# Draft 2020 Annual Work Plan and Budget



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 Annual Work Plan will be made publicly available after its adoption by the Governing Board

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NOTICE

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

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

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

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

In the long term, these activities will help IMI2 JU to achieve its goals of accelerating and improving medicines development and ensuring that new discoveries are rapidly transformed into benefits for both the wider medical research community, 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 three 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 enable the IMI2 JU programme achieve its goals. Given the global nature of the challenges being addressed these outreach activities will also focus on bringing on board actors from outside of the EU and associated countries.

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

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

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

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

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

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

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

## Risks & mitigations

Risks 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 IMI Strategic research Agenda (SRA) might not be developed. IMI 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 political (including Brexit outcome), economic and scientific environment surrounding the IMI2 JU activities is changing quickly (new European Commission and new Parliament, new legal framework for research and innovation, etc.). These factors may affect the final implementation and the future of the 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. 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 IMI objectives and challenges of the legal framework (e.g. no EU funds for industry, 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 (IMI website); iii) involving the IMI2 advisory bodies 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 three competitive Calls for proposals, each covering several topics (see table at the end of this section), with predefined launch dates foreseen for Q1 and Q2 in 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.

**"Pain" portfolio:**

3. **Digital endpoints and placebo effect in chronic pain.** The primary aim of this call is to progress digital endpoint(s) to Health Authority acceptance as primary / surrogate endpoints or key secondary endpoints for evaluation of chronic pain in pivotal clinical trials. The intention of this call is not to simply explore digital endpoint space in chronic pain, but to deliver endpoints ultimately via medical grade devices that can subsequently be used for regulatory approval. As the placebo effect in pain clinical trials is substantial, an additional aim is to assess new methods to better understand and control placebo effects to determine the real treatment advantage offered by analgesic agents.

**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)
- Enable more efficient and cost-effective clinical trials and real-world studies in chronic pain.
- Allow for close interactions with digital technology companies to help validating digital endpoints for integrated care solutions.

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 optimizing 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.

4. **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.
5. **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.
6. **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; (i) *in silico* platform for knowledge management and mathematical modelling of the immune system; (ii) novel controlled human infection models (CHIMs); (iii) next-generation human in vitro systems and assays; and (iv) *in silico* platform for modelling vaccine substance and product attributes in biomanufacturing.
7. **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 (EU ad not EU countries) 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.

**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 deliveryof 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 governalmental 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 biomanufacturing 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

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 maximize 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 proactive return of clinically relevant information to study participants during and after a clinical trial:** The objective of this topic is to deliver a successful proof of concept for returning clinical trial data to study participants in Europe during and after the trial. The sharing of data collected in a clinical trial with study participants is still uncommon. The main reasons for this include the complexities in setting up the infrastructure, processes and a common data format to enable this and concerns around protecting the integrity of the study, maintaining the blinding. However, there is an increasing awareness that greater transparency and engagement with study participants is needed in clinical research. While the moral and ethical case for returning data back to study participants is clear, there are also pragmatic reasons for undertaking this. Firstly, data returned to patients post trial may enable patients to better engage with their on-going disease management. Secondly, data returned during the trial may improve the overall clinical trial experience for patients and in doing so also optimise adherence to study protocol procedures and improve overall study retention. Finally, returning clinical trial data in a meaningful format and connecting this to data captured in routine clinical care creates a valuable bank of information that the patient can choose to utilise for their health care decisions or for research purposes.

**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 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 tumors" (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 determine if proton therapy in a trimodality 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.

**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 tumor 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 esophageal 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

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 early identify 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.

**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. In the interest of better and faster development of medicinal products for rare diseases, this topic will support activities for a 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 payors 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 neuromuscular disease 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)[1],[2] | Indicative in-kind contribution (in EUR) from EFPIA entities and Associated Partners |
|---|---|---|---|
| **IMI2 Call 20**<br>▪ *Infection control including vaccines*<br>▪ Academia and industry united innovation and treatment for tuberculosis (UNITE4TB)<br>▪ Innovations to accelerate vaccine development and manufacture<br>▪ *Oncology*<br>▪ Real-world clinical implementation of liquid biopsy<br>▪ Tumour plasticity<br>▪ Proton versus photon therapy for oesophageal cancer – a trimodality strategy<br>▪ *Immunology*<br>▪ Early diagnosis, prediction of radiographic outcomes and development of rational, personalised treatment strategies to improve long-term outcomes in Psoriatic Arthritis<br>▪ *Other enablers of research topics*<br>▪ Handling of protein drug products and stability concerns | 21 January 2020 | 136,832,000 | 144,509,500 |
| **IMI2 Call 20 process** | | | |
| Two-stage call with predefined submission deadline<br>Indicative Call deadline for **short proposals: 21 April 2020**<br>Indicative Call deadline for **full proposals: 5 November 2020**<br>Research and Innovation Actions (RIA) | | | |

[1] 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 Calls 14 and 15.
[2] The maximum possible rate of co-financing is 100 %.

| Call number and indicative topics | Indicative Call launch timing | Indicative IMI2 JU funding (in EUR)[3],[4] | Indicative in-kind contribution (in EUR) from EFPIA entities and Associated Partners |
|---|---|---|---|
| **IMI2 Call 21**<br>▪ *Neurodegeneration and other neuroscience priorities*<br>▪ Rare neurodegenerative and neurocognitive diseases clinical platform development<br>▪ Complement in neurodegenerative diseases<br>▪ Digital endpoints and placebo effect in chronic pain<br>▪ *Infection control including vaccines*<br>▪ Development of innovative personalized diagnostics and patient-guided therapies for the management of sepsis-induced immune suppression<br>▪ Modelling the impact of monoclonal antibodies and vaccines on the reduction of antimicrobial resistance<br>▪ *Big data, digital health, clinical trials and regulatory research*<br>▪ Data lakes<br>▪ Personalised endpoints<br>▪ Returning clinical trial data to patients: The proactive return of clinically relevant information to study participants during and after a clinical trial<br>▪ *Oncology*<br>▪ Microbiome<br>▪ *Translational safety*<br>▪ Pharmacodynamic drug-drug interaction predictive testing by learning algorithms to enhance safety<br>▪ Digital vivarium<br>▪ *Facilitating Rare Disease therapies (including Advanced Therapy Medical Products) reaching patients in Europe*<br>▪ Clinical outcomes assessments for rare diseases<br>▪ Defragmenting and shortening the path to rare disease diagnosis by using genetic | 23 June 2020 | 105,379,320 | 101,490,500 |

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

| Call number and indicative topics | Indicative Call launch timing | Indicative IMI2 JU funding (in EUR)[3,4] | Indicative in-kind contribution (in EUR) from EFPIA entities and Associated Partners |
|---|---|---|---|
| screening and digital technologies | | | |
| **IMI2 Call 21 process** | | | |
| Two-stage call with predefined submission deadline<br>Indicative Call deadline for **short proposals: 29 September 2020**<br>Indicative Call deadline for **full proposals: 17 March 2021**<br>Research and Innovation Actions (RIA) and Coordination and Support Actions (CSA) | | | |

| Call number and indicative topics | Indicative Call launch timing | Indicative IMI2 JU funding (in EUR)[5] | Indicative in-kind contribution (in EUR) from EFPIA entities and Associated Partners |
|---|---|---|---|
| **IMI2 Call 22**<br>*Restricted Call*[6]<br>Restricted Call to maximise impact of IMI2 JU objectives and scientific priorities | 23 June 2020 | 20,000,000 | 0 |
| **IMI2 Call 22 process** | | | |
| One-stage call with predefined submission deadline<br>Indicative Call deadline for **full proposals: 29 September 2020**<br>Research and Innovation Actions (RIA)<br>Restricted Call | | | |
| | | | |
| **Overall total IMI2 Call 20, IMI2 Call 21 and IMI2 Call 22** | | **262,211,320** | **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 the Annual Work Plan 2020.

### *Budget*

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

[5] The maximum possible rate of co-financing is 100 %.
[6] The launch of this Call is subject to the assessment of the outcome of the IMI2 Call 19 Restricted Call in 2019.

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

| | Heading Title 3 | Financial year 2020 | | Comments |
|---|---|---|---|---|
| **Chapter** | | Commitment Appropriation (CA) | Payment Appropriation (PA) | |
| **30** | Implementing the research agenda of IMI JU | 255,896,732 | 198,005,365 | Grant agreements - Payments |
| **30** | Implementing the research agenda of IMI JU - carry over from 2019 | 6,314,588 | | The amount carried over from 2019 (IMI2 Calls 14 and 15) |
| | ***Total operational costs Title 3*** | ***262,211,320*** | ***198,005,365*** | |

The difference between the total budget available for Title 3 and the budget available for new Calls in 2020 is EUR 6 314 588. This amount represents the unused commitment appropriations from IMI2 Call 14 and IMI2 Call 15 carried over from 2019 to the 2020 budget and available for IMI2 Call 20. There will be additional amounts carried-over from 2019 but it will be determined at the beginning of 2020 based on the final year budget execution.

A table overview of the 2020 Budget is set out in Chapter 3 to this Annual Work Plan.

### 2.2.3 Call management (planning, evaluation, selection, …)

Key activities in 2020 will comprise the launch of three competitive Calls for proposals implementing the 2020 scientific priorities with indicative launch dates on 21 January 2020 for the first call of the year and 23 June 2020 for the other two calls.

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

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

In addition, the evaluation of short proposals and full proposals submitted in response to Calls launched under the AWP 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.[7]

For Call management, IMI2 JU will utilise the Horizon 2020 IT infrastructure available under Funding & tender opportunities - Single Electronic Data Interchange Area (SEDIA)[8].

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

### 2.2.4 Activities to support and monitor ongoing projects

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 Calls 18 and 19 (launched in 2019) completes 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.

[7] 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'

[8] https://ec.europa.eu/info/funding-tenders/opportunities/portal/screen/home

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

| | | | Project periodic report due in 2020 | | | | | | Of which | |
|---|---|---|---|---|---|---|---|---|---|---|
| IMI Calls | ongoing in 2020 | Reports due after 31/10/2019 | 1st RP in 2020 | 2nd RP in 2020 | 3rd RP in 2020 | 4th RP in 2020 | 5th to 7th RP in 2020 | Total reports | Project ending in 2020 | Final report due in 2020 |
| 1 | | | | | | | | | | |
| 2 | | | | | | | | | | |
| 3 | | | | | | | | | | |
| 4 | | | | | | | | | | |
| 5 | | | | | | | | | | |
| 6 | 1 | | | | | | 1 | 1 | 1 | 1 |
| 7 | | | | | | | | | | |
| 8 | 1 | | | | | | 1 | 1 | 1 | 1 |
| 9 | 1 | | | | | | 1 | 1 | 1 | 1 |
| 10 | 1 | | | | | | 1 | 1 | 1 | 1 |
| 11 | 7 | | | | | | 7 | 7 | 3 | 4 |
| **IMI1** | **11** | **0** | **0** | **0** | **0** | **0** | **11** | **11** | **7** | **8** |
| IMI2 C1 | 1 | | | | | | 1 | 1 | | |
| IMI2 C2 | 1 | | | | | | 3 | 3 | | 2 |
| IMI2 C3 | 4 | | | | | 4 | | 4 | 1 | 1 |
| IMI2 C4 | | | | | | | | | | |
| IMI2 C5 | 5 | 1 | | | | 5 | | 6 | | |
| IMI2 C6 | 3 | 1 | | | 3 | | | 4 | | |
| IMI2 C7 | 6 | 1 | | | 6 | | | 7 | 1 | 1 |
| IMI2 C8 | 4 | | | 3 | 1 | | | 4 | | |
| IMI2 C9 | 6 | | | 1 | 5 | | | 6 | 2 | 2 |
| IMI2 C10 | 8 | | | 8 | | | | 8 | 2 | 2 |
| IMI2 C11 | 3 | | | 3 | | | | 3 | 3 | 3 |
| IMI2 C12 | 7 | | 7 | | | | | 7 | | |
| IMI2 C13 | 13 | | 13 | | | | | 13 | | |
| IMI2 C14 | 4 | | 4 | | | | | 4 | | |
| IMI2 C15 | 7 | | 7 | | | | | 7 | | |
| IMI2 C16 | 5 | | 5 | | | | | 5 | | |
| IMI2 C17* | 3 | | | | | | | 0 | | |
| IMI2 C18* | 6 | | | | | | | 0 | | |
| IMI2 C19* | 4 | | | | | | | 0 | | |
| **IMI2** | **90** | **3** | **36** | **15** | **15** | **9** | **4** | **82** | **9** | **11** |
| **Totals** | **101** | **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 Calls.

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 IMI 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).

**Patient engagement**

Building on the experience of patient engagement so far, the IMI2 JU Programme Office will continue to work on developing an open and transparent system of meaningful patient engagement at all levels.

Having already put in place a new initiative, the IMI 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 IMI 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 IMI Pool of patient experts, the IMI2 JU 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 IMI 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, IMI 2 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, the 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 Horizon 2020 Associated Countries, the IMI2 JU will remain engaged with SMEs and encourage their participation in IMI2 JU projects. In 2020, the IMI2 JU will continue to highlight SME opportunities in all topic texts and also embed SME participation at the earliest stages of topic development, for example through exploring call designs more appealing to SMEs.

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

**Regulators**
The regulatory environment is key 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 IMI founding members and relevant experts will be organised in order to identify gaps and bring new ideas for future topics.

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

### *2.2.7* Dissemination and information about projects results

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

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

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

In 2020, the 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.

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 and an additional assessment with a new methodology may be considered as a pilot project.

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 IMI1 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 2018-2020[9].

### LIST OF COUNTRIES AND APPLICABLE RULES FOR FUNDING

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

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

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

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

(ii) secondary and higher education establishments,

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

(c) the Joint Research Centre;

(d) international European interest organisations.

Participating legal entities listed in (b) above established in a third country may receive funding from the IMI2 JU provided their participation is deemed essential for carrying out the action by the IMI2 JU or when such funding is provided for under a bilateral scientific and technological agreement or any other arrangement between the Union and the country in which the legal entity is established[11].

### 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

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

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

[11] 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 condition[12] 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<br><br>***The following aspects will be taken into account, to the extent that the proposed work corresponds to the topic description in the call for proposals and referred to in the IMI2 JU annual work plan:*** | Impact<br><br>***The following aspects will be taken into account:*** | Quality and efficiency of the implementation<br><br>***The following aspects will be taken into account:*** |
|---|---|---|---|

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

| Type of action | Excellence<br><br>*The following aspects will be taken into account, to the extent that the proposed work corresponds to the topic description in the Call for proposals and referred to in the IMI2 JU annual work plan and, for two stage procedures, is consistent with the stage 1 proposal:* | Impact<br><br>*The following aspects will be taken into account:* | Quality and efficiency of the implementation<br><br>*The following aspects will be taken into account:* |
|---|---|---|---|
| **RIA**<br><br>**2nd stage of two-stage evaluation**<br><br>**and**<br><br>**Single stage evaluation** | ▪ Level to which all the objectives of the Call topic text are addressed;<br><br>▪ Soundness of the concept and credibility of the proposed methodology;<br><br>▪ Extent that the proposed work is beyond the state of the art and demonstrates innovation potential;<br><br>▪ Appropriate consideration of interdisciplinary approaches and use of stakeholder knowledge. | ▪ Demonstration of how the outputs of the project will contribute to each of the expected impacts mentioned in the relevant Call topic text;<br><br>▪ 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;<br><br>▪ Impacts on competitiveness and growth of companies including SMEs;<br><br>▪ Quality and effectiveness of the proposed measures to:<br>▪ Disseminate, exploit and sustain the project results;<br>▪ Manage research data;<br>▪ Communicate the project activities to relevant target audiences. | ▪ Quality and effectiveness of the work plan, including extent to which the resources assigned to work packages are in line with their objectives and deliverables;<br><br>▪ Appropriateness of the management structures and procedures, including management of risk and innovation;<br><br>▪ Appropriateness of the allocation of tasks, ensuring that all participants have a valid role and adequate resources in the project to fulfil that role;<br><br>▪ Complementarity of the participants and extent to which the consortium as whole brings together the necessary expertise;<br><br>▪ 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.[13]

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

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

Under the two-stage evaluation procedure, and on the basis of the outcome of the first stage evaluation, the applicant consortium of the highest ranked short proposal (first stage) for each topic[14] will be invited to discuss with the relevant industry consortium the feasibility of jointly developing a full proposal (second stage).

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

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

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

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

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

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

## INDICATIVE TIMETABLE FOR EVALUATION AND GRANT AGREEMENT

| | Information on the outcome of the evaluation<br><br>(single stage, or first stage of a two-stages) | Information on the outcome of the evaluation<br><br>(second stage of a two stages) | Indicative date for the signing of grant agreement |
|---|---|---|---|
| **Single-stage** | Maximum 5 months from the submission deadline at the single stage. | N/A | Maximum 8 months from the submission deadline. |
| **Two-stages** | Maximum 5 months from the submission deadline at the first stage. | Maximum 5 months from the submission deadline at the second stage. | Maximum 8 months from the submission deadline at the second stage. |

## BUDGET FLEXIBILITY

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

## ACTIONS INVOLVING FINANCIAL SUPPORT TO THIRD PARTIES

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

## CONDITIONS RELATED TO OPEN ACCESS TO RESEARCH DATA

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

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

## SUBMISSION TOOL

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

No other means of submission will be accepted.

## OTHERS

For proposals including clinical trials/studies/investigations, a specific template to help applicants to provide essential information on clinical studies in a standardised format is available under: 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. [15]

In order to ensure excellence in data and knowledge management consortia will be requested to Disseminate scientific publications on the basis of open access[16] (see 'Guidelines on Open Access to Scientific Publications and Research Data in Horizon 2020').

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

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

Applicants intending to submit a proposal in response to the IMI2 JU Calls should also read the topic text, the IMI2 JU Manual for submission, evaluation and grant award, and other relevant documents[17] (e.g. IMI2 JU model Grant Agreement).



[15] Article 19 of Horizon 2020 Framework Programme and Articles 13 and 14 of the Horizon 2020 Rules for Participation.
[16] Article 43.2 of Regulation (EU) No 1290/2013 of the European Parliament and of the Council laying down the rules for participation and dissemination in "Horizon 2020 - the Framework Programme for Research and Innovation (2014-2020)" and repealing Regulation (EC) No 1906/2006
[17] http://www.imi.europa.eu/apply-funding/call-documents/imi2-call-documents

## 2.4 Support to Operations

### 2.4.1 Communication and events

#### Communication objectives

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

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

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 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 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, etc.);
- media (general and specialist, mainly in Europe but also elsewhere);
- direct mailings;
- publications;
- videos;
- direct contacts with opinion leaders.

In 2020 IMI 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

IMI 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.

The 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, over a 4-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 IMI1 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*

IMI2 JU 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 objective 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 human resources 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 Stand Working Party 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 activates 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 activates.

IMI 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. Teambuilding activities will also be organised to strengthen the collaboration among staff members and to enhance the team spirit.

The human resource team will keep overseeing duties and responsibilities assigned to staff in order to achieve the fulfilment of 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 forecast 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 1.12% in 2020 compared to 2019, is mainly due to increase in staff related expenditures, rent costs as well as costs of evaluations. A comparison table of the financial years 2019 and 2020 is set out below.

| | Heading Title 1 | Financial year 2019 | Financial year 2020 | Evolution | Comments |
|---|---|---|---|---|---|
| Chapter | | Budget EUR | Budget EUR | | |
| 11 | Staff in active employment | 5,740,000 | 5,963,337 | 3.89% | 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 | Entertainment and representation | 20,000 | 19,538 | -2.31% | |
| | **Title 1 Staff expenditure - Total** | **6,330,000** | **6,570,961** | **3.81%** | |

| | Heading Title 2 | Financial year 2019 | Financial year 2020 | Evolution | |
|---|---|---|---|---|---|
| Chapter | | Budget EUR | Budget EUR | | |
| 20 | Office building and associated costs | 756,000 | 776,625 | 2.73% | Indexation and additional space. |
| 21 | Information technology purchases | 779,000 | 786,394 | 0.95% | 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. |
| | **Title 2 - Total** | **4,690,154** | **4,572,809** | **-2.50%** | |
| | **Total Administrative Costs** | **11,020,154** | **11,143,770** | **1.12%** | |

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 2018 revised Regulation (EU, Euratom) 2018/1046 on the financial rules applicable to the general budget of the Union, repealing Regulation (EU, Euratom) No 966/2012 (2012 Financial Regulation).

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

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

### 2.4.6 Data protection

The IMI2 JU will continue its efforts undertaken in the wake of the entry into effect of 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 the JU participates.

### 2.4.7 Access to documents

IMI2 JU will continue to address requests for access to IMI2 JU documents according to Regulation (EC) No 1049/2001, in a spirit of openness and transparency in order to bring its activities and outputs closer to the public. 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 chairmanship 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, the JU will pursue its action to attract a wide range of stakeholders from various sectors, notably by promoting the possibility to become **Associated Partners** at programme or topic level and supporting such an involvement. Practical information can be found at: http://www.imi.europa.eu/get-involved.

The **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 IMI2 JU Programme Office and the SC. Currently, the seven established SGGs focus on the following areas: immunology; diabetes / metabolic disorders; neurodegeneration; translational safety; infections control; oncology; and digital health and patient-centric evidence generation.

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.[18]



[18] 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 performance[19] 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 IMI2 JU 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 the IMI1 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 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 IMI since the last audited period to reach the audit coverage ratio set in IMI ex-post audit strategy and if necessary risk based audits will be launched according to IMI risk based audit strategy.

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 IMI1 programme 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.

[19] 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).

As regards the IMI2 programme, IMI's ex-ante and ex-post controls of grants are both aligned with the harmonised strategies adopted for the entire H2020 Programme. The IMI 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 IMI Programme Office contributes to the implementation of the H2020 audit strategy in close cooperation with the CAS and ensures that IMI ex-post audit strategy is complied with, including IMI audit coverage ratio. If necessary, risk based audits will be launched according to IMI risk based audit strategy.

The harmonised legal framework will enable the IMI 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 asses the implementation of the Internal Audit Service (IAS) of the European Commission and the European Court of Auditors (ECA) audit recommendations with the objective to confirm the effective implementation.

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

In 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 IMI2JU 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

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

| STATEMENT OF REVENUE | | | | |
|---|---|---|---|---|
| | **Heading Revenue** | **Financial year 2020** | | **Comments** |
| **Chapter** | | Commitment Appropriation (CA) | Payment Appropriation (PA) | |
| **10** | European Commission contribution (including EFTA contribution/Draft Budget 2020[20]) | 261,468,617 | 201,077,250 | Commitment appropriations include EUR 5,571,885 for administrative costs and EUR 255,896,732 for operational costs. Payment appropriations include administrative costs of EUR 5,571,885 and operational costs of EUR 195,505,365. |
| **C2** | Appropriations carried over | 6,314,588 | | The amount carried over from previous year. Operational expenditure - commitment appropriation. |
| | **Title 1 - Total** | **267,783,205** | **201,077,250** | |
| **20** | EFPIA contribution | 5,571,885 | 5,571,885 | 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 | Four EFPIA companies contribution to operational payment appropriations |
| | **Title 2 - Total** | **5,571,885** | **6,571,885** | |
| **30** | Associated Partners contributions | - | 1,500,000 | Bill and Melinda Gates Foundation contribution to operational payment appropriations |
| | **Title 3 - Total** | | **1,500,000** | |
| | **Total contributions** | **273,355,090** | **209,149,135** | |

[20] Subject to approval of European Union Draft Budget (DB) for 2020 by the Budgetary Authority (comprised of the Council of the European Union and the European Parliament) as proposed by the European Commission.

| STATEMENT OF EXPENDITURE | | | | |
|---|---|---|---|---|
| | **Heading Title 1** | **Financial year 2020** | | **Comments** |
| Chapter | | Commitment Appropriation (CA) | Payment Appropriation (PA) | |
| **11** | Staff in active employment | 5,963,337 | 5,963,337 | Salaries |
| **12** | Staff recruitments - miscellaneous expenditure | 19,538 | 19,538 | Miscellaneous expenditure on staff recruitment: travel expenses, etc. |
| **13** | Missions and duty travels | 185,608 | 185,608 | Mission expenses |
| **14** | Socio-medical structure | 207,100 | 207,100 | Other staff costs: training, language classes, medical service, |
| **15** | External staff services | 175,840 | 175,840 | Interim staff |
| **17** | Representation | 19,538 | 19,538 | Representation, receptions and internal meetings |
| | **Title 1 - Total** | **6,570,961** | **6,570,961** | |
| | **Heading Title 2** | **Financial year 2020** | | **Comments** |
| Chapter | | Commitment Appropriations (CA) | Payment Appropriations (PA) | |
| **20** | Office building and associated costs | 776,625 | 776,625 | Rent, works, common/IMI charges and parking. Additional costs: indexation, insurance, water/gas, electricity, heating, maintenance + repairs, security and surveillance. |
| **21** | Information technology purchases | 786,394 | 786,394 | IT purchases, software licences, software development, IMI website. |
| **22** | Office equipment (movable property and associated costs) | 154,348 | 154,348 | Purchases and rental of office equipment, maintenance and repair. |

| | Heading Title 2 | Financial year 2020 | | Comments |
|---|---|---|---|---|
| Chapter | | Commitment Appropriations (CA) | Payment Appropriations (PA) | |
| 23 | Current administrative expenditure | 122,111 | 122,111 | Office supply. Literature, subscriptions, translation services, bank charges and miscellaneous office expenditure. |
| 24 | Telecommunication and postal expenses | 78,151 | 78,151 | Data communication such as telephone, video conferences and postal services. |
| 25 | Expenditure on formal meetings | 156,302 | 156,302 | Official meetings such as IMI2 JU States Representatives Group, Scientific Committee, Governing Board and working groups created by the IMI2 JU Governing Board. |
| 26 | Running costs in connection with operational activities | 388,801 | 388,801 | Expenditure in connection with research activities and objectives of IMI (workshops, meetings and events targeting IMI projects). |
| 27 | External communication, information and publicity | 610,555 | 610,555 | External communication and events such as Info Days, stakeholder forums. |
| 28 | Service contracts | 522,635 | 522,635 | Studies, audits. |
| 29 | Expert contracts and cost of evaluations | 976,887 | 976,887 | Costs linked to evaluations, expert contracts. |
| | **Title 2 - Total** | **4,572,809** | **4,572,809** | |
| | ***Total administrative costs Title 1 + Title 2*** | ***11,143,770*** | ***11,143,770*** | |

| | Heading Title 3 | Financial year 2020 | | Comments |
|---|---|---|---|---|
| Chapter | | Commitment Appropriation (CA) | Payment Appropriation (PA) | |
| 30 | Implementing the research agenda of IMI2 JU | 255,896,732 | 198,005,365 | Grant agreements - Payments |
| C2 | Implementing the research agenda of IMI2 JU | 6,314,588 | | Appropriations carried over from 2019 |
| | ***Total operational costs Title 3*** | **262,211,320** | ***198,005,365***[21] | |
| | **Total contributions** | **273,355,090** | **209,149,135** | |



[21] In 2019, the IMI2 JU returned to the EC 139,100,891 EUR operational commitment appropriations following the reduction of IMI2 Call 18 commitment. Consequently, operational payment appropriations forecasts related to the pre-financing for new grant agreements for 2020 have been substantially reduced. In the interest of ensuring sound financial management of public funds and efficient operational planning, IMI2 JU is continuously reviewing all payment appropriation forecasts for 2020 and, if necessary, will request a reduction of 2020 payment appropriations in a future amendment of the AWP 2020.

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

| Expense budget line | Description | Commitment appropriations | Payment appropriations |
|---|---|---|---|
| A01100 | Staff in active employment and costs linked to employment | 3,838,337 | 3,838,337 |
| 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 (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 |

| Expense budget line | Description | Commitment appropriations | Payment appropriations |
|---|---|---|---|
| A01190 | Weightings (correction coefficient) | 4,000 | 4,000 |
| A01191 | Salaries adaptation | 0 | 0 |
| **11** | **Staff in active employment** | **5,963,337** | **5,963,337** |
| A01200 | Miscellaneous expenditure on staff recruitment | 19,538 | 19,538 |
| **12** | **Staff recruitments - miscellaneous expenditure** | **19,538** | **19,538** |
| A01300 | Mission expenses | 185,608 | 185,608 |
| **13** | **Missions and duty travels** | **185,608** | **185,608** |
| A01401 | Socio-medical structure, EU school | 80,000 | 80,000 |
| A01410 | Other trainings | 76,100 | 76,100 |
| A01430 | Medical service | 20,000 | 20,000 |
| A01440 | Trainings covered by the SLA | 31,000 | 31,000 |
| A01490 | Other interventions | 0 | 0 |
| **14** | **Socio-medical structure** | **207,100** | **207,100** |
| A01500 | External staff expenditures | 175,840 | 175,840 |
| **15** | **External staff services** | **175,840** | **175,840** |
| A01700 | Representation expenses | 19,538 | 19,538 |
| **17** | **Representation** | **19,538** | **19,538** |
| | **Title 1 Staff expenditure - Total** | **6,570,961** | **6,570,961** |

| Expense budget line | Description | Commitment appropriations | Payment appropriations |
|---|---|---|---|
| A02000 | Rentals | 566,625 | 566,625 |
| A02001 | Guarantees | 0 | 0 |
| A02002 | Contributions | 0 | 0 |
| A02010 | Insurance | 0 | 0 |
| A02020 | Water gas electricity and charges | 161,000 | 161,000 |
| A02030 | Cleaning and maintenance | 10,000 | 10,000 |
| A02040 | Furnishing of premises (works) | 10,000 | 10,000 |
| 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** |
| A02101 | Hardware, infrastructure and related services | 255,000 | 255,000 |
| A02102 | Software development, licenses and related services | 531,394 | 531,394 |
| A02103 | Other expenses maintenance and repair | 0 | 0 |
| **21** | **Information technology purchases** | **786,394** | **786,394** |

| Expense budget line | Description | Commitment appropriations | Payment appropriations |
|---|---|---|---|
| A02200 | Purchase | 124,348 | 124,348 |
| A02201 | Rentals | 10,000 | 10,000 |
| A02202 | Maintenance utilisation and repair | 20,000 | 20,000 |
| A02203 | Other office equipment | 0 | 0 |
| **22** | **Office equipment (movable property and associated costs)** | **154,348** | **154,348** |
| A02300 | Stationery and office supply | 40,000 | 40,000 |
| A02320 | Bank charges | 0 | 0 |
| A02321 | Exchange rate losses | 0 | 0 |
| A02329 | Other financial charges | 0 | 0 |
| A02330 | Legal expenses | 20000 | 20000 |
| A02350 | Other operating expenditure | 13,000 | 13,000 |
| A02351 | Petty expenses | 0 | 0 |
| A02360 | Library stocks purchase of books and subscriptions | 44,000 | 44,000 |
| A02370 | Translation interpretation | 5,111 | 5,111 |

| Expense budget line | Description | Commitment appropriations | Payment appropriations |
|---|---|---|---|
| **23** | **Current administrative expenditure** | **122,111** | **122,111** |
| A02400 | Correspondence and communication expenses | 78,151 | 78,151 |
| **24** | **Telecommunication and postal expenses** | **78,151** | **78,151** |
| A02500 | Formal meetings | 156,302 | 156,302 |
| **25** | **Expenditure on formal meetings** | **156,302** | **156,302** |
| A02600 | Administrative costs in connection with operational activities | 47,801 | 47801 |
| A02601 | Events | 10,000 | 10,000 |
| A02602 | Workshops | 325,000 | 325,000 |
| A02603 | Knowledge Management | 6,000 | 6,000 |
| **26** | **Administrative costs in connection with operational activities** | **388,801** | **388,801** |
| A02700 | External communication | 210,555 | 210,555 |
| A02701 | Events | 300,000 | 300,000 |
| A02702 | Material | 100,000 | 100,000 |
| **27** | **External communication, information and publicity** | **610,555** | **610,555** |

| Expense budget line | Description | Commitment appropriations | Payment appropriations |
|---|---|---|---|
| A02800 | Ex-post Audits | 250,000 | 250,000 |
| A02801 | Studies, consultancy | 177,635 | 177,635 |
| A02802 | Audit services | 60,000 | 60,000 |
| A02803 | Accounting services | 35,000 | 35,000 |
| **28** | **Service contracts** | **522,635** | **522,635** |
| A02900 | Evaluation Experts meetings | 956,887 | 956,887 |
| A02901 | Evaluation Facilities | 20,000 | 20,000 |
| A02902 | Evaluations ENSO | 0 | 0 |
| **29** | **Expert contracts and cost of evaluations** | **976,887** | **976,887** |
| | **Title 2 Infrastructure and operating expenditure - Total** | **4,572,809** | **4,572,809** |
| **B03000** | **Implementing the research agenda of IMI1 JU** | | **2,500,000** |
| **B03001** | **Call 1** | | |
| **B03002** | **Call 2** | | |
| **B03003** | **Call 3** | | |

| Expense budget line | Description | Commitment appropriations | Payment appropriations |
|---|---|---|---|
| B03004 | Call 4 | | |
| B03005 | Call 5 | | |
| B03006 | Call 6 | | 7,500,000 |
| B03007 | Call 7 | | |
| B03008 | Call 8 | | 7,500,000 |
| B03009 | Call 9 | | 2,400,000 |
| B03010 | Call 10 | | 600,000 |
| B03011 | Call 11 | | 14,500,000 |
| B03012 | ENSO 2012 | | |
| B03013 | ENSO 2013 | | |
| B03020 | Implementing the research agenda of IMI2 JU | | 23,405,365 |
| B03021 | IMI2 Call 1 | | 2,500,000 |
| B03022 | IMI2 Call 2 | | 7,400,000 |
| B03023 | IMI2 Call 3 | | 5,600,000 |

| Expense budget line | Description | Commitment appropriations | Payment appropriations |
|---|---|---|---|
| B03024 | IMI2 Call 4 | | |
| B03025 | IMI2 Call 5 | | 7,000,000 |
| B03026 | IMI2 Call 6 | | 6,000,000 |
| B03027 | IMI2 Call 7 | | 5,450,000 |
| B03028 | IMI2 Call 8 | | 6,500,000 |
| B03029 | IMI2 Call 9 | | 7,000,000 |
| B03030 | IMI2 Call 10 | | 19,000,000 |
| B03031 | IMI2 Call 11 | | 300,000 |
| B03032 | IMI2 Call 12 | | 6,600,000 |
| B03033 | IMI2 Call 13 | | 11,617,000 |
| B03034 | IMI2 Call 14 | | 7,614,000 |
| B03035 | IMI2 Call 15 | | |
| B03036 | IMI2 Call 16 | | 3,519,000 |
| B03037 | IMI2 Call 17 | | 10,600,000 |

| Expense budget line | Description | Commitment appropriations | Payment appropriations |
|---|---|---|---|
| B03038 | IMI2 Call 18 | | 19,400,000 |
| B03039 | IMI2 Call 19 | | 16,000,000 |
| B03040 | IMI2 Call 20 | 130,517,412 | |
| B03041 | IMI2 Call 21 | 105,379,320 | |
| B03042 | IMI2 Call 22 | 20,000,000 | |
| B03999 | Recovery Ex-post audit | | |
| 30-C1 | Implementing the research agenda of IMI2 JU | 255,896,732 | 198,005,365 |
| B03040 – C2 | IMI2 Call 20 – C2 | 6,314,588 | |
| | Title 3 - Total | 262,211,320 | 198,005,365 |
| | Total expenditures | 273,355,090 | 209,149,135 |

## 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 | TOTAL |
| 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 |
| 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 in 2018 | 2019 | 2020 |
|---|---|---|---|
| **FG IV** | 1 | 2 | 3 |
| **FG III** | 8 | 12 | 11 |
| **FG II** | 1 | 1 | 1 |
| **FG I** | 0 | 0 | 0 |
| **Total CA** | **15** | **15** | **15** |

| Seconded National Experts | 2019 | 2020 |
|---|---|---|
| | **2** | **2** |

# Annex I - IMI2 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 created[22] following the principles below:

Research related to the future of medicine should be undertaken in areas where societal, public health and biomedical industry competitiveness goals are aligned and require the pooling of resources and greater collaboration between the public and private sectors, with the involvement of Small and Medium-sized Enterprises (SMEs).

The scope of the initiative should be expanded to all areas of life science research and innovation.

The areas should be of public health interest, as identified by the World Health Organisation (WHO) report on priority medicines for Europe and the World[23].

The IMI2 JU objectives are usually implemented through Research and Innovation Actions (RIAs), and Coordination and Support Actions (CSAs) where public and private partners collaborate, joining their expertise, knowledge and resources.

The initiative should therefore seek to involve a broader range of partners, including mid-sized companies[24], 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)[25] 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.



[22] 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.
[23] http://www.who.int/medicines/areas/priority_medicines/en/
[24] 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.
[25] http://www.imi.europa.eu/sites/default/files/uploads/documents/About-IMI/research-agenda/IMI2_SRA_March2014.pdf

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.

Applicant consortia shall ensure that where relevant their proposals are in compliance with the General Data Protection Regulation (EU) 2016/679[26] and Clinical Trial Regulation (EU) 536/2014[27] (and/or Directive 2001/20/EC[28)] and any relevant legislation[29].

Before submitting a proposal, applicant consortia should familiarise themselves with all Call documents such as the IMI2 JU Manual for submission, evaluation and grant award[30], 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).



[26] 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.
[27] 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.
[28] 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.
29 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.
[30] 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 Strategic Research Agenda - Axis of Research | Innovative medicines |
| IMI2 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 enthesis. Cutaneous manifestations often precede articular symptoms and it has been estimated that about 20-30% of psoriatic patients develops arthritis or enthesitis over the time [1]. In fact, this 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 enthesis damage and inflammation. The newest discoveries in PsA pathogenesis have promoted the development of several drugs with different mechanisms of actions 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 treatment could influence the disease. It also seems that the physiopathology of PsA evolves with the “age” of the disease which may give 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;
- identification of patients at risk of progression to PsA early. 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 on such a multifactorial disease represented by its different forms through a wide patient population, which goes beyond the more homogeneous ones enrolled in clinical trials for registrations of new drugs, would require a broad spectrum of expertise 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, 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:

- To enable rheumatologists, dermatologists and general practitioners to make early diagnosis of PsA in patients with PsO and other rheumatic disorders;
- To early identify 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, 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;

- 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 (CyTOF and/or Fluidigm) 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.

## 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 to 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 impact on innovation, research & development; regulatory, clinical and healthcare practices, as relevant. This could include a strategy for the engagement with patients, healthcare professional associations, healthcare providers, regulators, HTA agencies, payers etc, where relevant.

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 standards.[31]

- Disseminate, exploit, and sustain the project results. This may involve engaging with suitable biological and medical sciences Research Infrastructures.[32]

- Communicate the project activities to relevant target audiences

## Potential synergies with existing consortia

Synergies and complementarities should be considered with relevant national, European and non-European initiatives (including suitable biological and medical sciences research infrastructures[64]) 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):

[31] 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
[32] http://www.corbel-project.eu/about-corbel/research-infrastructures.html

- 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 other IMI funded 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.

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 independent from, but carried out in connection with the action and 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 estimated in kind contribution for the prospective activities to generate these data and samples is EUR 9 880 000.

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** | **Number of involved patients** |
|---|---|---|---|
| Novartis | Phase 3, 2 arm study in PsA | Placebo arm only, 16 week treatment duration | 190 |
| UCB | Phase 3 PsA study | Placebo arm only, 16 week treatment duration | 200 |
| UCB | Phase 3 b PsO study | Placebo arm only | 50 |

These data and samples are essential for achieving the objectives of the project.

## 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 with past and present experience on genetic, transcriptomic, proteomic, biomarkers, AI/ML techniques and “big data” management techniques;
- 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 and/or clinical trial centres experienced in PsO/PsA clinical, biological and imaging assessments;
- Strong Data Management experience in managing and coordinating a multi-centre multi-node clinical-research data-generation activity of comparable scope. 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 and 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 (incl. samples and/or data from on-going 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;
- Skills in molecular epidemiology, clinical science, and 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 number 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 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 proposals applicants should:

- Give due visibility on data management; dissemination, exploitation and sustainability; and communication activities. This should include the allocation of sufficient resources for these tasks which will be further developed in stage 2 proposal.

- Consider including a strategy for ensuring the translation of the projects results to drug development, regulatory/ Health Technology Assessment (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.[33]

### Dissemination, exploitation and sustainability of results

[33] 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

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[34], 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).[35]

**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.



[34] As an additional dissemination obligation under Article 29.1 of the IMI2 Grant Agreement will apply
[35] 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.

[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

[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 Strategic Research Agenda - Axis of Research | Innovative medicines |
| IMI2 Strategic Research Agenda - Health Priority | Vaccines |

## Specific challenges to be addressed by public-private collaborative research

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]

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
- in silico platform for modelling 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]. There is the potential for these models to become more sophisticated and to predict how responses to pathogens and vaccines are affected by predisposition [12]]. 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].

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]. Some of these in vitro systems utilise human induced pluripotent stem (iPS) cells, allowing the potential to evaluate human pathogens with consideration to particular predispositions in the donor [30]. 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-sector and cross-sector 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 by developing 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.

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 predisposition;
- 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*, 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-organized *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 mucosas: gastro-intestinal, respiratory and urovaginal.
- Pathogens of interest include influenza, 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.[36]

### Subtopic 4: in silico biomanufacturing

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 the 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.

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 the section ‘Indicative budget’.

[36]Pathogens 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

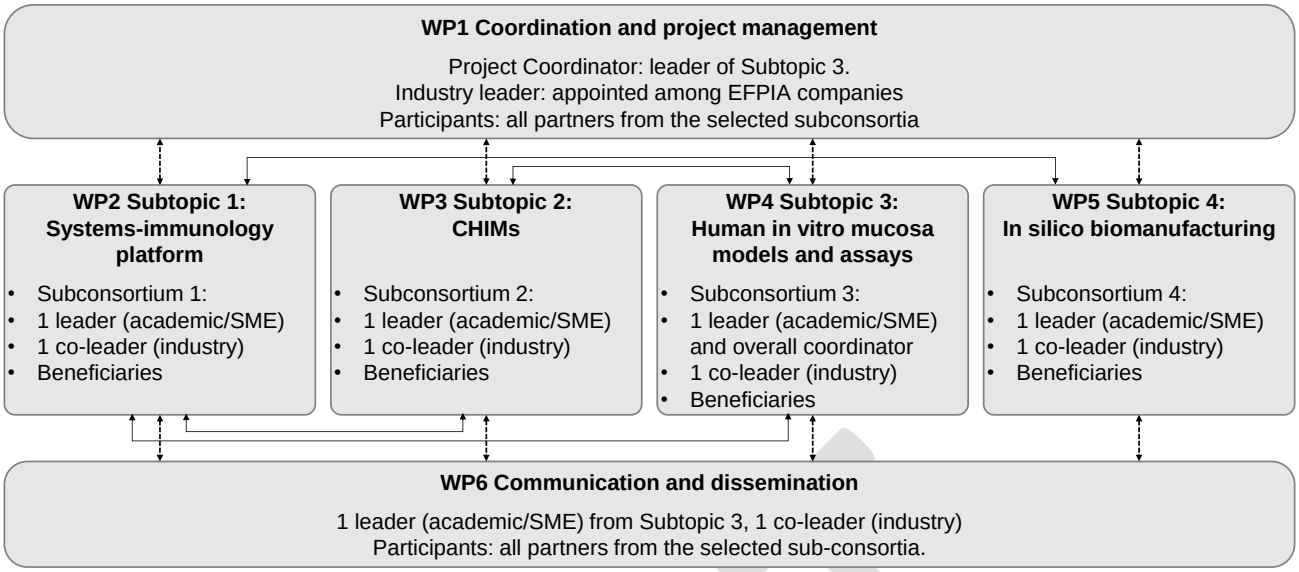


*Figure 1: Consortia composition and interactions between suggested work packages (WPs), where each of the four subtopics will constitute distinct work packages.*

## 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.

### Subtopic 2

- New CHIMs that can accelerate the development of vaccines against, influenza, RSV and C. difficile;
    - Definition of clinical and laboratory (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 predispositions;
    - Clear definitions of rescue therapy including appropriate infection control and contingency plans, and for using CHIMs in at-risk populations;
    - 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 mucosas, 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 vaccines-innovation ecosystem 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

- The 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, for personalised vaccines, or for 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 the engagement with 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 on 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;[37]

- Disseminate, exploit, and sustain the project results. This may involve engaging with suitable biological and medical sciences Research Infrastructures;[38]

- Communicate the project activities to relevant target audiences.

In addition, the following additional exploitation[39]/dissemination[40] obligations must be considered to maximise impact:

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

## Potential synergies with existing Consortia

Synergies and complementarities should be considered with relevant national, European and non-European initiatives (including suitable biological and medical sciences research infrastructures[64]) 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;

- CureVac AG - contribution to Subtopic 3;

- Takeda - contribution to Subtopic 3.

[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] http://www.corbel-project.eu/about-corbel/research-infrastructures.html
[39] Article 28.1 (Additional exploitation obligations) of the IMI2 Grant Agreement will apply
[40] Article 29.1 (Additional dissemination obligations) of the IMI2 Grant Agreement will apply

The industry consortium plan 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(ies) 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 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 with provision of 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 sevices
  - 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.

The indicative in-kind and financial contribution from EFPIA partners is EUR 19 870 000. 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. This will be achieved by launching at least two annual open calls[41] (starting after Year 2) based on a review of the project prior to the call that has identified objectives that could be better addressed by those new technologies.

[41] The conditions and criteria for the open call shall be established in the full proposal.

The need for enrolling the additional technology should be approved by the independent review panel during the mid-term project review.

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 further detailed in the full proposal.

A financial contribution of EUR 1 500 000 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.

## 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 short proposals should include suggestions for creating a full-proposal architecture for the subtopic. 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, existing ethical and regulatory frameworks.

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

## 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.

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

In their stage-1 proposals applicants should:

- Give due visibility on 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 redundanc;.

- 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.

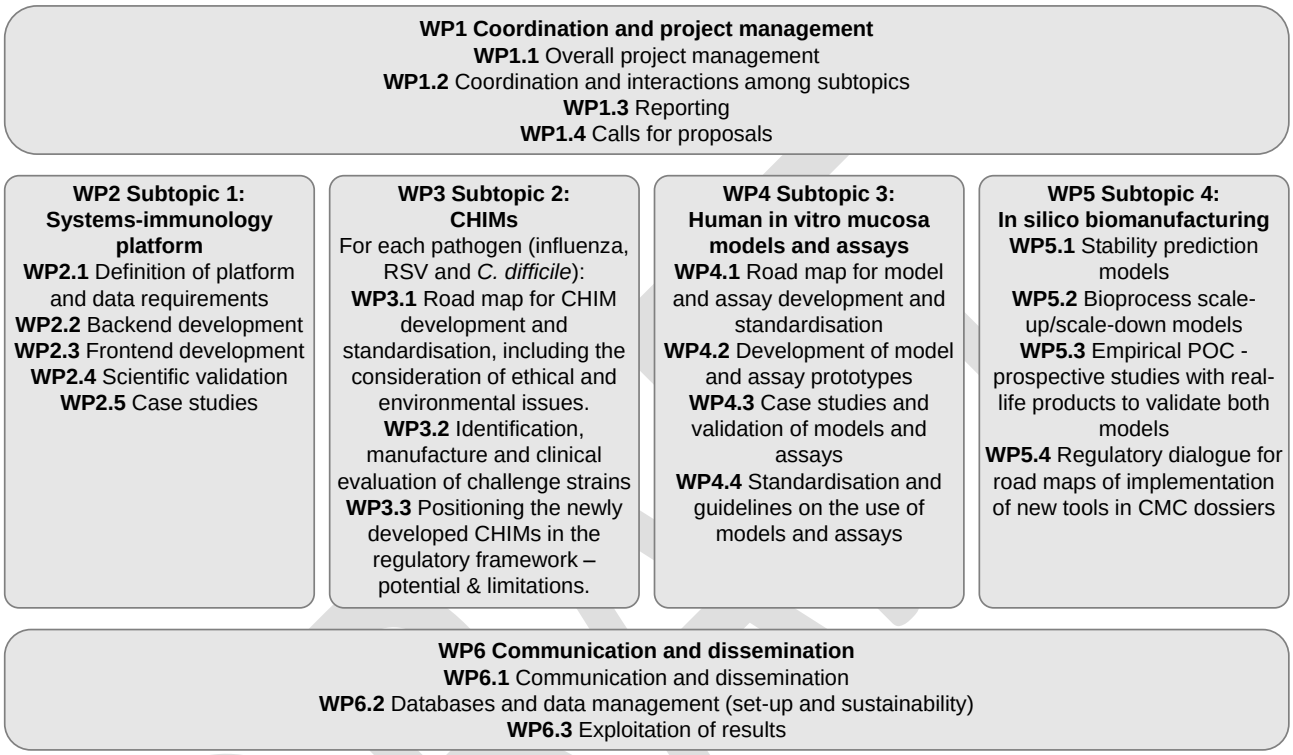


*Figure 2: The project could be composed of two horizontal work packages (WPs) for project management and communication and four subtopics, each comprising several workstreams.*

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.[42]

## 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[43], 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).[44]

## 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.



[42] 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
[43] As an additional dissemination obligation under Article 29.1 of the IMI2 Grant Agreement will apply
[44] http://www.corbel-project.eu/about-corbel/research-infrastructures.html

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# Topic 3: Real-world clinical implementation of liquid biopsy

## Topic details

| | |
|---|---|
| Topic code | IMI2-2020-20-03 |
| Action type | Research and Innovation Action (RIA) |
| Submission and evaluation process | 2 stages |
| IMI2 Strategic Research Agenda - Axis of Research | Adoption of innovative clinical trial paradigms |
| IMI2 Strategic Research Agenda - Health Priority | Cancer |

## Specific challenges to be addressed by public-private collaborative research

Advancing personalized approaches in cancer therapy, aiding identification and adaptation of treatment strategies for improved outcomes depends on clinical implementation of novel diagnostic technologies. Most precision medicine strategies are based on molecular stratification to select patients. Analysis of circulating nucleic acids in plasma, e.g. circulating tumour DNA (ctDNA) or exosomal RNA species, are options for minimally invasive Liquid Biopsy. While the spatial information and cellular resolution of a tissue biopsy remain highly important for characterization of the primary tumour, Liquid Biopsy can offer an integrated view of a tumour and its metastatic lesions that may better reflect the heterogeneity of the disease. Thereby, therapeutically targetable driver mutations of tumour growth and metastatic progression can be identified and serially assessed in settings where a surgical biopsy represents a risk for the patient or cannot be obtained. Furthermore, Liquid Biopsy could be applied to detect the presence of Minimal Residual Disease (MRD) after surgical resection and guide adjuvant therapy decisions [1][2]. Recently it has been reported that an increase in variant allele frequency (VAF) of potentially resistance-conferring mutations, e.g. in KRAS and EGFR T790M mutations, can precede the diagnosis of relapse according to RECIST v1.1 (Response Evaluation Criteria In Solid Tumours) [3], a phenomenon called molecular relapse. Detection of molecular relapse may open an opportunity to improve early detection of progressive disease providing treatment to patients faster in targeted as well as Immune Checkpoint Inhibitor (ICI) therapy. The frequency of follow-up CT scans may be reduced, and faster therapeutic intervention may prolong overall survival and improve the quality of life of the patients. A Liquid Biopsy-based monitoring of disease may potentially accelerate patient selection and enrolment in clinical trials of targeted therapies. Therefore, real-world implementation of Liquid Biopsy may improve progression-free and/or overall survival in the future as well as enhance therapeutic signal generation for targeted therapies.

In recent years, several ctDNA-based assays for mutation detection, which is the most advanced application for Liquid Biopsy, have entered the clinic and attained partial regulatory approval. In the case of EGFR inhibitors, selection of Non-small cell lung cancer (NSCLC) patients eligible for 2$^{nd}$ and 3$^{rd}$ generation inhibitors can be identified by FDA-approved ctDNA based assays (Roche Cobas® EGFR Mutation Test v2, Therascreen EGFR Plasma RGQ PCR Kit). So far, prospective clinical studies have focused on the analytical validity of Liquid Biopsy assays and concordance with invasive tissue biopsy findings to demonstrate non-inferiority of Liquid Biopsies (e.g. Inivata, NCT02906852 and the NILE study, Guardant Health, Inc., NCT03615443). In addition, prospective analysis of serial Liquid Biopsy ctDNA data after curative resection to monitor disease and to detect recurrence in early stage NSCLC may demonstrate clinical utility of Liquid Biopsy for therapy decision making (e.g. Guardant Health, Inc., NCT03791034).

To that end, implementation of Liquid Biopsy assays in a real-world clinical setting, i.e. detecting and monitoring genetic alterations in prospective multi-centric studies, is needed.

Such an observational study could provide evidence for the clinical utility of Liquid Biopsy in several applications:

- Treatment decisions based on ctDNA content and the presence of clinically relevant genetic alterations in blood, e.g. for targeted therapy approaches
- Early detection of signs of efficacy or failure of a treatment
- Early detection of relapse and shortened time to treatment decisions
- Identification of resistance mediating genetic alterations

The proposal funded by this call should be adaptive in nature and provide important insight into best practice for real-world clinical implementation of Liquid Biopsies in solid tumour indications, thus it may result from a pre-competitively planned clinical study or take advantage of an already ongoing study.

The above challenges would therefore greatly benefit from the multi-disciplinary consortium of several stakeholders in the cancer oncology precision medicine field:

- **Clinical partners and molecular pathologists** with their knowledge on conducting clinical studies and access to patients and samples;
- **Pharmaceutical companies**, with their knowledge on clinical study design, implementation of biomarkers in clinical studies and requirements for companion diagnostics development.
- **Diagnostic companies**, with well-established technologies in the Liquid Biopsy space;
- **Academic researchers** with their knowledge of molecular disease mechanisms and potential technical improvements to existing methods and protocols;
- **Regulators,** with their knowledge of requirements for the safe implementation of Liquid Biopsy assays in the clinic;
- **Patient advocacy groups,** with their insight into patients' perception of and experience with diagnostic procedures;
- **Health economists and payer organizations,** with their expertise in modelling the impact of diagnostic technologies and their clinical implementation on therapy cost effectiveness

In order to demonstrate the full potential of prospective clinical use of Liquid Biopsy, the suggested proposal will have the highest impact if it involved all aforementioned stakeholders.

## Scope

The overall objective of the call 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 RECIST. This would 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.

A focus should be put on commercially available, globally distributed and analytically validated Liquid Biopsy ctDNA assays in a real-world clinical setting with the aim to complement routine diagnostic procedures to detect genetic alterations and to monitor treatment efficacy and/or MRD.

The consortium is intended to implement a comprehensive prospective Liquid Biopsy protocol in either

- an investigator initiated multi-centric clinical study, in which in addition to standard diagnostic procedures (e.g. tissue biopsy and CT scans) the impact of data derived from Liquid Biopsy can be evaluated.
- and/or an ongoing clinical study or consortium, in which Liquid Biopsy samples can be shared and data can be compared to standard diagnostic procedures (see 'potential synergies with other consortia').

The selected proposal should focus on an advanced and established ctDNA analysis and evaluation workflow. In addition, exploratory analysis of less mature Liquid Biopsy analytes such as cfRNA and/or extracellular vesicles/exosomes may be considered as long as enough material is available. These exploratory markers may have the potential to provide additional clinically actionable information for more difficult to detect alterations like gene fusions.

The selected proposal should focus on one or two solid tumour indications and must include Lung Cancer (NSCLC and SCLC). Additional indications such as breast cancer or prostate cancer may be considered if enough cases and resources are available to prove statistical significance.

Per indication and study, only one assay/gene panel may be selected. Comparative studies between different assays/ gene panels are not within the scope of this call.

## Expected key deliverables

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

- Real world evidence of standardized clinical use of Liquid Biopsy in cancer patients;
- Liquid Biopsy sampling and handling protocol(s) established at all clinical study sites in alignment with current CEN/TS (European Committee for Standardization / technical specification) and ISO (International Organization for Standardization) standards;
- Decision-relevant Liquid Biopsy-based data for detection and monitoring of response/early detection of relapse and/or detection of MRD from a number of patients large enough to be statistically significant in the questions addressed but, in any case no less than 200 patients per cancer indication. All data (including raw data, patient history and clinical outcome data) needs to be shared with the entire consortium;
- Assessment of differences in therapeutic intervention when decision is based on standard diagnostic procedure vs. Liquid Biopsy;
- Providing data on non-inferiority with molecular profiling data derived from tumour tissue, if available;
- Clinical confirmation of assay parameters, e.g. sensitivity and specificity;
- Assessment of the impact of Liquid Biopsy implementation on patients' quality of life (e.g. more frequent sampling, less invasive);
- Regulatory guidance on using Liquid Biopsy in real-world clinical setting;
- Assessment of economic impact of Liquid Biopsy implementation as potential addition to today's standard procedures when compared to potential benefit for patients and payers.

## Expected impact

In their proposal, applicants should describe how the outputs of the proposed work would contribute to the following impacts and include baseline, targets and metrics to measure impact:

- Demonstrate suitability of Liquid Biopsy in clinical practice;

- Establish reliable and economically feasible Liquid Biopsy protocols in a routine clinical environment;
- Establish a network of clinical sites with necessary infrastructure and training to include serial Liquid Biopsy sampling and handling;
- Establish Liquid Biopsy markers to monitor disease progression, detect recurrence early and inform treatment choices, thereby increasing treatment success for patients, benchmarked to other treatment informing criteria (e.g. RECIST);
- Support reimbursement by public health care providers for Liquid Biopsy testing;
- Support establishment of regulatory processes for Liquid Biopsy in Europe.
- In their proposals, applicants should outline how to leverage the public private partnership model to maximise impact on innovation, research & development; regulatory, clinical and healthcare practices, as relevant. This could include a strategy for engagement with patients, healthcare professional associations, healthcare providers, regulators, HTA agencies, payers etc, where relevant.

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

In their proposals, applicants should outline the following:

- The management of data including use of H2020 data standards.[45]
- How to address dissemination, exploitation and sustainability of the results. This may involve engaging with suitable biological and medical sciences Research Infrastructures.[46]
- The communication of the project activities to relevant target audiences.

## Potential synergies with existing consortia

Synergies and complementarities should be considered with relevant national, European and non-European initiatives (including suitable biological and medical sciences research infrastructures[2]) 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 companies and partners:

- Bayer (Lead)
- Eli Lilly
- QIAGEN
- Servier

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

- Support with established Liquid Biopsy technologies and process clinical samples using these technologies (sample collection, stabilization, extraction, biomarker detection, analysis and interpretation);

[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] http://www.corbel-project.eu/about-corbel/research-infrastructures.html

- Implementation of CEN/TS and ISO Standards;
- Support with ctDNA testing and analysis and raw data processing;
- Expertise in clinical study design and biomarker operations know-how;
- Support in regulatory and health economic aspects;
- Support in Programme and Project management (all WP).

## 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 3 823 000.

The indicative in-kind contribution from EFPIA partners is EUR 4 300 000.

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

## Expertise and resources expected from applicants at stage 1

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

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

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

- Clinicians and molecular pathologists with expertise in the field and having access to clinical samples (longitudinal blood sample collection and processing and handling expertise), agreed-upon patient data (histology, treatment history, corresponding tumour molecular profiling at baseline) and RECIST assessment (CT and CT/PET scans)
- Academic research groups with a track record in the analysis of molecular profiling data in cancer and data base set-up with a understanding of what it takes to establish Liquid Biopsies as new method in clinical practise in oncology (network of clinicians, molecular pathologists, health insurers).
- Established clinical service laboratories with marketed Liquid Biopsy assays with appropriate certification
- SMEs to contribute with fit-for-purpose marketed Liquid Biopsy assays (use in clinical studies demonstrated and results published in peer-reviewed journals), or other relevant innovative service or technology solutions would be of high value for the proposal.
- Additional required expertise includes statistics and bioinformatics, regulatory and health economy.
- Patient-advocacy organizations helping to work on QoL aspects would be appreciated (either as beneficiaries or through involvement in consultations)

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:

- Proven access to clinical samples and agreed-upon patient data.
- Patient Informed Consent (PIC) of participating institutions which cover third party use, data storage and sample exchange across national borders and GDPR conformity.

The early involvement of regulatory authorities and health insurance providers in the proposed activities, either as official partners or as permanent members of the Advisory Board might be extremely beneficial for achieving the expected objectives.

### Considerations for the outline of project work plan

In their stage 1 proposals applicants should

- Give due visibility on data management; dissemination, exploitation and sustainability; and communication activities. This should include the allocation of sufficient resources for these tasks which will be further developed in stage 2 proposal.
- Consider including a strategy for ensuring the translation of the projects results to drug development, regulatory/ 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 applicant consortium should submit a short proposal which includes their suggestions for creating a full proposal architecture, taking into consideration the industry participation including their contributions and expertise.

The architecture outlined below is a suggestion. Different innovative project designs are welcome, if properly justified.

The consortium is expected to have a strategy for the translation of the relevant project outputs into regulatory practices, clinical and healthcare practices. A plan for interactions with Regulatory Agencies/health technology assessment bodies with relevant milestones, resources allocated should be proposed to ensure their advice on real-world implementation of Liquid Biopsies for cancer patients.

The proposed activities should focus on implementation of (a) Liquid Biopsy protocol(s) that is based on (a) marketed assay(s) with published analytical performance data. This could include but is not limited to NGS- or digital PCR-based approaches for ctDNA detection, monitoring and MRD. In addition, exploratory evaluation of new assay formats, e.g. circulating RNAs, or extracellular vesicle/exosome analysis could be considered, particularly when allowing orthogonal assay validation, if sample requirements can be accommodated. The applicant consortium is asked to plan for a centralized analysis of the samples in an appropriately qualified laboratory for quality assurance and comparability.

If synergies with existing and ongoing studies and consortia are used, work packages (WP) may be affected, in particular WP2 and 3.

**Work package 1 - project management and communication**

Dissemination of project results (e.g. press releases, website, meetings, interaction with stakeholder groups and other research initiatives in the field worldwide) and organization of the consortium administration including legal and ethical issues.

**Work package 2 - study planning**

Study protocol, ethics approval, set-up logistics, training and implementing SOPs. (Alternative: use of existing studies). Definition of primary and secondary outcome measures as well as analyses to be performed.

A rationale for the number of patients should be provided based on expected effect sizes and corresponding statistical calculations. Feasibility of timely recruitment of the required number of patients should be provided. In addition, the requirements for sample volume and handling that is needed for the suggested Liquid Biopsy approach must be considered and realistically accessible in the study population.

Regulatory implications using Liquid Biopsies should be addressed. Quality of Life (QoL) assessment should be considered.

Responsible for study implementation, logistics and training.

**Work package 3 - study management**

Clinical and bio sample operations: Recruitment and tracking of a sufficiently large patient cohort (dependent on therapeutic challenge to be addressed) and collection/tracking/shipment and storage of bio samples.

**Work package 4 - sample analysis**

- Shipment of bio samples to analytical laboratories for centralized testing (central lab); quality assurance, sample accession and reconciliation and data generation and reporting of results.
- Molecular analytics and improvement of analytical protocols as needed.
- Orthogonal testing of identified mutations by independent assay, e.g. by PCR.
- Molecular profiling of tumour tissue, if applicable.

**Work package 5 - data management**

Statistical analysis (including QC) and bioinformatics is suggested to be performed in a centralized manner in order to avoid bias.

**Work package 6 - health economic analysis**

The proposal should include cost-effectiveness analysis and cost-utility analysis of Liquid Biopsies in the EU and H2020 Associated countries, if applicable. Develop reimbursement strategy and work with health insurers.

## 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.[47]

## 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[48], and updated during the project lifetime and could include identification of:

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

Enough resources should be foreseen for activities related to dissemination and exploitation, including the plan for the sustainability of the project results. This may involve engaging with suitable biological and medical sciences Research Infrastructures (RIs).[49]



[47] 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
[48] As an additional dissemination obligation under Article 29.1 of the IMI2 Grant Agreement will apply
[49] http://www.corbel-project.eu/about-corbel/research-infrastructures.html

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# 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 Strategic Research Agenda - Axis of Research | Innovative medicines |
| IMI2 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.

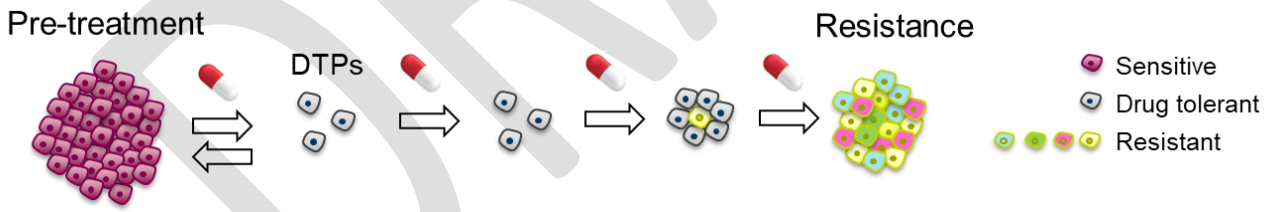


**Figure 1**. Schema of how drug tolerant persister cells (DTPs) arise from the bulk tumour following successful treatment, and ultimately contribute to the emergence of drug resistance.

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 arguably one of the most important barriers to curing in cancer today – drug resistance, 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 singe-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 at-scale is an activity that academic groups are typically not well set up to deliver. 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, 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 scientist and key opinion leaders in industry, 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 program. 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 5 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 outside of 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 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. 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 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 timepoints (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.

**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 IP Rights according in 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.

**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, and 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. KO, knock-out, knock-in, target perturbation) that will lead to opportunities for identification of novel targets in 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 impact 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 standards.[50]

[50] 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.[51]

- Communicate the project activities to relevant target audiences.

In addition, the following additional exploitation[52]/dissemination[53] 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 data set 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 infrastructures[64]) 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 programs 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

## Industry consortium

The industry consortium is composed of the following EFPIA partners:

- AstraZeneca (lead)

- Bayer

- Eli Lilly

- Transgene SA

[51] http://www.corbel-project.eu/about-corbel/research-infrastructures.html
[52] Article 28.1 (Additional exploitation obligations) of the IMI2 Grant Agreement will apply
[53] Article 29.1 (Additional dissemination obligations) of the IMI2 Grant Agreement will apply

- 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.

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 clinical studies independent from but carried out in connection with the action and 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 timepoints. 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 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 applicant consortium should submit a short proposal which includes their suggestions for creating a full proposal architecture, taking into consideration the industry participation including their contributions and expertise provided below.

The final architecture of the full proposal will be defined jointly by the industry and public participants in compliance with the IMI2 JU rules and with a view to the achievement of the project objectives.

The architecture outlined below (Figure 2) for the full proposal is a suggestion. Different innovative project designs are welcome, if properly justified. The architecture of the full proposal should be designed to fulfil the objectives and key deliverables within the scope of this proposal.

**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.

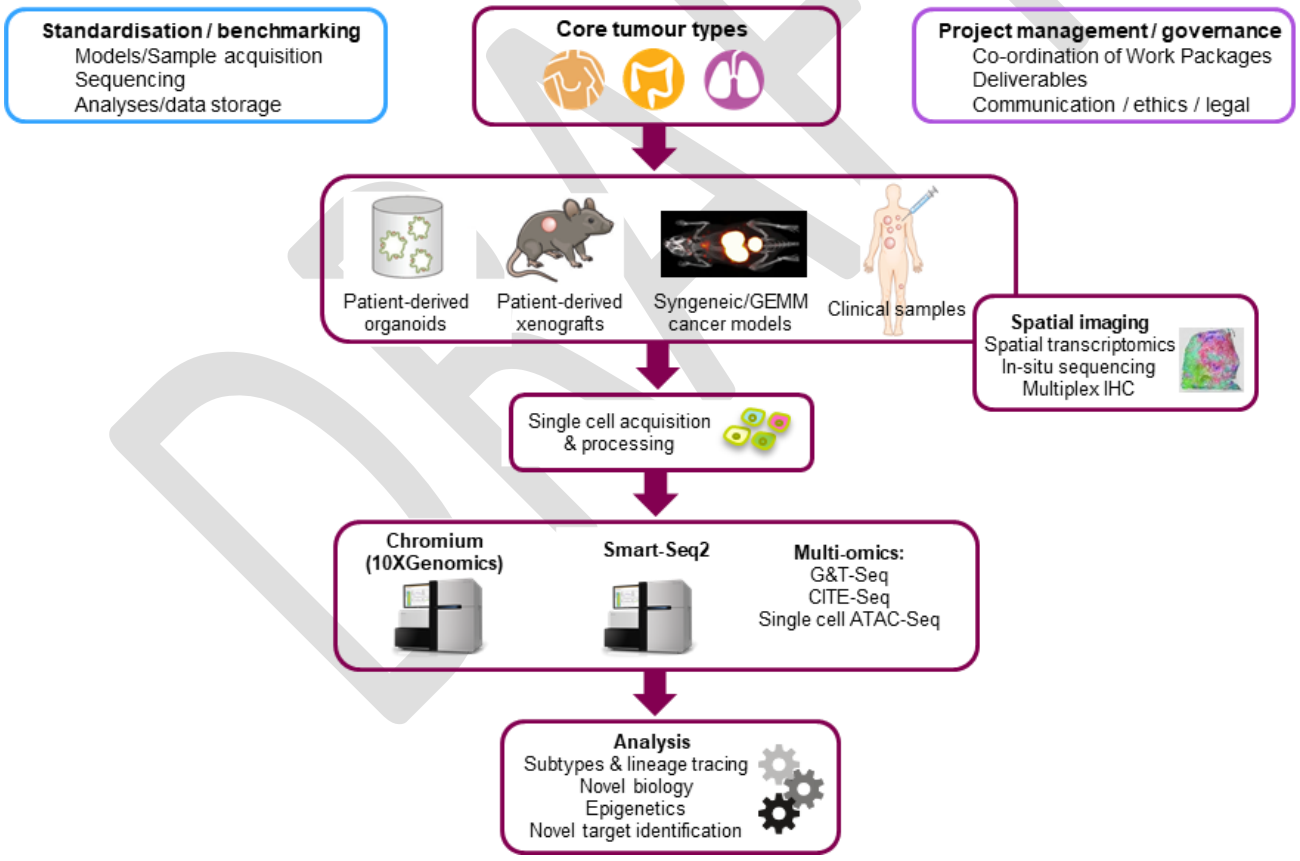


**Figure 2**. Work flow of the project. The various activities captured here form the basis for the 7 Work Packages detailed below.

**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 appropriate dissemination of the project progress and outcomes.

**Industry contribution:** Project leader, co-ordination across different work packages (including overall scientific and strategic oversight).

**Expected Applicant consortium contribution:** Project co-ordinator, 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 co-ordinator, technical advice on the quality of studies that are proposed. Allocation and phasing/timing of studies

**Work Package 3 – Standardization 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
- Include 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 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 ID, 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.

## 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.[54]

### 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.[55], 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).[56]

#### 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.

[54] 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
[55] As an additional dissemination obligation under Article 29.1 of the IMI2 Grant Agreement will apply
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# Topic 5: Proton versus photon therapy for oesophageal cancer – a trimodality strategy

## Topic details

| | |
|---|---|
| Topic code | IMI2-2020-20-05 |
| Submission and evaluation process | 2 stages |
| Action type | Research and Innovation Action (RIA) |
| IMI2 Strategic Research Agenda - Axis of Research | Innovative medicines |
| IMI2 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 clinical evidence for the effectiveness of PT is gradually increasing [1], there is still a critical need for high quality evidence from multi-centre trials to determine the potential 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 localized 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 more conformal radiotherapy and dose escalation provided by proton therapy could reduce the dose to surrounding normal organs including the lungs, heart and liver[5],[6],[7],[8] and could lead to better patient outcomes.

To build a robust evidence base to assess the potential of PT in oesophageal and other cancers, a public private collaboration of proton therapy oncologists, treatment centres, software developers and equipment manufacturers is needed.

## 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 determine if proton therapy in a trimodality treatment;

- reduces treatment related cardio-pulmonary toxicity;
- increases loco-regional tumour control and pathological complete response when similar dose or higher dose is delivered;
- 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. This will be achieved through publication of findings, 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 at least 440 oesophageal cancer patients. Patients should be treated with pre-operative concomitant chemo-radiation and randomized 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[57];

- **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).

## 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 impact on innovation, research & development; regulatory, clinical and healthcare practices, as relevant. This could include a strategy for the engagement with patients, healthcare professional associations, healthcare providers, regulators, HTA agencies, payers etc, where relevant.

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

- Manage research data including use of data standards[58];

[57] Findable, Accessible, Interoperable, Reusable, see: https://www.force11.org/group/fairgroup/fairprinciples
[58] 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

- Disseminate, exploit, and sustain the project results. This may involve engaging with suitable biological and medical sciences research infrastructures[59];
- Communicate the project activities to relevant target audiences.

## Potential synergies with existing consortia

Synergies and complementarities should be considered with relevant national, European and non-European initiatives (including suitable biological and medical sciences research infrastructures[64]) 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 development of dissemination and communication materials
- A financial contribution (detailed in the indicative budget section) to cover study related expenses. Details will be decided by the full consortium at stage 2 when preparing the full proposal.

## Indicative duration of the action

The indicative duration of the action is 60 months.

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 may be re-discussed 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.

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

- Extensive experience in the application of radiotherapy and proton therapy;

[59] http://www.corbel-project.eu/about-corbel/research-infrastructures.html

- 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);
- 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 minimum of 440 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:

- 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 Health Technology Assessment (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.[60]

## 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.[61], 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).[62]

### Communication

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



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

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# 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 Strategic Research Agenda - Axis of Research | Patient-tailored adherence programmes. |
| IMI2 Strategic Research Agenda - Health Priority | Other |

## Specific challenges to be addressed by public-private collaborative research

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 sensitively 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 mentioned (mis)handling [3].

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 including all relevant stakeholders.

DPs as described above are handled in pharmacies, hospitals and by patients after they have been released by the manufacturer. It is therefore outside the scope of full control of the pharmaceutical industry although the manufacturers influence the process by trying to consider the human factors, by providing training and instructions as well as making more robust DPs that should withstand a certain level of stress during usage. Understanding the handling conditions requires assistance from the experts in pharmacies, 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 pharmaceuticals are considered to be within the scope of the topic;
- 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 topic;
    - 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 can, among other ways, 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;
    - 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 for **development of 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 ensuring the stability of DP during handling are welcome;
- Improving the training materials and improving the handling culture are in the scope of the topic. Training aspects should cover training for professionals and patients;
- Utilisation of technologic tools (video, webinar, online media and creative manuals) for development of novel training methods and materials is within the scope of the topic.

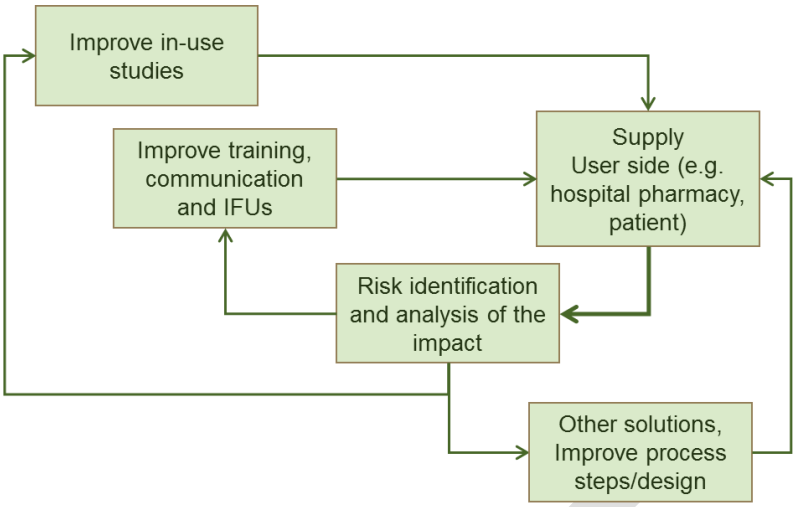


**Figure 1:** Good understanding of the drug product handling at the user side can lead to formulation of various solutions

## Expected key deliverables

The expected deliverables from the project are the following:

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

- Detailed outlining of the handling procedures in pharmacies and at homes including all steps (irrespective of the delivery method/device);
- Evaluation of the real impact of handling steps on 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 the 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).

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 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 a high-quality delivery and administration of protein DP;

- The project will help involved pharmaceutical companies to improve their processes towards development of more robust DPs that withstand the handling stresses;

- At the same time, access to the resulting improved methods to influence the handling culture can be used by both 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 manufacturer 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 the addressing of 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.

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 standards[63];

- Disseminate, exploit, and sustain the project results. This may involve engaging with suitable biological and medical sciences Research Infrastructures[64].

- Communicate the project activities to relevant target audiences.

## Potential synergies with existing consortia

Synergies and complementarities should be considered with relevant national, European and non-European initiatives (including suitable biological and medical sciences research infrastructures[64]) 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

[63] 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
[64] http://www.corbel-project.eu/about-corbel/research-infrastructures.html

- Boehringer Ingelheim
- Lonza
- Merck
- Pfizer
- Roche
- Teva

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

Resources and expertise in:

- the development and manufacturing of biologics;
- formulation and process development;
- clinical processes;
- protein and biologics analytic;

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.

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:

- A global understanding of the protein DP handling providing first-hand knowledge; The applicant consortium can also assign an expert advisory board to cover the needs of their proposal;
- The capacity to investigate the real-world handling procedures in hospitals, pharmacies and at homes and assess their impact on the stability and potentially on safety and efficacy of protein pharmaceuticals;

- Expertise in the available methods of communication and training for handling of protein DPs and have 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;
- Supporting industry partners to address the challenge and influence the process of handling of protein DP.
- The participation of SMEs adding value in the field by novel monitoring concepts, 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:

- Utilisation of expertise and resources, including data from past investigations or existing frameworks such as the AAPS community on DP handling;
- Use of experiences or technologies from SMEs that have been developed for other purposes but can be of use for this project;
- Networks and ecosystems involving the applicants to be leveraged.

### Considerations for the outline of project work plan

In their stage 1 proposals applicants should:

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

## Suggested architecture

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

## 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 the exploitation, including sustainability of results. A full plan as a distinct deliverable must be delivered within the first 6 months of the project.[66] 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).[67]

### 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.



[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

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# 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 that 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), the largest single contributor to AMR health, mortality, and economic impact.

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

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

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

## Overall objectives of the AMR Accelerator

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

The AMR Accelerator 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, progress potential new treatments through phase 1-3 clinical trials,

and analyse data from EFPIA-funded clinical trials to assist in the translation of preclinical data to clinical results of novel anti-infective agents and vaccines. The 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 as EU funding programmes within Horizon 2020 (including SME instruments) or future framework programmes, InnovFin instruments, Structural Funds, venture capitals, other internal R&D funding mechanisms, etc. In addition, the applicable principles from the Davos Declaration on Antimicrobial Resistance– January 2016 or the Industry Roadmap for Progress on Combatting Antimicrobial Resistance – September 2016 (https://www.ifpma.org/wp-content/uploads/2016/09/Roadmap-for-Progress-on-AMR-FINAL.pdf[68]) 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 of '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 consist 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 7) under Pillar B to complement the actions funded under IMI2 JU Call 15 and IMI2 JU Call 16.

Future call 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,

[68] 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 an action that will create 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 7 of IMI2 JU Call 20 will result in an action that will develop and implement innovative, state of the art adaptive clinical trial designs for the field of TB regimen development able to define the therapeutic dose for existing experimental New Chemical Entities (NCE's) within treatment combinations. Additionally, it will exploit innovative technologies (including biomarkers and diagnostics) to facilitate and monitor adherence in resource-poor settings, while generating evidence that shorter regimens improve adherence.

**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)[69]. 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 available budget. A total of at least 8-10 grant agreements are anticipated in the PBN (indicative number only).

## Collaboration agreements

To ensure smooth operation of the projects in the AMR Accelerator, the grant agreement of the first CBN action (COMBINE- 853967 selected under Pillar A from IMI2 JU Call 15 topic 7, and containing the coordination and support group[70]) 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 7 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

69 See 'Applicant consortium' section of IMI2 JU Call 16 topic text (Pillar C, "Portfolio Building Networks").
70 For additional details see the topic 7 "Capability Building Network" of IMI2 JU Call 15.

respective options of Article 2, Article 31.6 and Article 41.4 of the IMI2 JU Model Grant Agreement[71] 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 7) 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 7 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 have been the previous and current investments by the European Union and IMI (ND4BB, Model-based preclinical development of anti-tuberculosis drug combinations (PreDiCT-TB), More Medicines for Tuberculosis (MM4TB), Open Collaborative Model for Tuberculosis Lead Optimisation (ORCHID), anTBiotic), the NIH (Tuberculosis Research Units Network, TBRU-N) and the Bill & Melinda Gates Foundation (TB Drug Development Accelerator and TB Alliance discovery portfolio)). Multiple new drug candidates are in the pipeline for the treatment of TB for the first time in decades, and are reaching or about to reach the clinic. Existing drugs are being repurposed or optimised for TB with the potential of shortened treatment duration for drug-sensitive TB and safer, shorter treatments for MDR-TB. In ND4BB, immense progress has been made from basic science to discovery of novel lead molecules through to running interventional clinical trials.

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

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

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 key role in a EU AMR programme with connectivity into the broader global agenda on AMR;
    - enable SME, and/or academic groups to progress pre-competitive basic science project in the AMR field;
    - opportunity to work within a broad network of researchers focused on AMR science and gain additional experience in AMR science and drug discovery.

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

- Tuberculosis Drug Development Network:

    - enable SME and/or academic groups to progress pre-competitive basic science project in the TB field;
    - enable SME and/or academic groups to progress potential drugs from pre-candidate status through to ‘ready for phase 2’ status, including, but not limited to GLP and GMP scale up, formulation, toxicology studies, and phase 1 clinical studies, including preclinical combinations of drugs;
    - opportunity to work within a broad network on researchers focused on TB drug discovery.

- Portfolio Building Network:

    - 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 7: Academia and industry united innovation and treatment for tuberculosis (UNITE4TB)

## Topic details

| | |
|---|---|
| Topic code | IMI2-2020-20-07 |
| Action type | Research and Innovation Action (RIA) |
| Submission and evaluation process | 2 stages |
| IMI2 Strategic Research Agenda - Axis of Research | Innovative medicines |
| IMI2 Strategic Research Agenda - Health Priority | 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 high 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-respose.[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 be implemented currently 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 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 Tuberculosis, 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). 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 sterilizing cure/relapse at the individual patient level, and iii); a third, more ambitious objective, is 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 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 enroll 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 which ensures meeting the objectives.

## Collaboration agreement(s)

The action funded under this call topic will be 'Pillar B, (Topic 2)' of the AMR accelerator. Please refer to Call 15 and 16 topic texts regarding 'collaboration agreements', and 'Questions and answers'[72] associated with both calls. This topic will be complimentary to the actions funded under Pillar A and B 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 in common between AMR consortia

Moreover, this action will seek collaboration agreements 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

- Individual-level patient data will be made publicly available through a sustainable data-sharing platform developed in co-ordination with **COMBINE**, **ERA4TB** and **EU-PEARL**.

When reasonable, a MoU should be pursued between potential TB-focused actions under Pillar C of the Accelerator (resulting from IMI2 JU Call 16) with appropriate provisions to protect confidentiality of the interactions between the consortia and their intellectual property rights.

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 AMR accelerator projects.

## 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 1000 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.

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

- Applicant consortia 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.
- Applicant consortia 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 . 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 Strategic Development Goals and 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 individualize 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 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 exploitation[73]/dissemination[74] 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-

[73] Article 28.1 (Additional exploitation obligations) of the IMI2 Grant Agreement will apply
[74] Article 29.1 (Additional dissemination obligations) of the IMI2 Grant Agreement will apply

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;[75]
- Disseminate, exploit, and sustain the project results. This may involve engaging with suitable biological and medical sciences research infrastructures;[76]
- Communicate the project activities to relevant target audiences.

## Potential synergies with existing consortia

Synergies and complementarities should be considered with relevant national, European and non-European initiatives (including suitable biological and medical sciences research infrastructures[64]) 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 also is 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 with 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 Pharmaceutica
- 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.** 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. It is expected that in the region of eight NCEs will be made available to the consortium in the first year, consisting of ATPsynthse 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

[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

partners, TB Alliance, Gates MRI, ERA4TB or through other initiatives. Selection of molecules will be subject to due diligence by the governance bodies of the consortium

- 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.

- 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 independent from but carried out in connection with the action and contributing results 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 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 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 on 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. 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

## 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.

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.

- **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-funded 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 already 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 sterilizing cure should be complementary to existing mechanistic models;

- **Artificial Intelligence/Machine Learning** 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 around 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 around clinical trial simulations;
- Expertise in digital health technologies relevant to treatment adherence;
- Pharmacogenomic expertise in collection of host DNA, 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. Analyse genomic data and correlate this to drug PK and trial endpoints.

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

- Access 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 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;
- Present a strategy for ensuring the translation of the projects 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 would be 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 standardization and internal and external quality control strategy, management of clinical trial supplies/investigational product.
**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, sites 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, 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.

## 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 consent of 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 project co-leaders from among EFPIA beneficiaries/Associated Partners shall facilitate an efficient negotiation of project content and required agreements. 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/opencalls/Questions_and_answers_on_the_AMR_accelerator_programme.pdf.

## Data Management

A significant part of data generated in the funded action may be exploited in the development and, on the long term, market launch of new therapeutics against tubercular infections (validating targets, confirming lead compound candidates, developing and testing new drug regimens, further clinical trials). In particular, such data may have a significant commercial value since an important subset of the data will be needed for filing regulatory documents. Consequently, preliminary sharing of data outside of the consortium could hinder the exploitation of the project results and hence the overall objectives of the AMR Accelerator (bringing new

TB/NTM drugs on the market). Thus, the selected consortium should propose a strategy for access to data, which would be in addition or alternative to the H2020 policy for Open Access to Data under Art 29.3 of the Grant Agreement. Such a strategy should be presented in the funded action Data Management Plan (DMP)."

## 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.[77], and updated during the project lifetime. Itcould 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).[78]

**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.



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

## References


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[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

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[5] F. von Groote-Bidlingmaier, 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

# 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 144 509 500 |
| From the IMI2 JU | EUR 136 832 000 |

## Call Topics

| | | |
|---|---|---|
| **IMI2-2020-20-01**<br><br>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<br><br>The financial contribution from IMI2 JU is a maximum of EUR 10 211 000 | Research and Innovation Action (RIA)<br><br>Two-stage submission and evaluation process.<br><br>Only the applicant consortium whose proposal is ranked first at the first stage is invited for the second stage. |

| | | |
|---|---|---|
| **IMI2-2020-20-02**<br><br>Innovations to accelerate vaccine development and manufacture | The indicative contribution from EFPIA companies is EUR 19 870 000<br><br>The financial contribution from IMI2 JU is a maximum of EUR 18 600 000 | Research and Innovation Action (RIA)<br><br>Two-stage submission and evaluation process.<br><br>Only the applicant consortium whose proposal is ranked first at the first stage is invited for the second stage. |
| **IMI2-2020-20-03**<br><br>Real-world clinical implementation of Liquid Biopsy | The indicative contribution from EFPIA companies is EUR 4 300 000<br><br>The financial contribution from IMI2 JU is a maximum of EUR 3 823 000 | Research and Innovation Action (RIA)<br><br>Two-stage submission and evaluation process.<br><br>Only the applicant consortium whose proposal is ranked first at the first stage is invited for the second stage. |
| **IMI2-2020-20-04**<br><br>Tumour plasticity | The indicative contribution from EFPIA companies is EUR 8 500 000<br><br>The financial contribution from IMI2 JU is a maximum of EUR 7 058 000 | Research and Innovation Action (RIA)<br><br>Two-stage submission and evaluation process.<br><br>Only the applicant consortium whose proposal is ranked first at the first stage is invited for the second stage. |
| **IMI2-2020-20-05**<br><br>Proton versus photon therapy for oesophageal cancer – a trimodality strategy | The indicative IMI2 JU Associated Partners contribution is EUR 1 500 000<br><br>The financial contribution from IMI2 JU is a maximum of EUR 1 500 000 | Research and Innovation Action (RIA)<br><br>Two-stage submission and evaluation process.<br><br>Only the applicant consortium whose proposal is ranked first at the first stage is invited for the second stage. |
| **IMI2-2020-20-06**<br><br>Handling of protein drug products and stability concerns | The indicative contribution from EFPIA companies is EUR 3 959 500<br><br>The financial contribution from IMI2 JU is a maximum of EUR 3 140 000 | Research and Innovation Action (RIA)<br><br>Two-stage submission and evaluation process.<br><br>Only the applicant consortium whose proposal is ranked first at the first stage is invited for the second stage. |
| **IMI2-2020-20-07**<br><br>Academia and industry united innovation and treatment for tuberculosis (UNITE4TB) | The indicative contribution from EFPIA companies is EUR 62 500 000<br><br>The indicative IMI2 JU Associated Partners contribution is EUR 30 000 000<br><br>The financial contribution from IMI2 JU is a maximum of EUR 92 500 000 | Research and Innovation Action (RIA)<br><br>Two-stage submission and evaluation process.<br><br>Only the applicant consortium whose proposal is ranked first at the first stage is invited for the second stage. |

# 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 |
| **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 |
| **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 |
| **DTPs** | Drug Tolerant Persister Cells |
| **DZIF** | German Center For Infection Research |
| **E&T** | Education & Training |

| Acronym | Meaning |
|---|---|
| **EBA** | Early Bactericidal Activity |
| **EBiSC** | European induced pluripotent stem cell |
| **EC** | European Commission |
| **ECA** | European Court of Auditors |
| **EDPS** | European Data Protection Supervisor |
| **EEG** | Electroencephalograph |
| **EFPIA** | European Federation of Pharmaceutical Industries and Associations |
| **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** | 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.<br>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 |
| **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 |
| **HTS** | High-throughput screening |
| **IAC** | Internal Audit Capability |
| **IAPO** | International Alliance of Patients' Organisations |
| **IAS** | Internal Audit Service of the European Commission |

| Acronym | Meaning |
|---|---|
| **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 |
| **IMI1 JU** | Innovative Medicines Initiative 1Joint Undertaking |
| **IMI2 JU** | Innovative Medicines Initiative 2Joint Undertaking |
| **IMI JU** | Innovative Medicines Initiative Joint Undertaking |
| **IMPD** | Investigational Medicinal Product Dossier |
| **iMRM** | Immuno-Multiple Reaction Monitoring |
| **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 |
| **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 |
| **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 |

| Acronym | Meaning |
|---|---|
| **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 |
| **SAICM** | Strategic Approach to International Chemicals Management |
| **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 |
| **TDTDC** | Tuberculosis Drug Treatment Development Consortium |
| **TTG** | Time to Grant |
| **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 |

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