Sanguinetti, G., Kelsey, G., Marioni, J.C., *et al.* (2018). scNMT-seq enables joint profiling of chromatin accessibility DNA methylation and transcription in single cells. *Nat Commun* 9, 781.
- [9] Adey, A.C. (2019). Integration of Single-Cell Genomics Datasets. *Cell* 177, 1677-1679.
- [10] Wilkinson, M.D., Dumontier, M., Aalbersberg, I.J., Appleton, G., Axton, M., Baak, A., Blomberg, N., Boiten, J.W., da Silva Santos, L.B., Bourne, P.E., *et al.* (2016). The FAIR Guiding Principles for scientific data management and stewardship. *Sci Data* 3, 160018.

Topic 5: Proton versus photon therapy for oesophageal cancer – a trimodality strategy

Topic details

Topic code	IMI2-2020-20-05
Action type	Research and Innovation Action (RIA)
Submission and evaluation process	2 stages
IMI2 JU Strategic Research Agenda - Axis of Research	Adoption of innovative clinical trial paradigms
IMI2 JU Strategic Research Agenda - Health Priority	Cancer

Specific challenges to be addressed by public-private collaborative research

Alongside chemotherapy and surgery, radiotherapy (RT) has evolved to become one of the essential therapies for the treatment of cancer. However, radiotherapy is not suitable for all cancer types, and when used, the potential for negative side effects to surrounding organs can limit the dose administered leading to longer treatment times and reduced effectiveness. By delivering a high radiation dose, more precisely focused on the tumour site, proton therapy (PT) has the potential to reduce these adverse events and provide better outcomes for cancer patients.

Although the number of patients treated annually with PT is increasing, the clinical evidence supporting its effectiveness remains limited due to the lack of large multi-centre studies. There is a critical need [1] for high quality evidence from multi-centre trials to determine the potential role of PT for various cancer indications and to allow a consensus to be reached across Europe on the most suitable indications.

A robust evidence base on the effectiveness of PT has the potential to open a new treatment modality for cancers with currently very low survival rates, for example oesophageal cancer. Oesophageal cancer is the seventh most common cancer worldwide, with more than 570 000 new cases per year leading to more than 500 000 cancer deaths annually [2]. Until recently, surgery was the main treatment for patients with localised disease. In 2012, the results of the Chemoradiotherapy for Oesophageal Cancer Followed by Surgery Study (CROSS) randomised trial demonstrated that adding neoadjuvant chemo-radiation to surgery results in a beneficial effect on pathological complete response (pCR) and survival compared to surgery alone [3][4]. However, with a pCR of 30 % and a five-year overall survival rate of 45-50 %, there is still a large unmet need.

The unique properties of PT allow oesophageal cancer patients the opportunity to receive more conformal radiotherapy with the possibility of reducing the dose to the surrounding normal organs including the lungs, heart and liver [5][6]. Treatment of oesophageal cancer patients with PT is under evaluation by several institutions. Recent publications present the role and the potential benefits PT offers to those patients [7][19] and could lead to better patient outcomes. Nevertheless, none of those publications provide level 1 evidence.

To build a robust evidence base to assess the potential of PT in oesophageal and other cancers, multi-centre international trials have to take place. The current diversity of reimbursement and coverage policies across the EU makes these trials difficult. A public-private collaboration of proton therapy oncologists, treatment centres, software developers and equipment manufacturers is needed to define a methodology to conduct clinical trials in PT at a European scale. In addition, a key factor is the generation of robust clinical evidence which is neutral and unbiased. A clinical trial conducted in a European framework, in a collaboration between industry and public partners, has an inherent degree of independence and neutrality required by the highest standards of clinical research.

Scope

The main objective of this topic is to examine the value of proton therapy as a treatment modality through a clinical study in oesophageal cancer. The study will compare outcomes between pencil-beam scanning proton therapy and intensity-modulated radiation therapy (IMRT). The study will determine if proton therapy in a trimodality (radiotherapy-chemotherapy-surgery) treatment;

- (i) reduces treatment-related cardio-pulmonary toxicity;
- (ii) increases loco-regional tumour control and pathological complete response and the influence of dose escalation;
- (iii) improves disease-free and overall survival.

Oesophageal cancer is chosen due to its relatively high occurrence in the population and the possibility to extend findings to other cancer types.

A second objective is to use the evidence generated during the oesophageal cancer study to reach a consensus on which methodology is most suitable to evaluate PT treatment for other indications. To facilitate this objective, cost-effectiveness data should be collected during the duration of the action. This objective should be supported by engaging with selected stakeholders as advisors such as the broader oncology community including oncologists (e.g. through relevant European networks), healthcare providers, health technology assessment (HTA) agencies, payers, and patient associations. In addition, the findings of the proposed project should be disseminated via publications, presentations at relevant conferences, and other suitable dissemination methods.

Expected key deliverables

To achieve the objectives, the proposed project should deliver:

- A **study protocol** for a non-blinded multi-centre randomised phase III study on a statistically significant number of oesophageal cancer patients. Patients should be treated with pre-operative concomitant chemo-radiation and randomised between irradiation to be delivered as either RT or PT. This protocol should include a rapid, clinically relevant primary endpoint to allow effectiveness to be demonstrated as early as possible.
- **Annual updates** on the progress of the study to include:
 - recruitment reports;
 - data collection reports;
- A final **dataset** collected in compliance with the FAIR principles;⁶⁸
- A proposal for a European methodology for multi-centric clinical trials in proton therapy;
- Publications & conference presentations on the results of the study;
- Publication and active dissemination of a **summary of results** to relevant authorities (e.g. healthcare providers, HTA bodies, payers).

⁶⁸ Findable, Accessible, Interoperable, Reusable, see: <https://www.force11.org/group/fairgroup/fairprinciples>

Expected impact

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

- The outcome of this research is potentially practice-changing as it may define a new and improved standard for the treatment of oesophageal cancer patients and potentially patients with other cancer indications.
- The morbidity data from the study will allow better understanding of the dose-volume relationships for normal tissue complications, enabling refined selection of patients for proton therapy in the future.
- The results should allow health authorities and healthcare providers to improve the quality of care through better evidence of benefits and patient outcomes and support reimbursement decisions.

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

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

- Manage research data including use of data standards.⁶⁹
- Disseminate, exploit, and sustain the project results. This may involve engaging with suitable biological and medical sciences research infrastructures.⁷⁰
- Communicate the project activities to relevant target audiences.

Potential synergies with existing consortia

Synergies and complementarities should be considered with relevant national, European and non-European initiatives (including suitable biological and medical sciences research infrastructures⁷¹) in order to incorporate past achievements, available data and lessons learnt where possible, thus avoiding unnecessary overlap, and duplication of efforts and funding.

Industry consortium

The industry consortium includes the following IMI2 JU Associated Partners:

- Ion Beam Applications SA
- Varian Medical Systems Particle Therapy GmbH

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

- in-depth knowledge of proton therapy solutions, including equipment and treatment planning software;
- contribution to the development of dissemination and communication materials;
- a financial contribution (detailed in the indicative budget section) to cover study related expenses.

⁶⁹ Guidance on data management is available at

https://ec.europa.eu/research/participants/docs/h2020-funding-guide/cross-cutting-issues/open-access-dissemination_en.htm

⁷⁰ <http://www.corbel-project.eu/about-corbel/research-infrastructure.html>

⁷¹ <http://www.corbel-project.eu/about-corbel/research-infrastructure.html>

Indicative duration of the action

The indicative duration of the action is 60 months.

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

Indicative budget

The financial contribution from IMI2 JU is a maximum of EUR 1 500 000.

The indicative in-kind and financial contribution from the IMI2 JU Associated Partners is EUR 1 500 000, which includes a financial contribution of EUR 1 000 000.

Therefore, the stage 1 applicant consortium is expected to allocate up to **EUR 2 500 000** (IMI2 JU financial contribution + IMI2 Associated Partner financial contribution) in the budget of their stage 1 proposal. The allocation of the IMI2 Associated Partner financial contribution of EUR 1 000 000 to cover study related expenses may be fine-tuned by the full consortium when preparing the stage 2 proposal.

Expertise and resources expected from applicants at stage 1

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

This may require mobilising, as appropriate the following expertise:

- Extensive experience in the application of radiotherapy and proton therapy;
- Clinical expertise in the area of oesophageal cancer;
- Proven ability to design and conduct relevant studies to obtain high quality clinical data;
- Experience in dealing with the legal and ethical challenges associated with integrating multi-centre patient-derived data, as well as data-processing and management practices (e.g. privacy). Candidates should mention how they plan to integrate possible bias resulting from centre-specificity in the data analysis;
- Strong project management expertise;
- Access to HTA expertise and expertise from oesophageal patients or patient groups in an advisory capacity would be considered an advantage.

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

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

- Participating centres with the ability to include a statistically significant number of patients (with a minimum of 20 patients per centre) over the duration of the action;
- Applicants must demonstrate that they can secure access to:
 - relevant, state-of-the art radiotherapy and proton therapy equipment;
 - data centre and study monitoring infrastructure.
- Access to historical data that can be incorporated in the analysis would be considered an advantage. If relevant, applicants should indicate the volume and type of data they could bring to the project in their proposals.

Considerations for the outline of project work plan

In their stage 1 proposals applicants should:

- Provide the outline of a study protocol for the non-blinded multi-centre randomised phase III study. This should include a justified sample size of oesophageal cancer patients to ensure statistical significance. Applicants should also propose a rapid, clinically relevant primary endpoint to allow effectiveness to be demonstrated as early as possible.
- Give due visibility on data management; dissemination, exploitation and sustainability; and communication activities. This should include the allocation of sufficient resources for these tasks which will be further developed in stage 2 proposal.
- Consider including a strategy for ensuring the translation of the projects results to HTA settings (e.g. through scientific advice/ qualification advice /opinion, etc.), clinical and healthcare practices and/or decision-making processes.

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

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

In the spirit of the partnership, and to reflect how IMI2 JU call topics are built on identified scientific priorities agreed together with the IMI2 Associated Partners, 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 IMI2 Associated Partners shall facilitate an efficient negotiation of project content and required agreements. All beneficiaries are encouraged to discuss the project architecture and governance and the weighting of responsibilities and priorities therein.

Data management

In their stage 2 proposal, applicants should give due visibility to data management including use of data standards. A full 'data management plan' (DMP) as a distinct deliverable must be delivered within the first 6 months of the project. The DMP needs to be kept up to date with the needs of the project and as such be updated as necessary during its lifetime.⁷²

Dissemination, exploitation and sustainability of results

In their stage 2 proposal, applicants must provide a draft plan for dissemination and the exploitation, including sustainability of results. A full plan as a distinct deliverable must be delivered within the first 6 months of the project.⁷³, and updated during the project lifetime and could include identification of:

- different types of exploitable results;
- potential end-users of the results;
- results that may need sustainability and proposed sustainability roadmap solutions.

Sufficient resources should be foreseen for activities related to dissemination and exploitation, including the plan for the sustainability of the project results. This may involve engaging with suitable medical sciences research infrastructures (RIs).⁷⁴

⁷² 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

⁷³ As an additional dissemination obligation under Article 29.1 of the IMI2 Grant Agreement will apply

Communication

The proposed communication measures for promoting the project and its findings during the period of the grant should also be described.

References

- [1] For example: H. Thomas, B. Timmermann. Paediatric proton therapy. *Br J Radiol.* 2019:20190601. <https://doi.org/10.1259/bjr.20190601>, M. Alahmari, Y. Temel. Skull base chordoma treated with proton therapy: A systematic review. *Surg Neurol Int.* 2019;10:96. <https://doi.org/10.25259/SNI-213-2019>
- [2] Global Cancer Observatory (GCO). <http://gco.iarc.fr>
- [3] P. van Hagen, M.C.C.M. Hulshof, et al. for the CROSS Group. Preoperative Chemoradiotherapy for Esophageal or Junctional Cancer. *New England Journal of Medicine* Volume 366. Pages 2074-84 (2012). <https://doi.org/10.1056/NEJMoa1112088>
- [4] Shapiro et al. for the CROSS Group. Neoadjuvant chemoradiotherapy plus surgery versus surgery alone for oesophageal or junctional cancer (CROSS): long-term results of a randomised controlled trial. *The Lancet Oncology* Volume 16, issue 9. Pages 1090–98 (2015). [https://doi.org/10.1016/S1470-2045\(15\)00040-6](https://doi.org/10.1016/S1470-2045(15)00040-6)
- [5] T.C. Ling, J.M. Slater, et al. Analysis of Intensity-Modulated Radiation Therapy (IMRT), Proton and 3D Conformal Radiotherapy (3D-CRT) for Reducing Perioperative Cardiopulmonary Complications in Esophageal Cancer Patients. *Cancers* Volume 6. Pages 2356-68 (2014). <https://doi.org/10.3390/cancers6042356>
- [6] X. Zhang, K.L. Zhao, T.M., et al. Four-dimensional computed tomography-based treatment planning for intensity-modulated radiation therapy and proton therapy for distal esophageal cancer. *International Journal of Radiation Oncology, Biology, Physics* Volume 72. Pages 278-87 (2007). <https://doi.org/10.1016/j.ijrobp.2008.05.014>
- [7] S.H. Lin, R. Komaki, et al. Proton beam therapy and concurrent chemotherapy for esophageal cancer. *International Journal of Radiation Oncology, Biology, Physics* Volume 83. Pages 345-51 (2012). <https://doi.org/10.1016/j.ijrobp.2012.01.003>
- [8] A. Takada, T. Nakamura, et al. Preliminary treatment results of proton beam therapy with chemoradiotherapy for stage I-III esophageal cancer. *Cancer Medicine* Volume 5. Pages 506-15 (2016). <https://doi.org/10.1002/cam4.607>
- [9] Garant A, Whitaker TJ, Spears GM, et al. A Comparison of Patient-Reported Health-Related Quality of Life During Proton Versus Photon Chemoradiotherapy for Esophageal Cancer. *PubMed/31310815. Pract Radiat Oncol.* 2019 Jul 13. <https://doi.org/10.1016/j.prr.2019.07.003>
- [10] Ono T, Wada H, Ishikawa H, et al. Clinical Results of Proton Beam Therapy for Esophageal Cancer: Multicenter Retrospective Study in Japan. *PubMed/31315281. Cancers (Basel).* 2019 Jul 16;11(7). <https://dx.doi.org/10.3390%2Fcancers11070993>
- [11] Routman DM, Garant A, Lester SC, et al. A Comparison of Grade 4 Lymphopenia With Proton Versus Photon Radiation Therapy for Esophageal Cancer. *PubMed/30706012. Adv Radiat Oncol.* 2019 Jan 17;4(1):63-69 <https://doi.org/10.1016/j.adro.2018.09.004>
- [12] Badiyan SN, Hallemeier CL, Lin SH, et al. Proton beam therapy for gastrointestinal cancers: past, present, and future. *PubMed/30505599. J Gastrointest Oncol.* 2018 Oct;9(5):962-971. <http://dx.doi.org/10.21037/jgo.2017.11.07>

⁷⁴ <http://www.corbel-project.eu/about-corbel/research-infrastructures.html>

- [13] Haque W, et al. Utilization of neoadjuvant intensity-modulated radiation therapy and proton beam therapy for esophageal cancer in the United States, PubMed 29755767, J Gastrointest Oncol. 2018 Apr;9(2):282-294. <http://dx.doi.org/10.21037/jgo.2017.11.14>
- [14] Prayongrat A, et al. Clinical outcomes of intensity modulated proton therapy and concurrent chemotherapy in esophageal carcinoma: a single institutional experience, PubMed 29114596, Adv Radiat Oncol. 2017 Jun 13;2(3):301- 307. <https://doi.org/10.1016/j.adro.2017.06.002>
- [15] Shiraishi Y, et al. Severe lymphopenia during neoadjuvant chemoradiation for esophageal cancer: A propensity matched analysis of the relative risk of proton versus photon-based radiation therapy, PubMed 29248170, Radiother Oncol. 2017 Dec 13. pii: S0167-8140(17)32751-2. <https://doi.org/10.1016/j.radonc.2017.11.028>
- [16] Verma V et al. Advances in Radiotherapy Management of Esophageal Cancer,(PubMed 27775643, J Clin Med. 2016 Oct 21;5(10). <https://dx.doi.org/10.3390%2Fjcm5100091>
- [17] Chuong M.D. et al., "Improving Outcomes for Esophageal Cancer using Proton Beam Therapy", PubMed 27084662, International Journal of Radiation Oncology, Biology, Physics, 2016 May; 95(1):488-97. <https://doi.org/10.1016/j.ijrobp.2015.11.043>
- [18] Makishima H. et al., "Comparison of adverse effects of proton and X-ray chemoradiotherapy for esophageal cancer using an adaptive dose volume histogram analysis", PubMed 25755255, Journal of Radiation Research, 2015 May, 56(3):568-76. <https://dx.doi.org/10.1093%2Fjrr%2Frrv001>
- [19] Lin S H et al. Multi-institutional analysis of radiation modality use and postoperative outcomes of neoadjuvant chemoradiation for esophageal cancer, PubMed 28455153, Radiother Oncol. 2017 Jun;123(3):376-381. <https://doi.org/10.1016/j.radonc.2017.04.013>

Topic 6: Handling of protein drug products and stability concerns

Topic details

Topic code	IMI2-2020-20-06
Action type	Research and Innovation Action (RIA)
Submission and evaluation process	2 stages
IMI2 JU Strategic Research Agenda - Axis of Research	Patient-tailored adherence programmes.
IMI2 JU Strategic Research Agenda - Health Priority	Other

Specific challenges to be addressed by public-private collaborative research

In the past two decades, protein pharmaceuticals have become the fastest growing class of therapeutics owing to their beneficial impacts on the treatment of severe and life-threatening conditions and diseases. Development and manufacturing of protein pharmaceuticals is, however, challenging and requires overcoming various manufacturing hurdles such as issues with the purity of the protein product. The safety and efficacy of protein pharmaceuticals depend on their purity. Impurities in marketed protein pharmaceuticals may be present due to limitations in manufacturing processes or may also be a result of degradation processes occurring not only during manufacturing, but also during long-term storage of the bulk drug substance and/or final drug product (DP) [1]. Impurities within therapeutic protein products can cause severe adverse drug reactions (ADRs) in patients, that may be acute, as is the case for infusion-induced anaphylaxis and pseudo-allergy responses, which may even result in patient death, or long-term like unwanted immunogenicity.

Physical aggregation and chemical degradation can occur throughout a protein product's life history, and even modest environmental stresses can cause extensive damage. Development of effective upstream and downstream processes as well as robust formulations and filling processes are crucial for maintaining product quality, and hence, for the safety and efficacy of protein pharmaceuticals. The pharmaceutical industry has made great progress in improving bulk and DP manufacturing as well as storage and transportation conditions to minimise the level of degradation. However, there exists only low control over the many factors that may affect product quality after the protein pharmaceuticals are released and shipped. Routine handling or unintentional mishandling of therapeutic protein products may cause protein degradation that remains unnoticed but can potentially compromise the clinical safety and efficacy of the product [2]. Storage of the DP outside the recommended condition ranges, use of incompatible supply and/or technology, careless handling of drug during preparation for administration and during delivery to patient are just a few examples of such (mis)handling [3]. When it comes to handling of DP by patients, the social, cultural, logistical and environmental differences between different geographies and cultures can also impact the handling conditions.

There has been increasing expression of concern in the past decade regarding the significance of the post-production handling of protein pharmaceuticals. At the same time, studies revealed that the consequences of presence of impurities in DP can be severe. Potentially high likelihood and/or severity in consequences in combination with the low level of control over the processes by the industry make these concerns a significant risk that needs to be addressed in a public-private partnership that includes all relevant stakeholders.

DPs as described above are handled in pharmacies, hospitals and by patients after they have been released by the manufacturer. Consequently, although manufacturers can influence the process by making more robust DPs that can withstand a certain level of stress during usage, and by providing training, the pharmaceutical industry does not have full control over handling processes. Collaboration with other

stakeholders including those in the public sector is therefore necessary to address handling conditions, as already outlined in literature [1]. Indeed, understanding the handling conditions requires assistance from experts in pharmacies and medical institutions as well as organisations that can gather and document information on the patients' side, e.g. academic and research organisations or structured patients communities, all of which are envisioned to become part of the applicant consortium.

Alongside a good understanding of the various (and probably most common) handling steps and the stresses they imply for protein drugs, there is a need for research in estimating the impact of each handling step on DP quality and potentially the safety and efficacy of the drug.

It is only through the above-mentioned process that the risky handling steps are identified and addressed. Working out a meaningful framework for sharing the information between the manufacturer and the healthcare professionals and/or patients (that might go beyond the current communication channels and exchange of standard pharmacy manuals and training) is only possible through close collaboration among all involved. A consortium comprised of the pharmaceutical industry, medical institutions, pharmacies, academia and SMEs and potentially patient organisations can fully address all the aspects of the complex topic and help to develop technological and process solutions.

Scope

The first objective of this topic is **to improve the understanding of real-world stressful drug product handling steps and their effects on protein product quality.**

- All protein DPs are considered to be within the scope of the topic though a subset of use cases may be identified upon formation of the full consortium during the stage 2 submission;
- All handling steps for preparation, transport and administration should be addressed:
 - Studying the effects of the handling steps on drug product quality is in the scope of the project;
 - Supplies that are used for handling of the protein pharmaceuticals are also to be investigated and evaluated. Evaluation of new technologies that are used to handle protein pharmaceuticals such as closed-system transfer devices are of interest;
 - Handling practices include the ones that are performed by healthcare professionals in hospital and compounding pharmacies and the ones in hands of patients. The understanding should be as thorough as possible and may be , obtained by the use of new technologies and digital tools that record details visually or by sensors of conditioning parameters during storage and administration processes, among other methods;
 - Routine handling procedures, i.e. the ones that are currently used as standard procedures for protein drug products in pharmacies and by patients should be addressed.
- These risks associated with the handling of protein DPs should be assessed and potential solutions developed;
- Mishandling cases with high level of likelihood or severe impacts should also be examined.

The second objective of this topic is to use this understanding **to develop guidelines and operating processes to improve the DP robustness and pharma processes**, and to develop **more efficient training** (see Figure 1)

- Improving the in-use studies and other processes in development of protein pharmaceuticals is in the scope of the topic;
- Innovative solutions that help to ensure the stability of DP during handling are welcome;
- Improving training materials and improving handling culture are in the scope of the topic. Training should target both professionals and patients;

- Utilisation of technologic tools (video, webinar, online media and creative manuals) for the development of novel training methods and materials is within the scope of the topic.

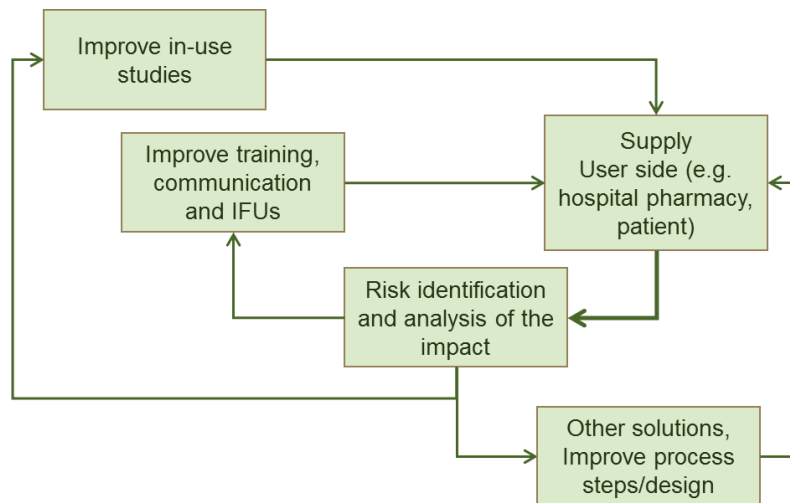


Figure 1: Good understanding of drug product handling at the user side can lead to the formulation of various solutions

Expected key deliverables

The expected deliverables from the action are the following:

Clear insight into the drug product handling procedures and their impact:

- Detailed outlining of handling procedures in pharmacies and homes, including all steps (irrespective of the delivery method/device);
- Evaluation of the real impact of handling steps on the stability of protein DP;
- Outlining of the protein drug preparation and administration supplies available to pharmacies and clinics considering the major geographic markets investigated in the project;
- Assessment of the potential impacts on delivered dose;
- Estimation of potential impacts on clinical safety and efficacy.

Improved protein drug product development processes

- Tools and methods to improve DP robustness (rational and realistic in-use studies);
- Determination of critical parameters, improvements in processes and definition of DP handling requirements.

Improved training on drug product handling

- Improved professional user training including development of training materials (e.g. videos) that can be used to educate and as reference in pharmacy manuals/instructions;
- Improved patient/caregiver training (at both strategy and execution levels).

Training materials and tools should be compatible with the needs of the different target groups. For instance, the training material for patients should have different characteristics than the SOPs and tools used for professional personnel in a pharmacy.

These key deliverables lead to improvements in assessment and management of the risks associated with handling of protein drug products and improved efficacy and safety of protein drug products for patients.

Expected impact

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

- Through this project, a better understanding of the handling procedures of protein DPs and associated stresses in hospitals and in the hands of patients will be obtained. The project will assess the risks associated with these handling steps and provide solutions to ensure high-quality delivery and administration of protein DP;
- The project will help participating pharmaceutical companies to improve their processes with regards to the development of more robust DPs that can withstand handling stresses;
- At the same time, access to the resulting improved methods to influence the handling culture can be used by both the private and public sectors in the interest of patients. Foremost amongst the expected impacts is the improved training for professionals and patient/caregivers to ensure the stability of protein DP. This will have global effects on the manufacturing side as well as the user side at pharmacies, hospitals and with patients, thus providing benefits to all healthcare stakeholders;
- Generation of knowledge in the area of stress-stability will help all the stakeholders involved and can be directly applied to the design of the processes and addressing important but challenging issues around the development of therapeutics and delivery to patients;
- Overall, the project is expected to lead to improvements in the safety and efficacy of protein drug therapies.
- While specific use cases may be chosen upon formation of the full consortium during the stage 2 submission, the results of the project should apply as broadly as possible to all protein DPs.

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

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

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

- manage research data, including use of data standards⁷⁵;
- Disseminate, exploit, and sustain the project results. This may involve engaging with suitable biological and medical sciences research Infrastructures⁷⁶;
- Communicate the project activities to relevant target audiences.

⁷⁵ Guidance on data management is available at http://ec.europa.eu/research/participants/docs/h2020-funding-guide/cross-cutting-issues/open-access-data-management/data-management_en.htm

⁷⁶ <http://www.corbel-project.eu/about-corbel/research-infrastructures.html>

Potential synergies with existing consortia

Synergies and complementarities should be considered with relevant national, European and non-European initiatives (including suitable biological and medical sciences research infrastructures⁷⁷) in order to incorporate past achievements, available data and lessons learnt where possible, thus avoiding unnecessary overlap, and duplication of efforts and funding.

Industry consortium

The industry consortium is composed of the following EFPIA partners:

- Sanofi (lead)
- AbbVie
- AstraZeneca
- Boehringer Ingelheim
- Lonza
- Merck
- Pfizer
- Roche
- Teva

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

- the development and manufacture of biologics;
- formulation and process development;
- clinical processes;
- protein and biologics analytics;

as well as interaction with public health stakeholders and authorities.

Indicative duration of the action

The indicative duration of the action is 48 months.

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

Indicative budget

The financial contribution from IMI2 JU is a maximum of EUR 3 140 000.

The indicative in-kind and financial contribution from EFPIA partners is EUR 3 959 500.

⁷⁷ <http://www.corbel-project.eu/about-corbel/research-infrastructures.html>

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

Expertise and resources expected from applicants at stage 1

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

The stage 1 submitted short proposals should include suggestions for creating a full proposal architecture.

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

- A global understanding of the protein DP handling, attained from first-hand knowledge;
- The capacity to investigate the real-world handling procedures in hospitals, pharmacies and at homes and assess their impact on the stability, and potentially safety and efficacy, of protein pharmaceuticals;
- Expertise in the available methods of communication and training for handling of protein DPs and a strong capacity to come up with novel training concepts and materials;
- The ability to implement new technologies to achieve relevant data for handling conditions and also to produce novel and efficient training materials and methods;
- Support for industry partners to address the challenge and influence the process of handling protein DP;
- The participation of SMEs with novel monitoring concepts and training tools is highly encouraged.

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

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

- Resources, including data from past investigations or existing frameworks on DP handling;
- Technologies from SMEs that have been developed for other purposes but can be of use for this project;
- Networks and ecosystems the applicants are already members of.

Considerations for the outline of project work plan

In their stage 1 proposals, applicants should:

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

Applicants should not select specific protein DPs at stage 1. A subset of use cases may be identified upon formation of the full consortium during the stage 2 submission.

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

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

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

Data Management

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

Dissemination, exploitation and sustainability of results

In their stage 2 proposal, applicants must provide a draft plan for dissemination and the exploitation, including sustainability of results. A full plan as a distinct deliverable must be delivered within the first 6 months of the project⁷⁹ and updated during the project lifetime and could include identification of:

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

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

Communication

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

⁷⁸ Guidance on data management is available at http://ec.europa.eu/research/participants/docs/h2020-funding-guide/cross-cutting-issues/open-access-data-management/data-management_en.htm

⁷⁹ As an additional dissemination obligation under Article 29.1 of the IMI2 Grant Agreement will apply

⁸⁰ <http://www.corbel-project.eu/about-corbel/research-infrastructures.html>

References

- [1] Nejadnik M.R., Randolph T.W., Volkin D.B., Schöneich C., Carpenter J.F., Crommelin D.J.A., Jiskoot W.: Postproduction Handling and Administration of Protein Pharmaceuticals and Potential Instability Issues; *J Pharm Sci.* 2018 Aug 107:2013-2019
- [2] Jiskoot W., Nejadnik M.R., Sediq A.S.: Potential Issues With the Handling of Biologicals in a Hospital; *J Pharm Sci.* 2017 Jun 106:1688-1689
- [3] Vlieland N.D., Gardarsdottir H., Bouvy M.L., Egberts T.C., van den Bemt B.J.: The majority of patients do not store their biologic disease-modifying antirheumatic drugs within the recommended temperature range; *Rheumatology (Oxford)* 2016 Apr 55:704-709

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 20 should read this topics text, the [IMI2 JU Manual for submission, evaluation and grant award](#) and other relevant documents (e.g. [IMI2 JU Model Grant Agreement](#)).

Call Identifier	H2020-JTI-IMI2-2020-20-two-stage
Type of actions	Research and Innovation Action (RIA)
Publication Date	21 January 2020
Stage 1 Submission start date	21 January 2020
Stage 1 Submission deadline	21 April 2020 (17:00:00 Brussels time)
Stage 2 Submission deadline	05 November 2020 (17:00:00 Brussels time)
Indicative Budget	
From EFPIA companies and IMI2 JU Associated Partners	EUR 140 209 500
From the IMI2 JU	EUR 133 009 000

Call Topics

IMI2-2020-20-01		Research and Innovation Action (RIA)
Early diagnosis, prediction of radiographic outcomes and development of rational, personalised treatment strategies to improve long-term outcomes in psoriatic arthritis	The indicative contribution from EFPIA companies is EUR 13 880 000 The financial contribution from IMI2 JU is a maximum of EUR 10 211 000	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.

<p>IMI2-2020-20-02</p> <p>Innovations to accelerate vaccine development and manufacture</p>	<p>The indicative contribution from EFPIA companies is EUR 19 870 000</p> <p>The financial contribution from IMI2 JU is a maximum of EUR 18 600 000</p>	<p>Research and Innovation Action (RIA)</p> <p>Two-stage submission and evaluation process.</p> <p>Only the applicant consortium whose proposal is ranked first at the first stage is invited for the second stage.</p>
<p>IMI2-2020-20-03</p> <p>Academia and industry united innovation and treatment for tuberculosis (UNITE4TB)</p>	<p>The indicative contribution from EFPIA companies is EUR 62 500 000</p> <p>The indicative IMI2 JU Associated Partners contribution is EUR 30 000 000</p> <p>The financial contribution from IMI2 JU is a maximum of EUR 92 500 000</p>	<p>Research and Innovation Action (RIA)</p> <p>Two-stage submission and evaluation process.</p> <p>Only the applicant consortium whose proposal is ranked first at the first stage is invited for the second stage.</p>
<p>IMI2-2020-20-04</p> <p>Tumour plasticity</p>	<p>The indicative contribution from EFPIA companies is EUR 8 500 000</p> <p>The financial contribution from IMI2 JU is a maximum of EUR 7 058 000</p>	<p>Research and Innovation Action (RIA)</p> <p>Two-stage submission and evaluation process.</p> <p>Only the applicant consortium whose proposal is ranked first at the first stage is invited for the second stage.</p>
<p>IMI2-2020-20-05</p> <p>Proton versus photon therapy for oesophageal cancer – a trimodality strategy</p>	<p>The indicative IMI2 JU Associated Partners contribution is EUR 1 500 000</p> <p>The financial contribution from IMI2 JU is a maximum of EUR 1 500 000</p>	<p>Research and Innovation Action (RIA)</p> <p>Two-stage submission and evaluation process.</p> <p>Only the applicant consortium whose proposal is ranked first at the first stage is invited for the second stage.</p>
<p>IMI2-2020-20-06</p> <p>Handling of protein drug products and stability concerns</p>	<p>The indicative contribution from EFPIA companies is EUR 3 959 500</p> <p>The financial contribution from IMI2 JU is a maximum of EUR 3 140 000</p>	<p>Research and Innovation Action (RIA)</p> <p>Two-stage submission and evaluation process.</p> <p>Only the applicant consortium whose proposal is ranked first at the first stage is invited for the second stage.</p>

Annex II - IMI2 JU Call 21 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 created⁸¹ 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 World⁸².

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 companies⁸³, 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)⁸⁴ is the main reference for the implementation of research priorities for IMI2 JU. The scientific priorities for 2020 for IMI2 JU have been prepared based on the SRA.

Applicant consortia are invited to submit a proposal which should address at least one of the objectives of the topic. 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.

⁸¹ 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.

⁸² http://www.who.int/medicines/areas/priority_medicines/en/

⁸³ 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.

⁸⁴ 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) 2016/679⁸⁵ and Clinical Trial Regulation (EU) 536/2014⁸⁶ (and/or Directive 2001/20/EC⁸⁷) and any relevant legislation⁸⁸.

Before submitting a proposal, applicant consortia should familiarise themselves with all Call documents such as the IMI2 JU Manual for submission, evaluation and grant award⁸⁹, 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).

⁸⁵ 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.

⁸⁶ 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.

⁸⁷ [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.

⁸⁸ 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.

⁸⁹ https://www.imi.europa.eu/sites/default/files/uploads/documents/apply-for-funding/call-documents/imi2/IMI2_ManualForSubmission_v1.7_November2018.pdf

Development of therapeutics and diagnostics combatting coronavirus infections

Topic details

Topic code	IMI2-2020-21-01
Action type	Research and Innovation Action (RIA)
Submission and evaluation process	Single stage
IMI2 Strategic Research Agenda - Axis of Research	Adoption of innovative clinical trial paradigms
IMI2 Strategic Research Agenda - Health Priority	Other

Specific challenges to be addressed by public-private collaborative research

Coronaviruses (CoV) are a large family of enveloped positive-stranded RNA viruses that typically result in respiratory and enteric infections. CoV are zoonotic in origin, but they can evolve into a strain that can infect human beings leading to fatal illness. Typically, CoV infections were considered relatively benign to humans before the severe acute respiratory syndrome (SARS-CoV) outbreak in 2002/2003 in China, and the Middle East respiratory syndrome coronavirus (MERS-CoV) outbreak in 2012 in the Middle Eastern countries.

On 31 December 2019, the local authorities of Wuhan, Hubei province, China, reported a cluster of pneumonia cases of unknown origin. On 9 January 2020, the China Centre for Disease Control reported a novel coronavirus - now referred as SARS-CoV-2 to be the causative agent.

As of 24 February 2020, 79 360 cases of novel coronavirus infection COVID-19 (in accordance with the applied case definitions in the affected countries) have been reported, including 2 618 deaths. The disease has already spread to 31 countries outside China, with new cases continuing to emerge daily [1]. The COVID-19 outbreak has been declared by WHO as a Public Health Emergency of International Concern according to the International Health Regulation [2].

Bearing in mind that the SARS-CoV epidemic in 2003 resulted in over 8 000 cases reported (and a 10% fatality ratio), it is crucial to rapidly gain a better understanding of the newly-identified virus and the virus family that it represents, especially in relation to potential clinical and public health measures that can be put to immediate use to improve patients' health and/or contain the spread of COVID-19.

Considering the public health and humanitarian implications, there is a need for all stakeholders across the public and private sectors to collaborate in global efforts to care for those affected, contain the outbreak, and develop the much-needed resources to prepare for the future. A collaboration of private companies, academia, international organisations, public bodies etc. has the potential to accelerate the development of therapeutics and diagnostics to tackle the current and future outbreaks. The actions resulting from this Call will contribute to the pan-European efforts responding to this Public Health Emergency and address one of the eight immediate research actions agreed at the WHO global research and innovation forum held on 11-12 February 2020 [3].

Scope

Proposals submitted under this topic are expected to advance our knowledge of SARS-CoV-2 specifically and the wider coronavirus family in general with the aim of contributing to an efficient patient management and/or public health preparedness and response to current and future outbreaks of coronavirus infection.

Considering that this is a newly-identified virus, the scope of this topic remains broad and must address at least one of the following objectives:

- **Development of antivirals as well as other types of therapeutics to address a rapid response to the current COVID-19 outbreak**
Relevant “clinical ready”-assets include approved therapies or compounds in development, which could be repurposed for use in treating patients with the coronavirus. For example, this could include (but is not limited to), angiotensin-converting-enzyme (ACE) inhibitors, protease inhibitors or immunotherapies (for example antibodies/antibody-like molecules) that could be relevant in the context of CoV. If repurposing is proposed, this should be supported by a preliminary rationale of the compound’s potential efficacy against COVID-19. Where relevant, evidence of regulatory and ethics approvals for the investigational products included in the study(ies) must be presented.
- **Development of therapeutics to address the current and/or future coronavirus outbreaks**
Identification of new potential assets and approaches that could be utilised including preventive strategies and combination approaches, and that could also address potential resistance. This may also include the optimisation of promising treatments used in rapid response (e.g. reformulation).
- **Development of diagnostics, ensuring rapid evaluation of candidates based on existing technologies.**
Diagnostic tests will be essential for clinical trials of new or repurposed drugs, to help stratify patients and assess treatment efficiency (surrogate endpoint such as viral clearance).
- **Development of fast and reliable tools that go beyond the state of the art for detection of COVID-19 carriers and symptomatic individuals suspected of COVID-19 infection**
These are essential and of utmost importance to manage the outbreak, isolate patients at risk and treat people accordingly. It is crucial to differentiate and identify respiratory pathogens with similar clinical symptoms (e.g. flu, respiratory syncytial virus, other viruses or bacteria) and/or detect emerging pathogens such as SARS-CoV-2. This can be achieved through point-of-care (POC) testing or centralised testing.

Preventive vaccines are specifically excluded from the scope of the Call.

For increased impact, proposals should build on promising avenues from previous or ongoing research, taking into account the recommendations from the WHO and ensuring complementarity and ideally synergy with the work carried out under the auspices of Coalition for Epidemic Preparedness Innovations (CEPI), Wellcome, Biomedical Advanced Research and Development Authority (BARDA), the Bill and Melinda Gates Foundation, Global Research Collaboration for Infectious Disease Preparedness (GloPID-R) and H2020 Call SC1-PHE-CORONAVIRUS-2020.

The European Medicines Agency (EMA) has activated its plan for emerging health threats, which includes the possibility for fast-tracked Scientific Advice [4]. Proposals covering investigation of a therapeutic should engage with the EMA to ensure adequacy from a regulatory point of view.

Collaboration agreement(s)

To ensure the interactions between actions funded under this Call, the selected consortia are expected to cooperate with each other and share their learnings for the purpose of achieving the objectives of their respective actions, in order to maximise the impact. Therefore, all grants awarded under this Call will be complementary grants. The respective options under Article 2, Article 31.6 and Article 41.4 of the IMI2 JU Model Grant Agreement⁹⁰ will apply. Accordingly, the relevant consortia will conclude collaboration agreement(s) to ensure the exchange of relevant information, exploration of synergies, and collaboration where appropriate.

Expected key deliverables

⁹⁰ See: https://www.imi.europa.eu/sites/default/files/uploads/documents/reference-documents/h2020-mga-imi_en_v5.pdf

Each proposal must include at least one of the following key deliverables:

- antivirals as well as other types of therapeutics to be used in the current outbreak, including preventive and symptomatic treatments;
- novel therapeutics including combination treatments to ensure appropriate treatment for current and/or future outbreaks and/or to prevent resistance;
- diagnostics.

In the context of achieving the above deliverables, i.e. development of therapeutics and diagnostics, it is recognised that studies related to the understanding of the mechanism of action will generate new knowledge on the virology, immunology and pathogenesis of the coronavirus, and that new analytical technologies and reagents may be developed.

When relevant, deliverables should include:

- Hit identification of suitable assets (e.g. existing libraries, approved drugs and assets that have passed phase 1 for repurposing; protease and (non)-nucleoside inhibitors) against SARS-CoV-2 and/or pan-coronavirus; implementation of high-throughput screening assays in collaboration with Europe-based centres of excellence.
- Lead optimisation: initiating target-based discovery programmes based for instance on literature for the identification of promising approaches. Proof of Concept: pre-clinical animal studies and clinical studies including at least first in human (FIH) and phase 2A and/or 2B studies for both repurposed and new molecular entities.

For the clinical studies applicants should consider the Therapeutic Trial Synopsis in the WHO's Global Research and Innovation Blueprint on the novel Coronavirus COVID-19 [3].

- Diagnostics and associated enablers (e.g. production of antibodies and viral proteins); characterisation of nCoV strains and evolution; sustainability plans for data repositories, sample repositories etc.; documentation supporting regulatory submission.

Expected impact

Proposals must be timely, with rapid activation, to enable early and valuable outcomes to be established.

On the basis of the proposed activities, applicants should describe how the outputs of the project will contribute to the following impacts and include wherever possible targets and metrics to measure them:

- fast-track development and availability of therapeutics and/or diagnostics to be used in the clinical management of patients infected by COVID-19 and/or future outbreaks of coronaviruses, and to ensure that a variety of drugs are available for patients, including tackling resistance, and combination therapy;
- contribution to public health preparedness and response in the context of the ongoing epidemic of COVID-19 and/or future outbreaks of pan-coronaviruses;
- significant impact on global health, both at the individual and the public health level by leading to results that have a direct impact on people at risk of exposure to coronavirus or on patients suffering from coronavirus disease.

To ensure maximum impact for patients, applicants should demonstrate their operational capacity as well as their readiness and access to asset(s) to progress through clinical development and reach patients as rapidly as possible.

Although actions to be funded should be centred around SARS-CoV-2 and CoV, applicants should explain how the knowledge and new concepts arising from the action can be applied in more general terms to the preparedness strategy that could be applied to new outbreaks as a rapid response.

In addition, considering the unknown evolution of this COVID-19 outbreak, applicants should develop strategies on how to develop their proposals and continuity plans, allocate their funds and implement sustainability measures in the different scenarios that could occur: 1) rapid regression of the epidemic with no patients left for clinical trials, 2) pandemic, 3) seasonal reoccurrence as typically seen with influenza.

Applicants must maximise the IMI2 JU public-private partnership value by harnessing support from different stakeholders, including the mobilisation of resources through the inclusion of contributing partners⁹¹, providing contributions (in kind and/or financial), to reflect the public-private character of IMI2 JU actions.

To maximise the potential for public health impact, applicants should outline in their proposals a strategy for engagement with patients, healthcare professional associations, healthcare providers, and public health bodies where relevant

Beneficiaries in grants awarded under this topic must make available their research data, at the latest within 30 days after it has been generated, through open access or, if agreed by the IMI2 JU or the European Commission, by giving access rights to those third parties that need the research data to address the public health emergency. Therefore, the relevant option (1c) of Article 29.3 of the Grant Agreement shall apply.

Potential synergies with existing consortia

Synergies and complementarities are expected with relevant national, European and non-European initiatives (including suitable biological and medical sciences research infrastructures⁹²) 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, applicants are expected to collaborate with any relevant project or initiative targeting the current COVID-19 outbreak supported by, including but not restricting to, the European Commission (H2020 call SC1-PHE-CORONAVIRUS-2020), CEPI, Wellcome, BARDA, The Bill and Melinda Gates Foundation, GloPID-R, and others.

Applicants should also consider building on achievements of relevant IMI projects such as the COMBACTE projects, ZAPI, and the European Lead Factory (ELF/ESCLAB).

Where relevant applicants might consider the advantages of the use of the European supercomputing centres (PRACE network) to accelerate the process of diagnosis and therapeutics research, using the exiting high-end computing, data and simulation resources.

Indicative duration of the action

Proposals should include a proposed duration for the action in relation to the activities and expected impact.

Successful applicants may request a starting date prior the entry into force of the GA, but no earlier than the date of grant proposal submission.

Indicative budget

Applicant consortia will be competing for the maximum total financial contribution from IMI2 JU up to EUR 45 000 000.

Within this budgetary envelope, each proposal must include a sound justification of the requested IMI2 JU financial contribution. This should take into account the proposed in-kind contributions from contributing partners that will complement the IMI2 JU financial contribution, i.e. EFPIA constituents or affiliated entities and/or, when relevant, IMI2 JU Associated Partners.

All proposals submitted under this Call and evaluated above the threshold will be ranked in one single list. Proposals will be invited in order of ranking to prepare a Grant Agreement within the limits of the available overall budget.

⁹¹ 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.

⁹² <http://www.corbel-project.eu/about-corbel/research-infrastructures.html>

Applicant consortium

Applicant consortia are expected to address at least one of the objectives of the topic and demonstrate the necessary expertise and access to facilities to meet the relevant key deliverables and ensure the expected impact.

The size and composition of each consortium should be adapted so as to respond to the objectives and the key deliverables of the Call while ensuring its manageability.

In accordance with the Horizon 2020 Rules for Participation, in order to be eligible, a proposal must be made by a consortium of at least three independent legal entities, each established in a different Member State or associated country.

While preparing their proposals, applicant consortia should ensure that needs of patients are adequately addressed and, where appropriate, patient involvement is encouraged.

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.⁹³

Applicants should be aware that data must be deposited in a relevant established international data platform, such as the one by WHO and/or European Molecular Biology Laboratory (EMBL).

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.⁹⁴ 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.

Applicants should be aware that beneficiaries in grants awarded in this Call for proposals are expected to apply the principles established in the [Statement on Data Sharing in Public Health Emergency](#).

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.

The proposed plan should also ensure that the new concepts for rapid response developed in the projects can be applied to new outbreak situations.

⁹³ Guidance on data management is available at https://ec.europa.eu/research/participants/docs/h2020-funding-guide/cross-cutting-issues/open-access-data-management/data-management_en.htm

⁹⁴ As an additional dissemination obligation under Article 29.1 of the IMI2 JU Grant Agreement will apply

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).⁹⁵

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.

Regulatory strategy

Applicants are expected to have a strategy for the translation of the relevant outputs into 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.

References

- [1] ECDC. Novel Coronavirus(COVID-19) Situation - Worldwide. 2020.
<https://www.ecdc.europa.eu/en/geographical-distribution-2019-ncov-cases>
- [2] World Health Organisation. Statement on the second meeting of the International Health Regulations (2005) Emergency Committee regarding the outbreak of novel coronavirus (COVID-19). 2020.
[https://www.who.int/news-room/detail/30-01-2020-statement-on-the-second-meeting-of-the-international-health-regulations-\(2005\)-emergency-committee-regarding-the-outbreak-of-novel-coronavirus-\(2019-ncov\)](https://www.who.int/news-room/detail/30-01-2020-statement-on-the-second-meeting-of-the-international-health-regulations-(2005)-emergency-committee-regarding-the-outbreak-of-novel-coronavirus-(2019-ncov))
- [3] World Health Organisation. 2019 Novel Coronavirus: Global Research and Innovation Blueprint. 2020.
<https://www.who.int/blueprint/priority-diseases/key-action/novel-coronavirus/en/>
- [4] EMA to support development of vaccines and treatments for novel coronavirus
<https://www.ema.europa.eu/en/news/ema-support-development-vaccines-treatments-novel-coronavirus>

⁹⁵ <http://www.corbel-project.eu/about-corbel/research-infrastructures.html>

Conditions for this Call for proposal

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 21 should read this topics text, the [IMI2 JU Manual for submission, evaluation and grant award](#) and other relevant documents (e.g. [IMI2 JU Model Grant Agreement](#)).

Call Identifier	H2020-JTI-IMI2-2020-21-single-stage
Type of actions	Research and Innovation Action (RIA)
Publication Date	3 March 2020
Submission start date	3 March 2020
Submission deadline	31 March 2020
Indicative Budget	
From EFPIA companies and IMI2 JU Associated Partners	to be defined based upon selected proposals
From the IMI2 JU	EUR 45 000 000

Call Topics

<p>IMI2-2020-21-1</p> <p>Development of therapeutics and diagnostics combatting coronaviruses infections</p>	<p>The indicative contribution from EFPIA companies is to be defined based upon selected proposals.</p> <p>The financial contribution from IMI2 JU is a maximum of EUR 45 000 000</p>	<p>Research and Innovation Action (RIA)</p> <p>Single stage submission and evaluation process.</p> <p>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.</p>
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LIST OF ACRONYMS

Acronym	Meaning
AAPS	American Association Of Pharmaceutical Scientists
ABAC	Accrual Based Accounting System
AD	Alzheimer's disease
AD (HR)	Administrator
ADR	Adverse Drug Reaction
AER	Average error rate
AI	Artificial Intelligence
AMR	Antimicrobial Resistance
APs	IMI2 JU Associated Partners
API	active pharmaceutical ingredient
AST	Assistant
AWP2018	Annual Work Plan 2018
CA (Budget)	Commitment Appropriation
CA (HR)	Contractual Agent
CASPAR	Classification Criteria For Psoriatic Arthritis
CDISC	Clinical Data Interchange Standards Consortium
CEA	Cost-Effectiveness Analysis
CEN/TS	European Committee For Standardization / Technical Specification
CEOi	Global CEO Initiative
CFAST	Coalition for Accelerating Standards and Therapies
cfDNA	Circulating Free DNA
CFS	Certificates on Financial Statements
CHIM	Controlled Human Infection Model
Chromium	Single-Cell RNA Sequencing Platform (10xgenomics) – Reads 3' End Of Transcript
CMC	Chemistry, Manufacturing, And Control
CoV	Coronaviruses
COVID-19	Coronavirus disease 2019
C-Path	Critical Path Institute
CPD	Continuing professional development
CPTR	Critical Path To Tb Drug Regimens
CRO	Contract research organisation
CROSS	ChemoRadiotherapy for Oesophageal Cancer Followed by Surgery Study
CSC	Common Support Centre
CSTD	Closed System Drug Transfer Devices
CT	Computer Tomography
ctDNA	Circulating Tumour DNA
CUA	Cost-Utility Analysis
CyTOF	Mass cytometry by time-of-flight.
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
DP	Drug Product
DPH	Drug Product Handling
DPO	Data protection officer
DSUR	Developmental Safety Update Report

Acronym	Meaning
DTPs	Drug Tolerant Persister Cells
DZIF	German Centre For Infection Research
E&T	Education & Training
EBA	Early Bactericidal Activity
EBiSC	European induced pluripotent stem cell
EC	European Commission
ECA	European Court of Auditors
ECDC	European Centre for Disease prevention and Control
EDPS	European Data Protection Supervisor
EEG	Electroencephalograph
EFPIA	European Federation of Pharmaceutical Industries and Associations
EGFR	Epidermal Growth Factor Receptor
EHR	Electronic Health Record
EMA	European Medicines Agency
EQAs	External Quality Assessment Schemes
ERA	environmental risk assessment
ESFRI	European Strategy Forum on Research Infrastructures
EU	European Union
EUR	Euros
ExPEC	Extra-Intestinal Pathogenic Escherichia Coli
FAIR	Findable, Accessible, Interoperable, Reusable
FDA	Food and Drug Administration
FG	Function Group
FTE	Full-Time Equivalent
fNIH	Foundation for the National Institute of Health
FP	Full Proposal
FP7	Seventh Framework Programme
FWC	Framework Contract
GA	Grant Agreement
GAP	Global Alzheimer's Platform
Gates MRI	Gates Medical Research Institute
GB	Governing Board
GCP	Good Clinical Practice
GDPR	General Data Protection Regulation
GEMM	Genetically Engineered Mouse Models
GLP	Good Laboratory Practice
GMP	Good Manufacturing Practice
GPCRs	G-protein-coupled receptors
GRAPPA	Group For Research And Assessment Of Psoriasis And Psoriatic Arthritis
GSK	Glaxosmithkline
H2020	<p>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.</p> <p>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</p>
HCA	Human Cell Atlas
HCT	Human challenge trials
Helmsley Charitable Trust	Leona M. and Harry B. Helmsley Charitable Trust
HR	Human resources
HTA	Health Technology Assessment

Acronym	Meaning
HTS	High-throughput screening
IAC	Internal Audit Capability
IAPO	International Alliance of Patients' Organisations
IAS	Internal Audit Service of the European Commission
ICC	Internal Control Coordinator
ICH	International Conference On Harmonisation Of Technical Requirements For Registration Of Pharmaceuticals For Human Use
ICI	Immune Checkpoint Inhibitor
ICS	Internal Control Standards
ICT	Information Communications Technology
ILG	Industry Liaison Group
IMI JU	Innovative Medicines Initiative Joint Undertaking
IMI2 JU	Innovative Medicines Initiative 2 Joint Undertaking
IMI2 JU AP	IMI2 JU Associated Partner
IMPD	Investigational Medicinal Product Dossier
iMRM	Immuno-Multiple Reaction Monitoring
IMRT	Intensity-Modulated Radiation Therapy
INDSR	Investigational New Drug Study Report
IPD	Individual Patient Data
iPS	Induced Pluripotent Stem
iPS cells	Induced pluripotent stem cells
ISA	Information System for Absences
ISO	International Organization For Standardization
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
KUM	Klinikum Of The University Of Munich
LAM	Lipoarabinomannan, A Component Of The Mycobacterium Tuberculosis Cell Wall.
MAPPs	Medicines adaptive pathways to patients
MDR-TB	Multidrug Resistant-Tuberculosis
MEP	Member of the European Parliament
MERS-CoV	Middle East respiratory syndrome coronavirus
ML	Machine Learning
MOA	mechanisms-of-action
MRD	Minimal Residual Disease
MRI	Magnetic resonance imaging
MS	Multiple sclerosis
MTA	Material transfer agreement
MTB	Mycobacterium Tuberculosis
NCE	New Chemical Entity (A Candidate Medicine Or Drug)
ND4BB	New Drugs for Bad Bugs
NGS	Next Generation Sequencing
NIMH	National Institute of Mental Health
NSCLC	Non-Small Cell Lung Cancer
OAC	Obesity Action Coalition
OECD	Organisation for Economic Co-operation and Development
OLAF	European Anti-Fraud Office
PA	Payment Appropriation
pCR	Pathological Complete Response
PCR	Polymerase Chain Reaction

Acronym	Meaning
PDO	Patient-Derived Organoid
PDX	Patient-Derived Xenograft
PEC	Predicted Environmental Concentration
PET	Positron emission tomography
PBT	persistent, bioaccumulative and toxic
PIC	Patient Informed Consent
PIE	pharmaceuticals in the environment
PKPD	Pharmacokinetic-Pharmacodynamic
PM	Person/month
PMDA	Pharmaceuticals and Medical Devices Agency
PPP	Public-private partnership
PRO	Patient reported outcomes
PsA	Psoriatic Arthritis
PsO	Psoriasis
PSRI	Periodic Safety Reports For Investigators
PT	Proton Therapy
QST	Quantitative sensory testing
R&D	Research and development
RA	Rheumatoid arthritis
RAE	Risk assessment exercise
RCSA	Risk and control self-assessment
RECIST	Response Evaluation Criteria In Solid Tumours
RepER	Representative error rate
ResER	Residual error rate
RI	Research Infrastructure
RIA	Research and Innovation Action
RNA	Ribonucleic Acid
RP	Reporting Period
RSV	Respiratory Syncytial Virus
RT	Radiotherapy with photons
RTOs	Research and Technology Organisations
SAICM	Strategic Approach to International Chemicals Management
SARS-CoV	Severe acute respiratory syndrome
SC	Scientific Committee
scRNA-seq	Single-Cell RNA-Sequencing – Expression Of The Transcriptome Per Single Cell
SEND	CDISC SEND Controlled Terminology
SGGs	Strategic Governing Groups
Smart-seq2	(Switching Mechanism At 5' End Of RNA Template) Technology Which Enables Sensitive And Robust Sequencing Of Single-Cell Or Ultra-Low-Input RNA Samples – Sequences Entire Transcript
SMEs	Small and medium-sized enterprises
SLC	Solute carriers
SOFIA	Submission of Information Application
SOP	Standard operating procedure
SP	Short Proposal
SRA	Strategic Research Agenda
SRG	States Representatives Group
SUSAR	Suspected Unexpected Serious Adverse Reaction
T1D	Type 1 diabetes
T2D	Type 2 diabetes
TA	Temporary Agent
TB	Tuberculosis
TDTC	Tuberculosis Drug Treatment Development Consortium
TTG	Time to Grant

Acronym	Meaning
TTP	Time to Pay
UK	United Kingdom Of Great Britain And Northern Ireland
US	United States
USD	US Dollar
VAF	Variant Allele Frequency
WHO	World Health Organisation
WP(s)	Work Package(s)
XDR-TB	Extensively Drug Resistant-Tuberculosis

