



Third amended Annual Work Plan and Budget for 2020

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In accordance with Article 16 of the Statutes of the IMI2 JU annexed to Council Regulation (EU) No 557/2014 of 6 May 2014 and with Article 33 of the Financial Rules of the IMI2 JU.

The third amended Annual Work Plan will be made publicly available after its adoption by the Governing Board.

Sole annex to the Decision of the Governing Board of the Innovative Medicines Initiative 2 Joint Undertaking no. IMI2-GB-DEC-2020-20 adopted on 19.06.2020

Table of Contents

1	Introduction	5
2	Annual Work Plan Year 2020	6
2.1	Executive Summary	6
2.2	Operations	6
2.2.1	Objectives & indicators - risks & mitigations	6
2.2.2	Scientific priorities for 2020	14
A.	Neurodegeneration and other neuroscience priorities	15
B.	Infection control including vaccines	16
C.	Big data, digital health, clinical trials and regulatory research	18
D.	Oncology	19
E.	Immunology	21
F.	Facilitating Rare Disease therapies (including Advanced Therapy Medical Products) reaching patients in Europe	22
G.	Other enablers of research topics	23
H.	Restricted Call to maximise the impact of IMI2 JU objectives and scientific priorities	24
	<i>Calls for Proposals</i>	25
	<i>Budget</i>	29
2.2.3	Call management (planning, evaluation, selection, ...)	30
2.2.4	Activities to support and monitor ongoing projects	30
2.2.5	Monitoring and analysis of projects' results	32
2.2.6	Stakeholders' engagement and external collaborations	32
2.2.7	Dissemination and information about projects results	34
2.2.8	Socio-economic impact assessment	34
2.3	Call management rules	35
2.4	Support to Operations	42
2.4.1	Communication and events	42
2.4.2	Procurement and contracts	43
2.4.3	IT and logistics	44
2.4.4	Human Resources	45
2.4.5	Administrative budget and finance	46
2.4.6	Data protection	48
2.4.7	Access to documents	48
2.5	Governance	49
2.6	Internal Control framework	51
2.6.1	Ex-ante and ex-post controls	51
2.6.2	Internal and External audits	52
3	Budget 2020	53
3.1	Staff Establishment Plan 2020	65
	Annex I - IMI2 JU Call 20 topics text	67
	Annex II - IMI2 JU Call 21 topic text	141
	Annex III - IMI2 JU Call 22 topic text	150
	Annex IV - IMI2 JU Call 23 topics text	160
	List of acronyms	232

NOTICE

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

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

Chronology and list of reviews

Version	Date of the adoption by the Governing Board	Items
Version 1.0	13.12.2019	Annual Work Plan and Budget for 2020
Version 2.0	28.02.2020	<p>Update of the following sections:</p> <ul style="list-style-type: none"> ▪ Notice ▪ 2.1 Executive Summary ▪ 2.2.1 Objectives & indicators - risks & mitigations ▪ 2.2.2 Scientific priorities for 2020 ▪ 2.2.3 Call management (planning, evaluation, selection, ...) ▪ 2.2.4 Activities to support and monitor ongoing projects ▪ 2.3 Call management rules ▪ 3 Budget ▪ List of acronyms <p>Insertion of Annex II - IMI2 JU Call 21 topic text</p>
Version 3.0	08.05.2020	<p>Update of the following sections:</p> <ul style="list-style-type: none"> ▪ 2.2.2 Scientific priorities for 2020 ▪ 2.2.3 Call Management ▪ 2.2.4 Activities to support and monitor ongoing projects ▪ 3 Budget ▪ Annex I IMI2 JU Call 20 topics text ▪ Annex II IMI2 JU Call 21 topic text ▪ List of acronyms
Version 4.0	19.06.2020	<p>Update of the following sections:</p> <ul style="list-style-type: none"> ▪ 2.2.2 Scientific priorities for 2020 ▪ 2.2.4 Activities to support and monitor ongoing projects ▪ 2.2.5 Monitoring and analysis of projects' results ▪ 2.2.7 Dissemination and information about projects results ▪ 2.4.2 Procurement and contracts ▪ 2.5 Governance ▪ 3 Budget ▪ 3.1 Staff Establishment Plan 2020 ▪ List of acronyms <p>Insertion of Annexes III and IV - IMI2 JU Call 22 and 23 topics texts</p>

1 Introduction

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

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

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

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

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

Pierre Meulien

Executive Director

2 Annual Work Plan Year 2020

2.1 Executive Summary

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

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

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

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

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

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

2.2 Operations

2.2.1 Objectives & indicators - risks & mitigations

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

Key operational objectives for 2020 as follows:

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

IMI2 KPIs

Reporting on measuring and outcomes on the ten following Key Performance Indicators will be provided yearly as part of the IMI2 JU Annual Activity Reports for year 2020 and beyond.

KPI	Definition	Comment	Relates to	Baseline	Target
1	Number of relevant priority areas in the WHO 'Priority Medicines for Europe and the World 2013 Update' reflected in the IMI2 JU Strategic Research Agenda (SRA) and addressed by IMI2 JU projects.	Based on the SRA and including the WHO priority medicines therapeutic areas: - expressed as a number of areas reflected in the IMI2 JU portfolio; - complemented by the number and budget of grant agreements that delivered them.	IMI2 JU Regulation ¹ objective b1: b1: 'increase the success rate in clinical trials of priority medicines identified by the WHO'	0	12
2	The number of project-developed assets which complete a significant milestone during the course of an IMI2JU project.	Assets are defined as new drug or diagnostic candidates, targets, biomarkers or other tools that can be shown to have reached a significant milestone or pass a significant stage gate.	IMI2 JU Regulation objective b1, b2, b4, b5 and b6: b1: 'increase the success rate in clinical trials of priority medicines identified by the WHO' b2: 'reduce the time to reach clinical proof of concept in medicine development...' b4: 'develop diagnostic and treatment biomarkers for diseases clearly linked to clinical relevance and approved by regulators' b5: 'reduce the failure rate of vaccine candidates in phase III of clinical trials through new biomarkers for initial efficacy and safety checks' b6: 'improve the current drug development process by providing	0	50

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

			the support for the development of tools, standards and approaches to assess efficacy, safety and quality of regulated health products'		
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KPI	Definition	Comment	Relates to	Baseline	Target
3	<p>New or improved guidelines, methodologies, tools, technologies or solutions accepted by regulatory authorities for use in the context of R&D, specifically for:</p> <ul style="list-style-type: none"> - new tools for preclinical drug development; - biomarkers and tools developed to predict clinical outcomes; - improved protocols to design and process of clinical trials; - new biomarkers developed for the efficacy and safety of vaccine candidates. 	<ul style="list-style-type: none"> - Measured by the number of the formal qualification procedures completed (letters of support, qualification opinions received). - Complemented by number of qualification procedures launched. - Expressed as net figure. - Complemented by the number and budget of grant agreements that delivered them. 	<p>IMI2 JU Regulation objective b1, b2, b4, b5 and b6:</p> <p>b1: 'increase the success rate in clinical trials of priority medicines identified by the WHO'</p> <p>b2: 'reduce the time to reach clinical proof of concept in medicine development...'</p> <p>b4: 'develop diagnostic and treatment biomarkers for diseases clearly linked to clinical relevance and approved by regulators'</p> <p>b5: 'reduce the failure rate of vaccine candidates in phase III of clinical trials through new biomarkers for initial efficacy and safety checks'</p> <p>b6: 'improve the current drug development process by providing the support for the development of tools, standards and approaches to assess efficacy, safety and quality of regulated health products'</p>	0	10 (for completed procedures)

KPI	Definition	Comment	Relates to	Baseline	Target
4	New taxonomies of diseases and new stratifications (such as the definition of patient subpopulations, development, validation and use of new diagnostics) developed.	<ul style="list-style-type: none"> - Expressed as net figure. - As published and/or implemented by industrial partners and evidenced in annual reporting. - Complemented by the number and budget of grant agreements that delivered them. 	<p>IMI2 JU Regulation objective b3 and b4:</p> <p>b3: 'develop new therapies for diseases for which there is a high unmet need...'</p> <p>b4: 'develop diagnostic and treatment biomarkers for diseases clearly linked to clinical relevance and approved by regulators'</p>	0	30
5	Contribution (in-kind or in-cash) from non-pharma actors (e.g. non-pharma industries, foundations, charities, professional organisations).	Expressed as total amount in EUR.	<p>IMI2 JU Regulation objective a:</p> <p>a: 'to support... the development and implementation of pre-competitive research and of innovation activities of strategic importance to the Union's competitiveness and industrial leadership...';</p> <p>and IMI2 JU Regulation recital 8:</p> <p>'The initiative should consequently seek to involve a broader range of partners, including mid-caps, from different sectors, such as biomedical imaging, medical information technology, diagnostic and animal health industries.'</p>	0	EUR 300 Million

KPI	Definition	Comment	Relates to	Baseline	Target
6	Share of IMI2 JU projects whose resources/outputs are made accessible beyond the consortia partners (with or without fee), such as major databases, bio-banks, <i>in silico</i> tools, training materials, clinical trial networks, guidance etc.	<ul style="list-style-type: none"> - Complemented by the number and budget of grant agreements that delivered them. - Accessibility to be evidenced by online availability (with or without fee), and documented by project reports. 	<p>IMI2 JU Regulation objective a, b2 and b6:</p> <p>a: 'to support... the development and implementation of pre-competitive research and of innovation activities of strategic importance to the Union's competitiveness and industrial leadership...'</p> <p>b2: 'reduce the time to reach clinical proof of concept in medicine development'</p> <p>b6: 'improve the current drug development process by providing the support for the development of tools, standards and approaches to assess efficacy, safety and quality of regulated health products'</p>	0	50%
7	Co-authorships and cross-sector publications between European researchers on IMI2 JU projects (sectors include academia, small and mid-sized companies, pharma, regulators, patient organisations, etc.).	<ul style="list-style-type: none"> - Expressed as net figure - Complemented by the number and budget of grant agreements that delivered them. 	<p>IMI2 JU Regulation objective a:</p> <p>a: 'to support... the development and implementation of pre-competitive research and of innovation activities of strategic importance to the Union's competitiveness and industrial leadership...'</p>	0	1500

KPI	Definition	Comment	Relates to	Baseline	Target
8	New tools and processes generated by IMI2 JU projects that have been implemented by the industry participants of IMI projects.	<ul style="list-style-type: none"> - New tools and processes: e.g. animal models, standards, biomarkers, SOPs, use of screening platforms and clinical trial networks. - Expressed as net figure. - Complemented by the number and budget of grant agreements that delivered them. - Assessment based on yearly reporting by industrial partners until the project close-out meetings. 	<p>IMI2 JU Regulation objective a, b2 and b6:</p> <p>a: 'to support... the development and implementation of pre-competitive research and of innovation activities of strategic importance to the Union's competitiveness and industrial leadership...'</p> <p>b2: 'reduce the time to reach clinical proof of concept in medicine development'</p> <p>b6: 'improve the current drug development process by providing the support for the development of tools, standards and approaches to assess efficacy, safety and quality of regulated health products'</p>	0	50
9	Share of projects involving patient organisations and healthcare professionals' associations (as consortium partners, members of advisory boards, members of stakeholder groups etc.).	<ul style="list-style-type: none"> - Complemented by the number and budget of grant agreements that delivered them. 	<p>IMI2 JU Regulation objective a, and b1:</p> <p>a: 'to support... the development and implementation of pre-competitive research and of innovation activities of strategic importance to the Union's competitiveness and industrial leadership...'</p> <p>b1: 'increase the success rate in clinical trials of priority medicines identified by the WHO'</p>	Share of IMI JU projects involving patient organisations: (participants /advisory boards etc. 40%)	80%

10	Support to SMEs: share of SMEs participating as formal IMI2 JU project beneficiaries.	- To be complemented by the number of SMEs benefitting from IMI project support in other ways.	H2020 priority; IMI2 JU Regulation recital 9 '(...) should seek to foster the capacity of smaller actors such as research organisations, universities and SMEs for participating in open innovation models and to promote the involvement of SMEs in its activities, in line with its objectives'	Share of SMEs participating as formal IMI JU project beneficiaries: 15.96%	20%
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To ensure the monitoring of the above-mentioned 10 Key Performance Indicators, IMI2 JU has established a performance evaluation plan which aims at identifying appropriate sources of information, a suitable framework as well as consistent processes and tools.

Risks & mitigations

Risks management is a strategic element of planning activities as their identification enables the IMI2 JU to effectively customise its objectives and prioritise actions.

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

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

2.2.2 Scientific priorities for 2020

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

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

The actions resulting from the 2020 priorities will generate results that will have a high impact and facilitate the maximum number of stakeholders to join forces. The outcome and impact of these actions should bring great benefits to patients and society-at-large. There will also be engagement with regulatory agencies and other health bodies fostering the approval of research outcomes. Involving the wider community in this way should help to advance the development of new approaches and technologies for the prevention, diagnosis and treatment of diseases with an expected high impact on public health.

SMEs have an important role in strengthening the competitiveness and industrial leadership in the EU. In addition, SME involvement might offer a complementary perspective to industry and the academia, and help deliver the long-term impact of IMI2 JU. Thus, in 2020, 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 eight scientific priorities, broken down into several topics, taking into account the advice that the Strategic Governing Groups (SGGs) provided to the IMI2 JU Governing Board. As described in the following pages, each priority area will be implemented via the launch of one or more topics, which will generate multi-stakeholder actions, potentially including (or even driven by) Associated Partners. Further details regarding the expected multi-stakeholder actions are elaborated under the individual topics. Topics for 2020 have been prioritised based on criteria that include the highest impact on reducing attrition in drug development, speeding up patient access, improving health outcomes and enhancing the biomedical research ecosystem.

Additional topics for 2020 might also be considered at a later stage in the case of very urgent public health needs, such as rapid response to emerging diseases. The Annual Work Plan 2020 would then be updated accordingly.

To implement the 2020 priorities, IMI2 JU will initiate four competitive Calls for proposals, each covering several topics (see table at the end of this section), with predefined launch dates foreseen for Q1 and Q2 in 2020.

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

A. Neurodegeneration and other neuroscience priorities

Activities in 2020 will address the following topic:

- 1. A platform for accelerating biomarker discovery and validation to support therapeutics development for neurodegenerative diseases.** One of the key barriers to the development of treatments for neurodegenerative disease is an insufficient toolbox of biomarkers and associated clinical progression data for screening easily populations, diagnose patients, monitor progression and response to treatment, all of which would improve the efficiency of clinical trials. Key unmet needs limiting the use of samples and data for the discovery, development and validation of neurodegenerative disease biomarkers today include: 1) Sample and data access for research use: There is currently insufficient access to high-quality, longitudinal, and well-characterized samples (including clinically well diagnosed and controls) and accompanying clinical data to meet current and future demands. 2) Sample Quality: A lack of standardization in collecting on and processing of samples and linked datasets causes large disparities in sample quality and decreases the utility of banked samples for researchers. 3) Transparency: There is currently no centralized resource documenting what sample types and accompanying clinical datasets are available across different organizations (public and private), and what access restrictions may be in place. 4) Data sharing: Platforms and processes for sharing clinical data to accompany samples and then to enable reutilization of derived data are lacking or inadequate in terms of interoperability. To address these challenges, the topic will support activities for: 1) Creating a set of agreed principles to enable sharing and access to data and samples taking into consideration the established legal and ethical research standards and principles (e.g. General Data Protection Regulation (GDPR), legal, intellectual properties (IP), ethical, regulatory, societal). 2) Establishing a network that can house high quality data and samples, which could have federated and centralised elements. The overall solution has to be interoperable (e.g. with other global data platforms), scalable and suitable for a broad variety of both data types (including digital), and of samples, from public and private (e.g. proprietary clinical trials) sources, whether they be part of the consortium or provided from external donors. 3) Establishing fair and transparent governance and processes specifically to enable sharing and access to data and samples, 4) Testing the above with the defined case studies (see full topic text) and applying the learnings to fine-tune processes and use the outcomes to grow the platform. 5) Making the platform a self-sustainable entity by the end of the project.

Expected impact:

- A self-sustainable European biobank operation, and accompanying data platform, that will positively fuel and impact basic research and development as well as drug development campaigns;
- An infrastructure enabling worldwide sample and data sharing to substantially impact development and regulatory validation of biomarkers/diagnostics, with a positive cascading effect on accelerating therapeutic development.

Type of actions:

Research and innovation actions

B. Infection control including vaccines

Activities in 2020 will address the following topics:

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

2. 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.

3. Innovations to accelerate vaccine development and manufacture. Vaccination is one of the greatest achievements in healthcare. However, developing a vaccine remains costly, time consuming, and risky (approximately EUR 800 million, 11 years in clinical development with <10% chance of entering the market). Advances in immunology, disease modelling, in silico modelling, including the analysis of big data and the application of machine learning (ML) artificial intelligence (AI), provide opportunities to innovate, de-risk and accelerate the vaccine-development process. Many of these advances have occurred in the academic sector. These advances can be harnessed to nurture and expand a vaccines innovation ecosystem by bringing together academics, small & medium size enterprises (SMEs) and industry. The overall objective of the topic is to accelerate and de-risk the development of new vaccines by incorporating scientific and technological advances from the academic and biotech sectors into industry and developing more predictive biological and mathematical models of vaccine performance. The topic is structured as four subtopics, addressing how to integrate and standardise into the vaccine-development programme four key areas of challenge. Subtopics 1 and 4 are centred on developing in silico model platforms for the immune system and biomanufacturing, respectively, which should be sustainable after the completion of the project; and subtopics 2 and 3 seek to widen the use of controlled human infection models (CHIMs) and next-generation in vitro models and assays in vaccine development. All subtopics in the programme relate to the use of novel modelling technologies (biological or mathematical) to accelerate the development of vaccines. Hence, by bringing together stakeholders from all areas of vaccine R&D (preclinical, clinical and manufacturing), the programme offers a unique opportunity to explore and open up an interdisciplinary dialogue on the future use, acceptance and further co-ordinated development of these technologies.

4. Modelling the impact of monoclonal antibodies and vaccines on the reduction of antimicrobial resistance: Vaccines and monoclonal Antibodies (mAb) may reduce antimicrobial resistance (AMR). However, individual vaccine developers and manufacturers, as well as organisations developing mAbs or health authorities do not have on their own, the resources and the full expertise required to make a realistic and comparable assessment of the use of the different products on the reduction of AMR, which could instead be possible through the development of a mathematical model. For such a model to be representative, it should incorporate both cost elements and perspective from the industry and from public health. To address these challenges this topic supports activities towards the development of a framework for setting up antimicrobial resistance (AMR)-focused economic evaluations of vaccines and

mAbs. This should include measurement of the present rate of growth of AMR, its main drivers, its health and economic consequences, and which vaccines and mAbs might have the best chance of reducing the rate of AMR growth and the related health and economic consequences. The model should build upon the work done by previous models in depicting the infection dynamics of key pathogens in specific populations leading to antibiotic consumption and AMR, and will simulate the impact of mAb and vaccination strategies on the chain of events.

- 5. Development of therapeutics and diagnostics combatting coronavirus infections:** On 30 January 2020, the novel coronavirus outbreak (COVID-19) was declared by WHO as a Public Health Emergency of International Concern according to the International Health Regulation 2005. Considering the public health and humanitarian implications of the COVID-19 outbreak, there is a need to advance our knowledge of SARS-CoV-2 specifically and the wider coronavirus family in general with the aim of contributing to an efficient patient management and/or public health preparedness and response to current and future outbreaks of coronavirus infection. There is therefore an opportunity to support collaboration of private companies, academia, international organisations, public bodies etc. to accelerate the development of therapeutics and diagnostics to tackle the current and future outbreaks and to contribute the pan-European effort responding to this Public Health Emergency.

Expected impact:

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

Type of actions:

Research and innovation actions

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

Activities in 2020 will address the following topic:

- 6. Returning Clinical Trial Data to Study Participants within a GDPR compliant and approved ethical framework:** A large amount of high-quality health data is collected during clinical studies (interventional and non-interventional), but, beyond the immediate objectives of the study, these valuable data are not used to the extent they merit. Subject to the research participant's approval, these data could be used to enrich patients' health care records to improve clinical decision-making and reduce duplication in procedures/investigations. In addition, returning clinical trial data to patients could allow them to contribute their data for additional scientific research (e.g. patient-powered research), in particular for rare diseases where treatments and data are scarce or unavailable. Finally, the lack of transparency and sharing of clinical trial data could contribute to the lack of patient willingness to be involved in studies, delays in clinical study set up and conduct, and delays in conducting health research in Europe to the detriment of vulnerable patients and public interest in general. However several challenges hamper returning clinical trials to patients. First, there are the complexities of determining acceptable common data format, processes or infrastructure. Second, there are complexities of the International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (ICH), Good Clinical Practice (GCP) and EU Clinical Trial Regulation (CTR) (e.g. including study integrity, privacy and confidentiality). Third, the national legal framework related to processing of health related data is not evenly harmonised across Member States and more clarification on some practical aspects of the implementation of the General Data Protection Regulation (GDPR) are needed. At the same time, there is an increasing awareness of the need for greater transparency and engagement with study participants in clinical research, and that the return of study participants' clinical trial data can address those needs. To foster progress in these areas this topic has two main objectives: The first one is to align local and pan-European implementations and best practice for handling personal data protection aspects in order to foster the legal harmonisation of the legal framework applicable to medical research across Member States. The second one is to deliver a pan-European prototype process to return clinical trial data to study participants, taking into account ongoing and previous activities on European interoperable Electronic Health Record (EHR) exchange and citizen-centric access to health records. This prototype process will be delivered as part of the project alongside a robust business plan to ensure its sustainability.

Expected impact:

- Patient centric data collection and data re-use based on the established ethics standards for medical research
- Development of new ways to source, manage process, and analyse data in compliance with ethical, General Data Protection Regulation (GDPR) and security standards
- An aid for health care practitioners in better clinical decision making, and a reduction in duplication of patient procedures/investigations.
- Improvement of adherence to study procedures and improvement of overall patient retention.
- Facilitation of conduct and set up of clinical studies as well as access to health data for research..
- An increase in the transparency of clinical studies and therefore an increase of the trust of patients in clinical research, helping with recruitment for studies and improving oversight by patients and regulators on clinical data re-use.
- Improved interoperability of Electronic Health Records (EHRs).

Type of actions:

Research and innovation actions

D. Oncology

Activities in 2020 will address the following topics:

- 7. 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.
- 8. Proton versus photon therapy for oesophageal cancer – a trimodality strategy.** The main objective of this topic is to examine the value of proton therapy (PT) as a treatment modality through a clinical study in oesophageal cancer. The study will compare outcomes between pencil-beam scanning proton therapy and intensity-modulated radiation therapy (IMRT). The study will determine if proton therapy in a trimodality (radiotherapy-chemotherapy-surgery) treatment; (i) reduces treatment related cardio-pulmonary toxicity (ii) increases loco-regional tumour control and pathological complete response when similar dose or higher dose is delivered, (iii) improves disease-free and overall survival. Oesophageal cancer is chosen due to its relatively high occurrence in the population and the possibility to extend findings to other cancer types. A second objective is to use the evidence generated during the oesophageal cancer study to reach a consensus on which indications are most suitable for PT treatment by engaging with the broader oncology community including oncologists, healthcare providers, health technology assessment (HTA) agencies, and payers among others.
- 9. Optimal treatment for patients with solid tumours in Europe through Artificial Intelligence**
Demands of cancer care in Europe continue to increase significantly; the number of incident cancer cases in Europe is projected to increase by 14.1% by 2030.¹ This leads to a growing demand for innovative cancer treatments among patients, payers, physicians, and society. At the same time, the complex biology of cancer is getting more deciphered and as a result, pharmaceutical companies are developing a multitude of new therapeutic agents. This includes, but is not limited to, novel kinase inhibitors, immunotherapy combinations, and cell therapies. The scope of this topic is to establish guideline-based decision support and platform solutions to generate knowledge discovery for breast, lung and prostate cancer with applicability to other indications, in several European 'model' regions. The results obtained from these model regions should be of relevance to countries with different socioeconomic backgrounds. The focus will be on breast, lung and prostate cancer to ensure a high number of cases per year, a high-unmet medical need, multiple available therapeutic options and a fast-evolving treatment environment. To this end, the topic supports activities for: 1) establishing a guideline-based decision support for prioritized indications. 2) The development of a decision support tool that automatically extracts relevant clinical information from electronic health records (EHRs) and facilitates guideline-compliant treatment approaches for the defined solid tumors. 3) Establishing a structured and interoperable data platform to unlock real-world-data potential in an oncology network. 4) Leveraging the real world data gathered by the action to establish an artificial intelligence (AI)-knowledge base and support treatment decisions for prioritized indications.

Expected impact:

- Improved monitoring of disease progress
- Improved selection of patients and inclusion in appropriate clinical trials
- Improved quality of life by preventing in-appropriate medication
- Better knowledge on tumour resistance mechanisms

- Improved understanding of the translational potential of patient-derived tumour models as indicators for the patient situation
- Access to data for functional studies and further opportunities to identify novel targets and drug combinations that delay or prevent the emergence of drug resistance in cancer
- Development of gold standards for the analysis of single-cell sequencing data
- New and improved standard for the treatment of oesophageal cancer patients and potentially patients with other cancer indications. Refined selection of patients.
- Improve the quality of care through better evidence of benefits and patient outcomes and support reimbursement decisions.

Type of actions:

Research and innovation actions

E. Immunology

Activities in 2020 will address the following topic:

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

Expected impact:

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

Type of actions:

Research and innovation actions

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

Activities in 2020 will address the following topic:

- 11. Shortening the path to Rare Disease diagnosis by using new born genetic screening and digital technologies.** Even though rare diseases (RD) span across a plethora of multisystemic syndromes, involving virtually every single organ or physiological function, most RD patients face common problems. These major hurdles can be summarised as delayed diagnosis, lack of R&D, and lack of access to or reimbursement of innovative medicines. One of the main challenges for RDs is related to diagnosis because RDs are characterised by a broad diversity of syndromic disorders and symptoms that vary from disease to disease and from patient to patient suffering from the same disease. In isolation, these symptoms can be very common, leading to misdiagnosis. Altogether, this leads to a lengthy and burdensome path to diagnosis that can take on average eight (8) years, often superposed with pointless treatments, and creates a heavy human and societal burden that could be avoided by earlier diagnosis. The overall objective of this call topic is to shorten the path to RD diagnosis by using new-born/paediatric (infants during their first weeks of life) genetic screening; and, via application of advanced digital technologies that enable rare disease suspicion / identification. The latter might require consolidation of existing fragmented efforts. This topic will as a first point support activities for assessment and development of a comprehensive, strategic overview of existing converging RD resources e.g. databases, registries, biobanks, natural history projects, platforms, reference networks, rare disease academic centers of excellence, and initiatives for evaluation / identification of potential collaboration and synergies. Secondly, it should generate a federation of available RD databases into a RD metadata repository amenable to machine learning or other advanced digital tools. A sustainable strategy for new-born genetic screening should be co-created and piloted. These results should guide repurposing of a pre-existing suspicion artificial intelligence (AI) algorithm to identify early onset RD patients in Electronic Health Records. This should include at least three pilots in better known rare diseases where more robust data is available to train and test the AI algorithm(s), and / or design and development of new AI algorithm(s). It is important that solutions and algorithms, developed or adapted, should be amenable or made amenable to be emulated for larger sets of better known RDs). A final aim is the generation (either repurposing or development) of a broad AI RD suspicion “symptom checker” to help undiagnosed RD patients, cycling through health care professionals (HCPs). In addition, exploration of viable further options to implement the symptom checker in actionable solutions for HCPs and patients should be sought

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

Type of actions:

Research and innovation actions

G. Other enablers of research topics

Activities in 2020 will address the following topic:

- 12. 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.
- 13. Behavioural Model of Factors Affecting Patient Adherence.** Patient non-adherence to prescribed treatment is an issue that affects patient health outcomes and healthcare system costs worldwide. It is estimated that it contributes to 200 000 premature deaths in the EU each year¹. The annual costs in Europe of avoidable hospitalisations, emergency care and adult outpatient visits are assessed at EUR 125 billion¹ and there are similar figures in the US². In addition, poor patient outcomes and resulting lower productivity affect the wider society, estimated in the US as 2.3 times direct healthcare costs². Addressing the issues of adherence would significantly improve both individual patient outcomes and reduce societal costs. This topic will support activities to achieve the following aims: first, develop a comprehensive understanding of the factors which affect patient needs and adherence, independently from the therapeutic area (i.e. generic or disease-agnostic), in a real-world context (as opposed to clinical setting). Second, identify the most significant factors. Third, evaluate existing models and then create an open access behavioural model or further develop an existing model. Forth, collect additional real-world data to refine the model, and provide tools that will enable healthcare stakeholders to cost-effectively develop and implement solutions to address patient needs and improve adherence rates.

Expected impact:

- Improve quality, safety and efficacy of therapeutic protein products by generating insight and improving development, supply, and use processes.
- Positive impact on healthcare at a societal level through enhanced adherence, targeted use of resources, and improved overall patient outcomes.
- Validated foundation to compile and understand factors affecting patient non-adherence to treatment regimes and the relative weighting of these factors.
- Guidance for identifying patient needs and tailoring support tools for patients and HCPs which most closely address patient adherence needs and improve patient outcomes and quality of life.

Type of actions:

Research and innovation actions

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

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

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

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

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

Applicants will have to demonstrate how the proposed follow-up research activities relate to an area with a high un-met need in the context of public health and industrial challenges, as relevant, and the very high relevance for addressing successfully the IMI2 JU objectives and scientific priorities. Activities supported by this Call will fall beyond the scope of the initial actions and could not be implemented within their financial and temporal framework.

The applicants will need to demonstrate the specific circumstances justifying that only the initial consortium (with some justified modifications of the partners list, if any, to cover the expertise needed for the newly proposed activities) can carry out activities successfully. For instance, that the initial consortium represents a unique and effective partnership with the expertise, equipment, methodologies, or access to unique resources and IP rights, that are not available from another consortium. The applicants will also need to justify that proposed follow-up activities are needed to further maximise the public-private partnership value of IMI2 JU as demonstrated both: 1) by the success of the initial public private partnership and 2) by a substantial amount of in-kind and financial contributions brought to the action by EFPIA constituent and affiliated entities and when relevant by IMI2 JU Associated Partners.

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

This Call will be:

- restricted to the original consortia of actions funded under topics published in the IMI2 JU Annual Work Plan of 2014, of 2015 and of 2016, since only these actions are sufficiently advanced in their implementation to be considered for follow-up research activities, and;
- limited to those actions derived from topics where the corresponding Work Plan already pre-informed potential applicants about the possibility of a later restricted Call.

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

Expected impact:

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

Type of actions:

Research and innovation actions

Calls for Proposals

Call number and topics	Indicative Call launch timing	Indicative IMI2 JU funding (in EUR) ^{2, 3 4}	Indicative in-kind contribution (in EUR) from EFPIA entities and Associated Partners
<p><u>IMI2 JU Call 20</u></p> <ul style="list-style-type: none"> ▪ <i>Infection control including vaccines</i> <ul style="list-style-type: none"> ▪ Academia and industry united innovation and treatment for tuberculosis (UNITE4TB) ▪ Innovations to accelerate vaccine development and manufacture ▪ <i>Oncology</i> <ul style="list-style-type: none"> ▪ Tumour plasticity ▪ Proton versus photon therapy for oesophageal cancer – a trimodality strategy ▪ <i>Immunology</i> <ul style="list-style-type: none"> ▪ Early diagnosis, prediction of radiographic outcomes and development of rational, personalised treatment strategies to improve long-term outcomes in psoriatic arthritis ▪ <i>Other enablers of research topics</i> <ul style="list-style-type: none"> ▪ Handling of protein drug products and stability concerns 	21 January 2020	133,009,000	140,209,500
IMI2 JU Call 20 process			
<p>Two-stage call with predefined submission deadline</p> <p>Indicative Call deadline for short proposals: 12 May 2020</p> <p>Indicative Call deadline for full proposals: 19 November 2020</p> <p>Research and Innovation Actions (RIA)</p>			

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

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

⁴ In case the budget of this given line cannot be consumed (totally or partially) the corresponding budget will be allocated to the topics under the other budget lines within the limits of the budget flexibility clause as set out Part I of the General Annexes to the Horizon 2020 Work Programme 2018-2020.

Call number and indicative topics	Indicative Call launch timing	Indicative IMI2 JU funding (in EUR) ^{5 6}	Indicative in-kind contribution (in EUR) from EFPIA entities and Associated Partners ⁷
<u>IMI2 JU Call 21</u> Development of therapeutics and diagnostics combatting coronavirus infections	03 March 2020	Up to 72,000,000	0
IMI2 JU Call 21 process			
Single-stage call with predefined submission deadline Indicative Call deadline for proposals: 31 March 2020 Research and Innovation Actions (RIA)			

Call number and indicative topics	Indicative Call launch timing	Indicative IMI2 JU funding (in EUR) ^{8 9}	Indicative in-kind contribution (in EUR) from EFPIA entities and Associated Partners
<u>IMI2 JU Call 22</u> <i>Restricted Call</i> Restricted Call to maximise impact of IMI2 JU objectives and scientific priorities	23 June 2020	11,427,098	0
IMI2 JU Call 22 process			
Single-stage call with predefined submission deadline Indicative Call deadline for proposals: 29 September 2020 Research and Innovation Actions (RIA) Restricted Call			

⁵ The maximum possible rate of co-financing is 100 %.

⁶ In case the budget of this given line cannot be consumed (totally or partially) the corresponding budget will be allocated to the topics under the other budget lines within the limits of the budget flexibility clause as set out Part I of the General Annexes to the Horizon 2020 Work Programme 2018-2020.

⁷ The indicative contribution from EFPIA companies and IMI2 JU Associated Partners will depend on the proposals eventually selected under the Call. See Annex II - IMI2 JU Call 21 topic text.

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

⁹ In case the budget of this given line cannot be consumed (totally or partially) the corresponding budget will be allocated to the topics under the other budget lines within the limits of the budget flexibility clause as set out Part I of the General Annexes to the Horizon 2020 Work Programme 2018-2020.

Call number and indicative topics	Indicative Call launch timing	Indicative IMI2 JU funding in EUR) ¹⁰¹¹	Indicative in-kind contribution (in EUR) from EFPIA entities and Associated Partners
<p><u>IMI2 JU Call 23</u></p> <ul style="list-style-type: none"> ▪ <i>Neurodegeneration and other neuroscience priorities</i> <ul style="list-style-type: none"> ▪ A platform for accelerating biomarker discovery and validation to support therapeutics development for neurodegenerative diseases. ▪ <i>Infection control including vaccines</i> <ul style="list-style-type: none"> ▪ Modelling the impact of monoclonal antibodies and vaccines on the reduction of antimicrobial resistance ▪ <i>Big data, digital health, clinical trials and regulatory research</i> <ul style="list-style-type: none"> ▪ Returning Clinical Trial Data to Study Participants within a GDPR compliant and approved ethical framework ▪ <i>Oncology</i> <ul style="list-style-type: none"> ▪ Optimal treatment for patients with solid tumours in Europe through Artificial Intelligence ▪ <i>Facilitating Rare Disease therapies (including Advanced Therapy Medical Products) reaching patients in Europe</i> <ul style="list-style-type: none"> ▪ Shortening the path to Rare Disease diagnosis by using new born genetic screening and digital technologies ▪ <i>Other enablers of research topics</i> <ul style="list-style-type: none"> ▪ Behavioural Model of Factors Affecting Patient Adherence 	23 June 2020	47,790,000	47,360,000

¹⁰ The maximum possible rate of co-financing is 100 %.

¹¹ In case the budget of this given line cannot be consumed (totally or partially) the corresponding budget will be allocated to the topics under the other budget lines within the limits of the budget flexibility clause as set out Part I of the General Annexes to the Horizon 2020 Work Programme 2018-2020.

IMI2 JU Call 23 process		
Two-stage call with predefined submission deadline		
Indicative Call deadline for short proposals: 29 September 2020		
Indicative Call deadline for full proposals: 17 March 2021		
Research and Innovation Actions (RIA)		
Overall total IMI2 JU Call 20, Call 21, Call 22 and Call 23	264,226,098	187,569,500

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

Budget

The budget for the financial year 2020 is based on the currently available information. There are no changes related to the total operational budget for the budget amendments no 2 and 3.

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

Heading Title 3	Budget 2020.0		Budget 2020 Amendment 1		Amended Budget 2020.3	
	Commitment Appropriation (CA)	Payment Appropriation (PA)	Commitment Appropriation (CA)	Payment Appropriation (PA)	Commitment Appropriation (CA)	Payment Appropriation (PA)
EU contribution to operational costs (including EFTA contribution EUR 5 867 096 in commitment appropriations and EUR 4 326 437 in payment appropriations)	255,971,716	195,055,294	-6,656,650	-4,908,659	249,315,066	190,146,635
Appropriations carried over from 2019	6,314,588		8,623,432	4,537,406	14,938,020	4,537,406
EFPIA and other Members contribution to operational costs		1,000,000			0	1,000,000
Associated Partners contribution to operational costs		1,500,000			0	1,500,000
Total operational costs Title 3	262,286,304	197,555,294	1,966,782	-371,253	264,253,086	197,184,041

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

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 four competitive Calls for proposals implementing the 2020 scientific priorities, one responding to the Public Health Emergency regarding the novel Coronavirus outbreak (COVID-19) as declared by the WHO on 30 January 2020. The indicative launch dates are 21 January 2020 for the first call of the year (IMI2 JU Call 20), 3 March for the second call of the year (IMI2 JU Call 21) and 23 June 2020 for the last two calls (IMI2 JU Calls 22 and 23).¹²

In the single-stage submission evaluation procedure, the submission deadline will be approximately three months from the publication of the Calls for proposals. In the case of IMI2 JU Call 21, since it addresses a very urgent public health emergency the submission deadline will be limited to four weeks from the publication of the Call for proposals.

In the two-stage submission evaluation procedure, the submission deadline will be:

- for stage 1: approximately three months from the publication of the Calls for proposals;
- for stage 2: approximately eight months from the publication of the Calls for proposals.

Submission deadlines provided in this Annual Work Plan are indicative.¹³

In addition, the evaluation of short proposals and full proposals submitted in response to Calls launched under the AWP for 2020 will be held according to the predefined timelines established in the relevant Call for proposals.

Timelines for the completion of the evaluation process and of preparation will be kept as lean as possible with the aim of completing the signature of the Grant Agreements within applicable time to grant (TTG), in compliance with the Horizon 2020 framework, i.e. a maximum of eight months from the final date of submission of the full proposals.¹⁴

For Call management, IMI2 JU will utilise the Horizon 2020 IT infrastructure available under Funding & tender opportunities - Single Electronic Data Interchange Area (SEDIA)¹⁵.

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

2.2.4 Activities to support and monitor ongoing projects

91 ongoing projects will be running at different stages of their life cycle in 2020, with additional projects coming in during the year when the IMI2 JU Calls 18, 19 (launched in 2019) and 21 (launched in 2020) complete the evaluation cycle (as indicated in the second column on the below table– ‘ongoing in 2020’). Most of the projects will submit to IMI2 JU a periodic report for the previous year summarising their progress and costs incurred. These reports form the basis for the Programme Office’s ex-ante controls.

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

Given the current planning and project durations, it is expected that IMI2 JU will organise a maximum of 24 reviews for projects launched under IMI2 JU Calls 1, 6, 7, 8, 9, 10, 12, 13 and 16.

¹² These dates are indicative; the IMI2 JU Executive Director may decide to open the call up to one month prior to or after the envisaged date of opening.

¹³ The IMI2 JU Executive Director may delay submission deadline by up to two months. The relevant submission deadline for each Call will be indicated in Submission Service section of the relevant topic page available under Funding & tender opportunities - Single Electronic Data Interchange Area (SEDIA).

¹⁴ 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’

¹⁵ <https://ec.europa.eu/info/funding-tenders/opportunities/portal/screen/home>

The following table presents a forecast of the on-going projects in 2020 and reporting expected for 2020:

Calls	Ongoing projects in 2020	Reports due after 31/10/2019	Project periodic reports due in 2020					Of which		
			1 st RP in 2020	2 nd RP in 2020	3 rd RP in 2020	4 th RP in 2020	5 th to 7 th RP in 2020	Total reports	Projects ending in 2020	Final reports due in 2020
IMI JU 1										
IMI JU 2										
IMI JU 3										
IMI JU 4										
IMI JU 5										
IMI JU 6	1						1	1	1	1
IMI JU 7										
IMI JU 8	1						1	1	1	1
IMI JU 9	1						1	1	1	1
IMI JU 10	1						1	1	1	1
IMI JU 11	7						7	7	3	4
IMI JU	11	0	0	0	0	0	11	11	7	8
IMI2 JU C1	1						1	1		
IMI2 JU C2	1						3	3		2
IMI2 JU C3	4						4	4	1	1
IMI2 JU C4										
IMI2 JU C5	5	1					5	6		
IMI2 JU C6	3	1			3			4		
IMI2 JU C7	6	1			6			7	1	1
IMI2 JU C8	4			3	1			4		
IMI2 JU C9	6			1	5			6	2	2
IMI2 JU C10	8			8				8	2	2
IMI2 JU C11	3			3				3	3	3
IMI2 JU C12	7		7					7		
IMI2 JU C13	13		13					13		
IMI2 JU C14	4		4					4		
IMI2 JU C15	7		7					7		
IMI2 JU C16	5		5					5		
IMI2 JU C17	3							0		
IMI2 JU C18*	6							0		
IMI2 JU C19	2							0		
IMI2 JU C21**	8									
IMI2 JU	96	3	36	15	15	9	4	82	9	11
Totals	107	3	36	15	15	9	15	93	16	19

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

** This is an estimated number of projects.

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

2.2.5 Monitoring and analysis of projects' results

A maximum of 93 project periodic reports will be submitted in 2020 (for ongoing projects and those finalised in 2019 see column 9 in the above table– 'Project periodic report due in 2020 – Total reports'). These reports will be used to track progress against their stated objectives and deliverables as laid out in the relevant description of the action.

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

In 2020, the analysis of the IMI2 JU project scientific outputs in terms of publications and collaboration among IMI researchers will be continued. Where feasible, monitoring and analysis approaches will be refined in line with observations from the European Court of Auditors (ECA) to ensure the highest possible standards.

2.2.6 Stakeholders' engagement and external collaborations

In 2020, IMI2 JU will continue to develop its relationships and engagement with key stakeholders such as patients, SMEs, regulators, payers and healthcare professions to ensure that its outputs are aligned with and address the needs of the society. In addition, IMI2 JU will organise one or more networking events and thematic workshops targeting specific stakeholders thereof (e.g. health care practitioners).

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

European Union Strategic Approach to Pharmaceuticals in the Environment:

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

Patient engagement

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

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

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

Additionally, IMI2 JU will lead efforts to ensure patient perspective is embedded in procedures surrounding the preparation of Call topics, proposal evaluation as well as project reviews.

SMEs

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

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

Regulators

The regulatory environment is key and it is critical to maximise the impact of research on innovative medicines. To ensure that the science generated by IMI-funded projects is translated into patient-centred healthcare, the regulatory environment is key to ensuring that safe and effective medicines reach the market for the benefit of patients. IMI2 JU will continue to engage with all relevant regulatory authorities, in particular, the European Medicines Agency (EMA). When possible and relevant, IMI2 JU will continue to strengthen engagement with other international agencies and competent national authorities, through for instance interactions with the heads of agencies. Similarly, IMI2 JU will continue to strengthen engagement with relevant health technology assessment (HTA) bodies, through interactions with EUnetHTA for instance in order to progress the goal of end-to-end integration in medicine development.

Other industries and stakeholders

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

IMI2 JU and ECSEL JU (www.ecsel.eu) initiated in 2017 the first discussions to explore possibilities for cooperation between both JUs in the domain of smart health along three thematic areas: sensors and diagnostics, imaging, and patient monitoring platforms. As a continuation of the first concrete interactions set up in 2018, participation of both JUs in their respective governance bodies (e.g. participation of ECSEL in SGG Digital Health & Patient Centric Evidence Generation, Immunology, etc.), interactions during topics design and consultation process, as well as dedicated workshops, are planned in 2020. The objective is to further support synergies between the JUs' activities and potential collaborations between projects of the respective JUs.

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

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

2.2.7 Dissemination and information about projects results

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

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

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

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

For the above mentioned respective projects, close-out meetings will be organised around the time of submission of the final report. The IMI2 JU will prepare specific communication materials for each project based upon information provided in the respective final report and close out meeting.

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

2.2.8 Socio-economic impact assessment

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

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

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

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

2.3 Call management rules

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

The following general conditions shall apply to the IMI2 JU Calls for Proposals. They are based on the General Annexes to the Horizon 2020 Work Programme 2018-2020¹⁶.

LIST OF COUNTRIES AND APPLICABLE RULES FOR FUNDING

By way of derogation¹⁷ 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 established¹⁸.

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.

¹⁶ http://ec.europa.eu/research/participants/data/ref/h2020/other/wp/2018-2020/annexes/h2020-wp1820-annex-ga_en.pdf

¹⁷ 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

¹⁸ In accordance with Article 10(2) of the Regulation (EU) No 1290/2013 and Article 1 of Commission Delegated Regulation (EU) No 622/2014

STANDARD ELIGIBILITY CONDITIONS

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

In addition, under all two-stage submission procedures the following additional condition¹⁹ applies:

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

Furthermore, the IMI2 JU Call 22, single-stage submission procedure, will be launched under the scientific priority ‘Restricted Call to maximise the impact of IMI2 JU objectives and scientific priorities’. This Call 22 intends to support further activities in those exceptional cases where it is necessary to enable successful consortia to build upon the achievements of their initial action in order to take full advantage of the impacts of the initial action results. In the context of the IMI2 JU Call 22, the following additional condition²⁰ applies:

- the IMI2 JU Call 22 is restricted to the original consortia of actions funded under topics published in the IMI2 JU Annual Work Plan of 2014, 2015 and 2016, since only these actions are sufficiently advanced in their implementation to be considered for follow-up activities, and;
- the IMI2 JU Call 22 is limited to those topics which already pre-informed potential applicants about the possibility for a later restricted Call

TYPES OF ACTION: SPECIFIC PROVISIONS AND FUNDING RATES

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

TECHNOLOGY READINESS LEVELS (TRL)

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

EVALUATION RULES

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

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

Award criteria and scores:

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

¹⁹ 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”

²⁰ 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 <i>The following aspects will be taken into account, to the extent that the proposed work corresponds to the topic description in the call for proposals and referred to in the IMI2 JU annual work plan:</i>	Impact <i>The following aspects will be taken into account:</i>	Quality and efficiency of the implementation <i>The following aspects will be taken into account:</i>
<p>RIA</p> <p>1st stage</p> <p>Evaluation of two-stage evaluation</p>	<ul style="list-style-type: none"> ▪ Level to which all the objectives of the Call topic text are addressed; ▪ Soundness of the concept and credibility of the proposed methodology; ▪ Extent that the proposed work is beyond the state of the art and demonstrates innovation potential; ▪ Appropriate consideration of interdisciplinary approaches and use of stakeholder knowledge. 	<ul style="list-style-type: none"> ▪ Demonstration of how the outputs of the project will contribute to each of the expected impacts mentioned in the relevant Call topic text; ▪ Outline of how the project plans to leverage the public-private partnership model to achieve greater impact on innovation within research and development, regulatory, clinical and healthcare practices, as relevant; ▪ Impacts on competitiveness and growth of companies including SMEs; ▪ Quality of the proposed outline to: <ul style="list-style-type: none"> ▪ Disseminate, exploit and sustain the project results; ▪ Manage research data; ▪ Communicate the project activities to relevant target audiences. 	<ul style="list-style-type: none"> ▪ Quality and effectiveness of the work plan outline, including extent to which the resources assigned to work packages are in line with their objectives and deliverables; ▪ Appropriateness of the outline management structures and procedures; ▪ Appropriateness of the allocation of tasks, ensuring that all participants have a valid role and adequate resources in the project to fulfil that role; ▪ Complementarity of the participants and extent to which the consortium as whole brings together the necessary expertise; ▪ Strategy to create a successful partnership with the industry consortium as mentioned in the Call topic text.

Type of action	Excellence <i>The following aspects will be taken into account, to the extent that the proposed work corresponds to the topic description in the Call for proposals and referred to in the IMI2 JU annual work plan and, for two stage procedures, is consistent with the stage 1 proposal:</i>	Impact <i>The following aspects will be taken into account:</i>	Quality and efficiency of the implementation <i>The following aspects will be taken into account:</i>
RIA 2nd stage of two-stage evaluation and Single stage evaluation	<ul style="list-style-type: none"> ▪ Level to which all the objectives of the Call topic text are addressed; ▪ Soundness of the concept and credibility of the proposed methodology; ▪ Extent that the proposed work is beyond the state of the art and demonstrates innovation potential; ▪ Appropriate consideration of interdisciplinary approaches and use of stakeholder knowledge. 	<ul style="list-style-type: none"> ▪ Demonstration of how the outputs of the project will contribute to each of the expected impacts mentioned in the relevant Call topic text; ▪ Demonstration of how the project plans to leverage the public-private partnership model to achieve greater impact on innovation within R&D, regulatory, clinical and healthcare practices, as relevant; ▪ Impacts on competitiveness and growth of companies including SMEs; ▪ Quality and effectiveness of the proposed measures to: <ul style="list-style-type: none"> ▪ Disseminate, exploit and sustain the project results; ▪ Manage research data; ▪ Communicate the project activities to relevant target audiences. 	<ul style="list-style-type: none"> ▪ Quality and effectiveness of the work plan, including extent to which the resources assigned to work packages are in line with their objectives and deliverables; ▪ Appropriateness of the management structures and procedures, including management of risk and innovation; ▪ Appropriateness of the allocation of tasks, ensuring that all participants have a valid role and adequate resources in the project to fulfil that role; ▪ Complementarity of the participants and extent to which the consortium as whole brings together the necessary expertise; ▪ Clearly defined contribution and effective integration of the industrial partners to the project.

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

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

For the evaluation of proposals under a two-stage submission procedure, at both stages (Stage 1 and Stage 2):

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

For the evaluation of proposals under a single-stage submission procedure:

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

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

The full evaluation procedure is described in the IMI2 JU Manual for submission, evaluation and grant award in line with the Horizon 2020 Rules for Participation.²¹

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 topic²² will be invited to discuss with the relevant industry consortium the feasibility of jointly developing a full proposal (second stage).

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

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

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

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

²¹ https://www.imi.europa.eu/sites/default/files/uploads/documents/apply-for-funding/call-documents/imi2/IMI2_ManualForSubmission_v1.7_November2018.pdf

²² In cases clearly identified in the relevant call for proposals where a given topic is composed of two or more sub-topics, one short proposal per sub-topic will be invited.

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

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

INDICATIVE TIMETABLE FOR EVALUATION AND GRANT AGREEMENT

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

BUDGET FLEXIBILITY

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

ACTIONS INVOLVING FINANCIAL SUPPORT TO THIRD PARTIES

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

CONDITIONS RELATED TO OPEN ACCESS TO RESEARCH DATA

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

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

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

Beneficiaries in grants awarded under IMI2 JU Call 21 must make available their research data, at the latest within 30 days after it has been generated, through open access or, if agreed by the IMI2 JU or the European Commission, by giving access rights to those third parties that need the research data to address the Public Health Emergency. Therefore, the relevant option of Article 29.3 (option 1c) of the IMI2 JU Model Grant Agreement²³ will apply. It is expected that quality-controlled data are shared in accordance with the FAIR principles. The use of harmonised protocols in collaboration with other actors is recommended for this purpose.

²³ https://www.imi.europa.eu/sites/default/files/uploads/documents/reference-documents/h2020-mga-imi_en_v5.pdf

SUBMISSION TOOL

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

No other means of submission will be accepted.

OTHERS

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

Ethical issues should be duly addressed in each submitted proposal to ensure that the proposed activities comply with ethical principles and relevant national, Union and international legislation. Any proposal that contravenes ethical principles or which does not fulfil the conditions set out in the H2020 Rules for Participation, or in the IMI2 JU Call for proposals shall not be selected.²⁴

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

In order to ensure excellence in data and knowledge management consortia will be requested to disseminate scientific publications on the basis of open access²⁵ (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 documents²⁶ (e.g. IMI2 JU model Grant Agreement).

²⁴ Article 19 of Horizon 2020 Framework Programme and Articles 13 and 14 of the Horizon 2020 Rules for Participation.

²⁵ 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

²⁶ <http://www.imi.europa.eu/apply-funding/call-documents/imi2-call-documents>

2.4 Support to Operations

2.4.1 Communication and events

Communication objectives

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

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

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

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

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

Communication support to IMI2 JU stakeholder strategies: patients and SMEs

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

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

Further develop IMI success stories

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

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

Media outreach

The coverage of IMI2 JU in both the general and specialist press tends to be either neutral or positive in tone. In 2020, IMI2 JU will work to ensure that this trend continues by building and maintaining links with journalists, issuing regular press releases, organising press interviews, and inviting journalists to IMI2 JU events.

Communication channels

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

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

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

Key events in 2020

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

Event	Timeline
Promote IMI2 JU projects	Throughout year
IMI2 JU presence in the European Parliament (including joint JU's events)	Throughout year
IMI2 JU presence at relevant external events, e.g. BIO, BIO-Europe, ESOF, BioFIT	Throughout year
IMI2 JU Stakeholder Forum 2020	Q4
Promote IMI2 JU Calls for proposals (webinars, info days, website, etc.)	Q1, Q2

2.4.2 Procurement and contracts

In order to reach its objectives and adequately support its operations and infrastructures, IMI2 JU will allocate funds to procure the necessary services and supplies.

IMI2 JU intends to launch an open call for tender for the conclusion of a service contract for corporate identity-related services for a total maximum value of EUR 200,000.

To make tender and contract management as effective and efficient as possible, IMI2 JU resorts extensively to multi-annual framework contracts and EU inter-institutional tenders. Most essential framework contracts are already in place and will be renewed beyond 2020.

2.4.3 IT and logistics

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

In order to achieve the afore-mentioned goal, the IMI2 JU IT team will focus its 2020 activities on three areas:

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

2.4.3.1 Business operations information systems

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

Since some IMI JU projects go on until at least 2024 and some of the IMI2 JU specific requirements (e.g. EFPIA and Associated Partners annual reporting of in-kind contributions) are not available in eGrants, we will continue the maintenance and development of the in-house SOFIA.

2.4.3.2 Collaboration, communication and administration management information systems

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

2.4.3.3 Infrastructure, security and office automation support

IMI2 JU shares IT infrastructure, related IT operations and office automation support with other JUs that are also located in the same premises. In the context of the common infrastructure, the following activities are foreseen for 2020 and are expected to provide efficiency gains in the operation of the organisation:

- monitoring and maintenance of the common infrastructure and end-user office-automation support covering incidents, service requests and improvements;
- renewal of wireless and wired network infrastructure in White Atrium building;
- renewal of conference audio visual equipment in Common meeting room 2 (subject of common JUs approval).

2.4.4 Human Resources

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

Staff management and recruitment

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

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

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

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

Legal Matters

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

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

Organisation development

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

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

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

Inter-JU cooperation

The efficiency and cost-effective management of IMI2 JU resources is also based on a close collaboration with other Joint Undertakings through arrangements and mechanisms of pooling expertise for specific time-bound tasks. In 2020, the JUs will continue to share the human-resource IT tools where necessary, common Calls for tender, as well as a common approach to implementing rules of the EU staff regulations.

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

2.4.5 Administrative budget and finance

The budget 2020 for staff (Title 1) and infrastructure and operating expenditure (Title 2) has been defined in line with the planning of the year. The increase of 1.2% in 2020 compared to 2019, is mainly due to increase in staff related expenditures, rent and IT costs as well as costs of evaluations.

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

	Heading	Financial year 2019	Financial year 2020	Evolution	Comments
Title Chapter		Budget EUR	Budget EUR		
2	Infrastructure expenditure				
20	Office building and associated costs	756,000	776,625	2.73%	Indexation and additional space.
21	Information technology purchases	779,000	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.
Total Title 2 (Infrastructure expenditure)		4,690,154	4,572,809	-2.5%	
Total Title 1+2 (Administrative expenditure)		11,020,154	11,152,482	1.2%	

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 implements the updated IMI2 JU Financial Rules in line with the Commission Delegated Regulation (EU) 2019/887 on the model financial regulation for public-private partnership bodies referred to in Article 71 of the Regulation (EU, Euratom) 2018/1046 on the financial rules applicable to the general budget of the Union, repealing Regulation (EU, Euratom) No 966/2012 (2012 Financial Regulation) and the two relevant Commission Decisions, namely C(2019) 8061 of 7.11.2019 and C(2020) 1343 of 6.03.2020 correcting C(2019) 8061 of 7.11.2019.

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

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

2.4.6 Data protection

The IMI2 JU will continue its efforts undertaken in the wake of the entry into effect of Regulation (EU) 2018/1725.

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

2.4.7 Access to documents

IMI2 JU will continue to address requests for access to IMI2 JU documents according to Regulation (EC) No 1049/2001, in a spirit of openness and transparency in order to bring its activities and outputs closer to the public in line with the policy developed by the Programme Office. IMI2 JU will continue the implementation of the standard operating procedure (SOP) on Access to documents and the training of the staff on access to documents issues.

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

2.5 Governance

Key objectives

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

Planned activities

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

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

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

The **Scientific Committee** (SC) will continue in its advisory role to the IMI2 JU and will notably be consulted on the scientific priorities to be addressed in Annual Work Plans (and subsequent amendment(s) and on the scientific achievements to be described in the Annual Activity Report. Three meetings of the SC are planned for 2020. The Chair will participate in the Governing Board meetings as an observer. The term of the current Scientific Committee members will come to end in 2020, and the Committee in its mandate may be renewed in 2nd half of 2020. Information can be found at: <http://www.imi.europa.eu/about-imi/governance/scientific-committee>.

The **States Representatives Group** (SRG) will be consulted on the Annual Work Plan (and subsequent amendment(s)) and will receive information on Calls outcomes and evaluation process. At least two meetings of the SRG are planned for 2020. A change of chairpersonship is planned for the beginning of 2020 (the current mandates ending on 3 February 2020). The Chair will participate in Governing Board meetings as an observer. Information can be found at: <http://www.imi.europa.eu/about-imi/governance/states-representatives-group>.

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

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

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

In 2020 the SGGs will continue to develop comprehensive strategies for future projects for their specific areas.

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

In 2020, facilitation of better cross-SGGs coordination will continue, notably through the dedicated IT platform, as well as a series of dedicated cross-SGGs meetings. These improved efficiency mechanisms will facilitate the increased flow of information not only within a given SGG, but also with IMI2 JU governance bodies (Governing Board, SC, SRG). In addition, they will be called upon to advise on how best to exploit IMI2 JU projects' outputs, enhance cross-projects' collaboration, as well as explore synergies with similar or complementary activities at national and global level.

In line with article 13.3 (b) of IMI2 JU Regulation, costs of activities related to allowing the SGGs perform these tasks and achieve their objectives are considered as eligible in-kind contributions under the conditions set out in the SGG charter.²⁷

²⁷ 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 performance²⁸ in order to ensure the achievement of its objectives. Specific actions will aim at:

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

2.6.1 Ex-ante and ex-post controls

Ex-ante controls

During 2020, the Programme Office will continue the implementation of its programme in line with H2020 legal framework in particular through initiation, verification and payments of invoices and cost claims, creation of commitments, recovery orders, validation of financial and technical reports and following-up on other financial and administrative aspects of the projects.

These activities will be conducted in a timely and efficient manner according to the principle of sound financial management. All activities will be monitored through the defined set of KPIs, in particular, the time to pay and the budget and work plan execution. Best practice and highest quality standards will be ensured through the implementation of IMI Financial Circuits manual and a set of Standard Operating Procedures and checklists.

Specific attention will be placed on:

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

Ex-post controls

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

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

²⁸ 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 14.2).

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

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

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

2.6.2 Internal and External audits

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

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

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

In 2020, the focus will be put on:

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

External audits are carried out by ECA. ECA will audit and issue opinions on the legality and regularity of the underlying transactions, revenue, and reliability of accounts. In accordance with the IMI2 JU Financial rules, IMI2 JU's 2020 annual accounts will be audited by an external audit company while the Court will draw an opinion on the basis of their work.

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

- liaising and supporting ECA auditors throughout the audit on 2019 and 2020 accounts;
- liaising with an independent financial audit firm throughout the audit of accounts for financial year 2019 and 2020.

3 Budget 2020

The amended Budget 2020.3 reflects correction of the transfer from the EC Health programme reflected in the first amended Budget 2020.1. The transfer was of EUR 14,700 to administrative expenditure from non spent 2014 EU contribution and it should have been reflected on the EC payment appropriations only. For the amended Budget 2020.3, following the correction, it resulted a total decrease of EUR 29,400 (50% EC - 50% EFPIA) on commitment appropriations and a decrease of EUR 14,700 on payment appropriations (EFPIA).

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

STATEMENT OF REVENUE										
	Heading Revenue	Budget 2020.0		Budget 2020 Amendment 1		Budget 2020 Amendment 3		Amended Budget 2020.3		Comments
Chapter		Commitment Appropriation (CA)	Payment Appropriation (PA)	Commitment Appropriation (CA)	Payment Appropriation (PA)	Commitment Appropriation (CA)	Payment Appropriation (PA)	Commitment Appropriation (CA)	Payment Appropriation (PA)	
10	European Commission contribution (including EFTA contribution EUR 5 998 321 in commitment appropriations and EUR 4 457 662 in payment appropriations)	261,547,957	200,631,535	-6,641,950	-4,893,959	-14,700		254,891,307	195,737,576	Commitment appropriations include EUR 5 576 241 for administrative costs and EUR 249 315 066 for operational costs. Payment appropriations include administrative costs of EUR 5 590 941 ²⁹ and operational costs of EUR 190 146 635.
C2	Appropriations carried over	6,314,588		8,623,432	6,612,304			14,938,020	6,612,304	The amount carried over from previous year
EC contribution		267,862,545	200,631,535	1,981,482	1,718,345	-14,700	0	269,829,327	202,349,880	

²⁹ European Commission contribution (including EFTA contribution): for administrative costs, on the E.U side, as year 2020 is the last year of H2020 Framework Programme, the full remaining amount is committed (EUR 27 867 587). In 2020, EUR 5 590 941 will be paid to IMI2 JU, the remaining amount will be paid over the following years. For administrative costs, the amount for 2020 in payment appropriations is 14.700 EUR higher than the commitment appropriations, to balance budget year 2014, where payment appropriations was 490.000 EUR and commitment appropriations was 504.700 EUR.

STATEMENT OF REVENUE										
	Heading Revenue	Budget 2020.0		Budget 2020 Amendment 1		Budget 2020 Amendment 3		Amended Budget 2020.3		Comments
Chapter		Commitment Appropriation (CA)	Payment Appropriation (PA)	Commitment Appropriation (CA)	Payment Appropriation (PA)	Commitment Appropriation (CA)	Payment Appropriation (PA)	Commitment Appropriation (CA)	Payment Appropriation (PA)	
20	EFPIA contribution	5,576,241	5,576,241	14,700	14,700	-14,700	-14,700	5,576,241	5,576,241	EFPIA contribution to IMI JU administrative costs.
21	Subsidy from other Members other than the Union and the Associated Partners, or their constituent entities or their affiliated entities		1,000,000					0	1,000,000	Four EFPIA companies contribution to operational payment appropriations
EFPIA and other Members contributions		5,576,241	6,576,241	14,700	14,700	-14,700	-14,700	5,576,241	6,576,241	
30	Associated Partners contributions		1,500,000					0	1,500,000	Bill and Melinda Gates Foundation contribution to operational payment appropriations
Associated Partners contributions			1,500,000	0	0			0	1,500,000	
Total revenues		273,438,786	208,707,776	1,996,182	1,733,045	-29,400	-14,700	275,405,568	210,426,121	

STATEMENT OF EXPENDITURE

Title Chapter	Heading Title 1	Budget 2020.0		Budget 2020 Amendment 1		Budget 2020 Amendment 3		Amended Budget 2020.3		Comments
		Commitment Appropriation (CA)	Payment Appropriation (PA)	Commitment Appropriation (CA)	Payment Appropriation (PA)	Commitment Appropriation (CA)	Payment Appropriation (PA)	Commitment Appropriation (CA)	Payment Appropriation (PA)	
1	Staff expenditure									
11	Staff in active employment	5,972,049	5,972,049					5,972,049	5,972,049	Salaries and allowances of current staff (TAs and CAs), SNE, promotion and indexation
12	Staff recruitments - miscellaneous expenditure	19,538	19,538					19,538	19,538	Miscellaneous expenditure on staff recruitment: publication of vacancy call, medical visit to take up duties, services provided by the European Personnel Selection Office (EPSO)
13	Mission expenses	185,608	185,608		8,954			185,608	194,562	Mission expenses
14	Socio-medical structure	207,100	207,100		51,874			207,100	258,974	Other staff costs: EU school, medical check-up, trainings
15	External staff services	175,840	175,840		68,782			175,840	244,622	Interim staff expenses
17	Representation	19,538	19,538		1,853			19,538	21,391	Representation expenses
Total Title 1 (Staff expenditure)		6,579,673	6,579,673	0	131,463			6,579,673	6,711,136	

	Heading Title 2	Budget 2020.0		Budget 2020 Amendment 1		Budget 2020 Amendment 3		Amended Budget 2020.3		Comments
Title Chapter		Commitment Appropriations (CA)	Payment Appropriation (PA)	Commitment Appropriation (CA)	Payment Appropriation (PA)	Commitment Appropriation (CA)	Payment Appropriation (PA)	Commitment Appropriation (CA)	Payment Appropriation (PA)	
2	Infrastructure expenditure									
20	Office building and associated costs	776,625	776,625		166,990			776,625	943,615	Building related expenditure: rent, works, charges, maintenance, repairs, security and surveillance
21	Information technology (hardware and software)	786,394	786,394	29,400	688,656	-29,400	-14,700	786,394	1,460,350	IT purchases, software licences, software development
22	Office equipment	154,348	154,348					154,348	154,348	Purchases and rental of office equipment, maintenance and repair
23	Current administrative expenditure	122,111	122,111		93,683			122,111	215,794	Office supply, newspaper subscriptions, translation services, bank charges and miscellaneous office expenditure
24	Telecommuni- cation and postal expenses	78,151	78,151		28,378			78,151	106,529	Data communication such as telephone, video and audio conferences and postal services
25	Formal meetings	156,302	156,302		50,761			156,302	207,063	Official meetings such as States Representative Group, Scientific committee, Governing Board and working groups created by the Governing Board

	Heading Title 2	Budget 2020.0		Budget 2020 Amendment 1		Budget 2020 Amendment 3		Amended Budget 2020.3		Comments
Title Chapter		Commitment Appropriations (CA)	Payment Appropriation (PA)	Commitment Appropriation (CA)	Payment Appropriation (PA)	Commitment Appropriation (CA)	Payment Appropriation (PA)	Commitment Appropriation (CA)	Payment Appropriation (PA)	
26	Administrative expenditure in connection with operational activities	388,801	388,801		115,520			388,801	504,321	Administrative expenditure in connection with research activities and objectives of IMI (workshops, meetings and events targeting IMI projects)
27	External communication, information and publicity	610,555	610,555		2,720			610,555	613,275	External communication and events such as Info Days, stakeholder forums
28	Service contracts	522,635	522,635		517,072			522,635	1,039,707	Ex-post audits, studies, audits, accounting services
29	Expert contracts and cost of evaluations	976,887	976,887		309,055			976,887	1,285,942	Costs linked to evaluations, expert contracts
Total Title 2 (Infrastructure expenditure)		4,572,809	4,572,809	29,400	1,972,835	-29,400	-14,700	4,572,809	6,530,944	
Total Title 1 + 2 (administrative expenditure)		11,152,482	11,152,482	29,400	2,104,298	-29,400	-14,700	11,152,482	13,242,080	

	Heading	Budget 2020.0		Budget 2020 Amendment 1		Budget 2020 Amendment 3		Amended Budget 2020.3		Comments
Title Chapter		Commitment Appropriation (CA)	Payment Appropriation (PA)	Commitment Appropriation (CA)	Payment Appropriation (PA)	Commitment Appropriation (CA)	Payment Appropriation (PA)	Commitment Appropriation (CA)	Payment Appropriation (PA)	
3	Operational expenditure									
30	Implementing the research agenda of IMI2 JU	255,971,716	197,555,294	-6,656,650	-4,908,659			249,315,066	192,646,635	Calls, Grant agreements - Payments
C2	Implementing the research agenda of IMI2 JU	6,314,588		8,623,432	4,537,406			14,938,020	4,537,406	Appropriations carried over from 2019
Total Title 3 (Operational expenditure)		262,286,304	197,555,294	1,966,782	-371,253			264,253,086	197,184,041	
Total expenditure		273,438,786	208,707,776	1,996,182	1,733,045	-29,400	-14,700	275,405,568	210,426,121	

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

Budget line Chapter	Description	Commitment Appropriations (CA)	Payment Appropriations (PA)	C2 - Payment Appropriations (PA)
A01100	Staff in active employment and costs linked to employees	3,847,049	3,847,049	
A01101	Family Allowances	374,000	374,000	
A01102	Transfer and expatriation allowances	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 allowances	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	0	0	
A01177	Other services rendered	60,000	60,000	
A01178	Paymaster Office (PMO) fees	60,000	60,000	
A01180	Sundry recruitment expenses	0	0	
A01181	Travelling expenses (including taking up duty)	0	0	
A01182	Installation allowance	43,000	43,000	
A01183	Moving expenses	0	0	
A01184	Temporary daily allowance	13,000	13,000	
A01190	Weightings (correction coefficient)	4,000	4,000	
A01191	Salaries adaptation	0	0	
11	Staff in active employment	5,972,049	5,972,049	
A01200	Miscellaneous expenditure on staff recruitment	19,538	19,538	

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

Budget line Chapter	Description	Commitment Appropriations (CA)	Payment Appropriations (PA)	C2 - Payment Appropriations (PA)
A02000	Rentals office building	566,625	566,625	
A02001	Guarantees	0	0	
A02002	Contributions	0	0	
A02010	Insurance	0	0	
A02020	Charges (water, gas, electricity, works)	161,000	161,000	125,543
A02030	Cleaning and maintenance	10,000	10,000	
A02040	Furnishing of premises	10,000	10,000	41,448
A02050	Security and surveillance	29,000	29,000	
A02090	Other expenditure on buildings	0	0	
20	Office building and associated costs	776,625	776,625	166,990
A02101	Hardware, infrastructure and related services	255,000	269,700	268,686
A02102	Software development, licenses and related services	531,394	531,394	390,570
A02103	Other expenses maintenance and repair	0	0	

Budget line Chapter	Description	Commitment Appropriations (CA)	Payment Appropriations (PA)	C2 - Payment Appropriations (PA)
21	Information technology purchases	786,394	801,094	659,256
A02200	Purchase office equipment	124,348	124,348	
A02201	Rentals office equipment	10,000	10,000	
A02202	Maintenance utilisation and repair	20,000	20,000	
A02203	Other office equipment	0	0	
22	Office equipment (movable property and associated costs)	154,348	154,348	
A02300	Stationery and office supply	40,000	40,000	2,200
A02320	Bank charges	0	0	
A02321	Exchange rate losses	0	0	
A02329	Other financial charges	0	0	
A02330	Legal expenses	20,000	20,000	25,000
A02350	Other operating expenditure	13,000	13,000	32,624
A02351	Petty expenses	0	0	
A02360	Library stocks purchase of books and subscriptions	44,000	44,000	29,358
A02370	Translation, interpretation	5,111	5,111	4,502
23	Current administrative expenditure	122,111	122,111	93,683
A02400	Correspondence and communication expenses	78,151	78,151	28,378
24	Telecommunication and postal expenses	78,151	78,151	28,378
A02500	Formal meetings	156,302	156,302	50,761
25	Expenditure on formal meetings	156,302	156,302	50,761
A02600	Administrative costs in connection with operational activities	47,801	47,801	6,000
A02601	Events targeting IMI projects	10,000	10,000	
A02602	Workshops	325,000	325,000	101,520
A02603	Knowledge Management	6,000	6,000	8,000
26	Administrative costs in connection with operational activities	388,801	388,801	115,520
A02700	External communication	210,555	210,555	
A02701	Events external communication	300,000	300,000	
A02702	Material	100,000	100,000	2,720

Budget line Chapter	Description	Commitment Appropriations (CA)	Payment Appropriations (PA)	C2 - Payment Appropriations (PA)
27	External communication, information and publicity	610,555	610,555	2,720
A02800	Ex-post Audits	250,000	250,000	226,572
A02801	Studies, consultancy	177,635	177,635	268,020
A02802	Audit services	60,000	60,000	22,480
A02803	Accounting services	35,000	35,000	
28	Service contracts	522,635	522,635	517,072
A02900	Evaluation Experts meetings	956,887	956,887	297,227
A02901	Evaluation Facilities	20,000	20,000	11,829
A02902	Evaluations Exploring New Scientific Opportunities (ENSO)	0	0	
29	Expert contracts and cost of evaluations	976,887	976,887	309,055
Total Title 2 (Infrastructure expenditure)		4,572,809	4,587,509	1,943,435

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

Budget line Chapter	Description	Commitment Appropriations (CA)	Payment Appropriations (PA)	C2 - Payment Appropriations (PA)
B03031	IMI2 JU Call 11		291,875	
B03032	IMI2 JU Call 12		7,124,448	
B03033	IMI2 JU Call 13		10,422,145	
B03034	IMI2 JU Call 14			
B03035	IMI2 JU Call 15		10,000,000	
B03036	IMI2 JU Call 16		3,256,921	
B03037	IMI2 JU Call 17		10,604,360	
B03038	IMI2 JU Call 18		18,212,957	
B03039	IMI2 JU Call 19		7,709,348	
B03040	IMI2 JU Call 20	126,694,412		
B03041	IMI2 JU Call 21	72,000,000	15,000,000	
B03042	IMI2 JU Call 22	2,830,654		
B03043	IMI2 JU Call 23	47,790,000		
B03999	Recovery Ex-post audit			
30-C1	Implementing the research agenda of IMI2 JU	249,315,066	192,646,635	
B03040 – C2	IMI2 JU Call 20	6,314,588		
B03042 – C2	IMI2 JU Call 22	8,596,444		
B03030 – C2	IMI2 JU Call 10			4,510,418
B03000 – C2	Implementing the research agenda of IMI JU	26,988		26,988
Total Title 3 (Operational expenditure)		264,253,086	192,646,635	4,537,406
Total expenditure		275,405,568	203,813,817	6,612,304

3.1 Staff Establishment Plan 2020

Grade	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)		
	PERM	TA	TOTAL	Posts filled on 31/12/20 19	Officials	TA - LT	TA - ST	Officials	TA - LT	TA - ST	Perm	TA - LT	TA - ST	PERM	TA	TOTAL
AD16																
AD15																
AD14		1	1	1											1	1
AD13																
AD12		2	2	1											2	2
AD11		2	2	2											2	2
AD10															1	1
AD9		6	6	5											7	7
AD8		7	7	4											6	6
AD7		3	3	6											2	2
AD6		4	4	4											8	8
AD5		8	8	9											4	4
Total AD		33	33	32											33	33
AST11																
AST10																
AST9																
AST8		1	1	1											1	1
AST7																
AST6																
AST5																
AST4		4	4	2											4	4
AST3				2												
AST2															1	1
AST 1		1	1	1											- 1	
Total AST		6	6	6											6	6
SC6																
SC5																
SC4																
SC3																
SC2																
SC1																
Total SC		0	0	0											0	0
Overall Total		39	39	38											39	39

Contract Agents Grade	2019	Posts filled on 31/12/19	2020
FG IV	2	2	3
FG III	12	11	11
FG II	1	1	1
FG I	0	0	0
Total CA	15	14	15

Seconded National Experts	2019	Posts filled on 31/12/19	2020
	1	1	2

Annex I - IMI2 JU Call 20 topics text

Introduction

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

The Innovative Medicines Initiative 2 Joint Undertaking (IMI2 JU) has been created³⁰ 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 World³¹.

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 companies³², from different sectors e.g. biomedical imaging, medical information technology, diagnostic and/or animal health industries. Involving the wider community in this way should help to advance the development of new approaches and technologies for the prevention, diagnosis and treatment of diseases with high impact on public health.

The IMI2 JU Strategic Research Agenda (SRA)³³ is the main reference for the implementation of research priorities for IMI2 JU. The scientific priorities for 2020 for IMI2 JU have been prepared based on the SRA.

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

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

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

³⁰ 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.

³¹ http://www.who.int/medicines/areas/priority_medicines/en/

³² 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.

³³ http://www.imi.europa.eu/sites/default/files/uploads/documents/About-IMI/research-agenda/IMI2_SRA_March2014.pdf

Applicant consortia shall ensure that where relevant their proposals are in compliance with the General Data Protection Regulation (EU) 2016/679³⁴ and Clinical Trial Regulation (EU) 536/2014³⁵ (and/or Directive 2001/20/EC³⁶) and any relevant legislation³⁷.

Before submitting a proposal, applicant consortia should familiarise themselves with all Call documents such as the IMI2 JU Manual for submission, evaluation and grant award³⁸, and the IMI2 JU evaluation criteria. Applicants should refer to the specific templates and evaluation procedures associated with the topic type Research and Innovation Actions (RIA).

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

³⁴ 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.

³⁵ 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.

³⁶ 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.

³⁷ 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.

³⁸ https://www.imi.europa.eu/sites/default/files/uploads/documents/apply-for-funding/call-documents/imi2/IMI2_ManualForSubmission_v1.7_November2018.pdf

Topic 1: Early diagnosis, prediction of radiographic outcomes and development of rational, personalised treatment strategies to improve long-term outcomes in psoriatic arthritis

Topic details

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

Specific challenges to be addressed by public-private collaborative research

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

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

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

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

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

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

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

Scope

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

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

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

Expected key deliverables

- Early diagnosis of PsA in PsO patients:
 - identification of predictors of disease progression, e.g. genetic, epigenetic, transcriptomic, proteomic and/or clinical biomarkers assessed through longitudinal follow-up until evidence of CASPAR;
 - identification and characterisation of biomarkers to predict, diagnose and monitor PsA in patients with PsO and to assess treatment response;
 - biomarkers of tissue damage, predicting disease progression among PsA patients;
 - ML/AI tools to identify novel biomarker signatures;
 - digital tool(s) developed for use by physicians and/or patients.
- Early prediction of bone/joint damages in PsA patients:
 - identification of poor radiographic outcomes;
 - biomarker assay(s) to identify patients that may rapidly develop bone or joint damages, indicating that these patients need strict control of PsA.
- Prediction of best treatment for patients at diagnosis:
 - biomarker assay(s) to assess response/non-response for various treatments of PsA;
 - development of a PsA specific algorithm to estimate the expected response to treatments.
- Creation of a tissue library, accessible by all involved parties, comprising skin, synovial tissue, synovial fluid and/or peripheral blood cells (including CD4+ and/or CD8+ T cells and/or other lymphocytes, monocytes) for analysis. This tissue library will have to be organised by the consortium with a perspective

of sustainability incorporated in its foundation documents. Existing libraries will also be considered and be contacted for possible sustainable collaboration;

- Development and implementation of new techniques for diagnostic use e.g. peptide immunoaffinity enrichment with targeted mass spectrometry (immuno-multiple reaction monitoring, iMRM), mass cytometry (e.g. CyTOF), (single cell) investigation of autoantibodies / DNA methylation (e.g. as marks for tissue damage), and other techniques for single cell analysis to support detailed investigation of signalling cross-talk within and between relevant cell populations;
- Novel methods for data mining and AI-driven information extraction;
- Letter of support from regulatory bodies (e.g. the European Medicines Agency, EMA and/or Food and Drug Administration FDA) on the potential for qualification/validation of the biomarker(s) and their clinical applications (context of use) in PsA.

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

Expected impact

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

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

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

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

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

- Manage research data including use of data standards;³⁹
- Disseminate, exploit, and sustain the project results. This may involve engaging with suitable biological and medical sciences research infrastructures;⁴⁰

³⁹ 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

- Communicate the project's activities to relevant target audiences.

Potential synergies with existing consortia

Synergies and complementarities should be considered with relevant national, European and non-European initiatives (including suitable biological and medical sciences research infrastructures⁴¹) in order to incorporate past achievements, available data and lessons learnt where possible, thus avoiding unnecessary overlap, and duplication of efforts and funding.

Industry consortium

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

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

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

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

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

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

⁴¹ <http://www.corbel-project.eu/about-corbel/research-infrastructure.html>

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

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

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

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

Indicative duration of the action

The indicative duration of the action is 60 months.

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

Indicative budget

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

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

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

Expertise and resources expected from applicants at stage 1

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

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

This may require mobilising, as appropriate the following expertise:

- SMEs & academia / research and technology organisations (RTOs) with past and present experience on genetic, epigenetic, transcriptomic, proteomic, biomarkers, AI/ML techniques and “big data” management techniques. Experience and capacity to manage large volumes of various data (clinical, biological, genetic, imaging) to potentially identify endotypes by using AI and ML systems;
- Patient associations and/or patient advocacy groups in PsO/PsA to ensure access to data and information;
- Regulatory agencies and/or HTA agencies and/or health authorities interested in innovative PsO/PsA assessments and new diagnostic tools to build a strategy for regulatory qualification/acceptance of project outputs;

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

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

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

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

Considerations for the outline of project work plan

In their stage 1 proposal, applicants should:

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

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

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

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

Data management

In their stage 2 proposal, applicants should give due visibility to data management including use of data standards. A full 'data management plan' (DMP) as a distinct deliverable must be delivered within the first 6 months of the project. The DMP needs to be kept up to date with the needs of the project and as such be updated as necessary during its lifetime.⁴²

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 project⁴³, and updated during the project lifetime and could include identification of:

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

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

Sufficient resources should be foreseen for activities related to dissemination and exploitation, including the plan for the sustainability of the project results. This may involve engaging with suitable biological and medical sciences research infrastructures (RIs).⁴⁴ Alternatively, if a sustainable organisation can be implemented as a follow-up to some activities generated by this topic consortium, and possibly in coordination with other related projects (e.g. BIOMAP (www.biomap-imi.eu/), this will be investigated.

Communication

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

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-infrastructure.html>

References

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- [2] Scher, JU, Ogdie A, Merola JF and Ritchlin C. Preventing psoriatic arthritis: focusing on patients with psoriasis at increased risk of transition. *Nat Rev Rheum,* 2019, 15;153-166. doi: 10.1038/s41584-019-0175-0.
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Topic 2: Innovations to accelerate vaccine development and manufacture

Topic details

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

Specific challenges to be addressed by public-private collaborative research

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

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

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

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

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

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

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

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

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

Scope

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

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

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

Subtopic 1: Systems-immunology platform for model development

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

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

Subtopic 2: CHIMs

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

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

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

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

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

- At least one in vitro model should be included for each of the following mucosae: gastro-intestinal, respiratory and urovaginal;
- Pathogens of interest are those relevant for global health, such as those with pandemic potential (influenza), or those for which vaccines are not yet available, including RSV, *C. difficile*, *Bordetella pertussis*, *Moraxella catarrhalis*, nontypeable *Haemophilus influenzae*, *Chlamydia trachomatis*, *Neisseria gonorrhoeae*, herpes simplex virus, norovirus, *Pseudomonas aeruginosa*, ExPEC (extra-intestinal pathogenic *Escherichia coli*) and cytomegalovirus.⁴⁵

Subtopic 4: Biomanufacturing platforms using mathematical modelling

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

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

This will also include:

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

Subtopics and the Call process

The Call process has two stages.

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

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

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

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

⁴⁵Pathogens 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

activities (proposed WP6), will be preferentially transferred to the Subtopic 2 leader, together with the amount of the relevant financial contribution identified for these activities under section 'Indicative budget'.

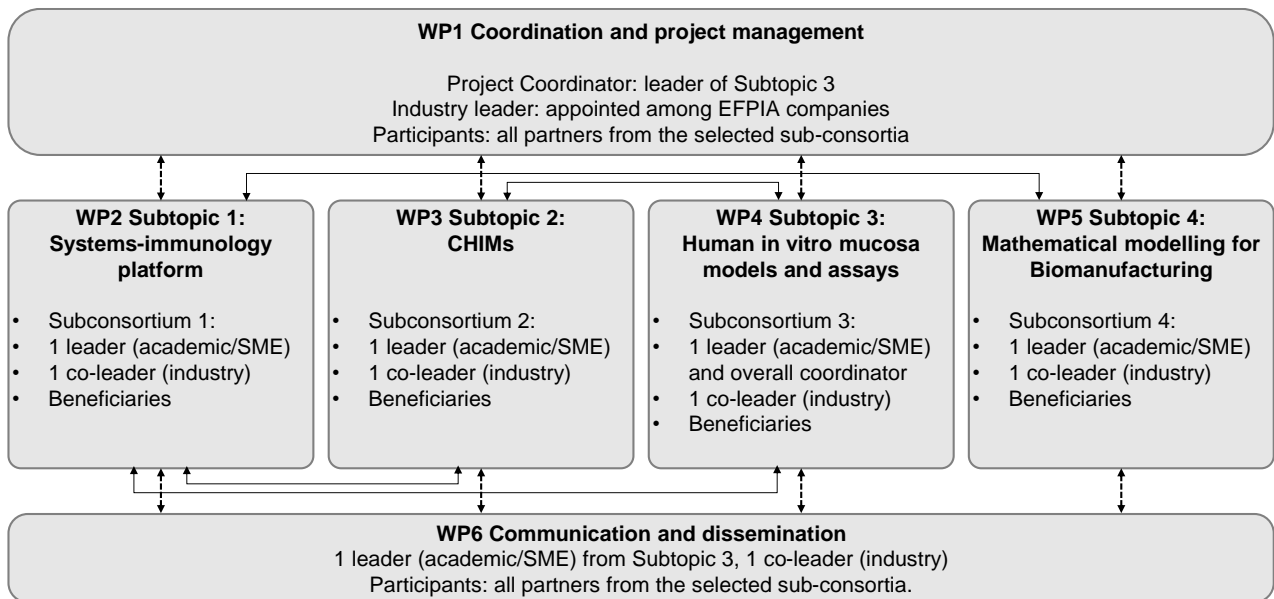


Figure 1: Consortia composition and interactions between suggested work packages (WPs), where each of the four subtopics will constitute distinct work packages.

Expected key deliverables

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

All subtopics (under the direction of the coordinator)

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

Subtopic 1

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

Subtopic 2

- New CHIMs that can accelerate the development of vaccines against, influenza, RSV and *C. difficile*;
 - Definition of clinical and laboratory (molecular, immunological and microbiological) endpoints for efficacy and/or safety, for use in larger field trials;
 - Improved or new comprehensive pre-screening methodologies that capture relevant pre-disposing factors, e.g. deep immunophenotyping and multi-layer omics;
 - Clear definitions of rescue therapy including appropriate infection control and contingency plans, and for using CHIMs in at-risk populations that could be included in the contemplated CHIMs studies;

- Identification of key parameters for CHIM standardisation, generalised adoption, and ultimately, regulatory acceptance.

Subtopic 3

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

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

Subtopic 4

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

Expected impact

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

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

All subtopics

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

Subtopic 1

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

Subtopic 2

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

Subtopic 3

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

Subtopic 4

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

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

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

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

- manage research data, including use of data standards;⁴⁶
- disseminate, exploit, and sustain the project results. This may involve engaging with suitable biological and medical sciences Research Infrastructures;⁴⁷
- communicate the project activities to relevant target audiences.

In addition, the following additional exploitation⁴⁸/dissemination⁴⁹ 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 infrastructures⁴⁷ 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:

⁴⁶ 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

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

⁴⁸ Article 28.1 (Additional exploitation obligations) of the IMI2 Grant Agreement will apply

⁴⁹ Article 29.1 (Additional dissemination obligations) of the IMI2 Grant Agreement will apply

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

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

All subtopics:

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

Subtopic 1

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

Subtopic 2

- Expertise:
 - Clinical and translational research, virology, immunology, biostatistics, bioinformatics, quantitative mathematics;
 - Good-manufacturing-practice (GMP) production of material and/or viral and bacterial strains for CHIM development;
 - Phenotypic and genetic characterisation of microbial strains.
- Contributions to clinical studies:
 - GSK intends to cover the cost of characterisation and GMP manufacturing of relevant challenge strains;
 - Sanofi Pasteur intends to contribute to the production of GMP RSV stocks;
 - Sanofi Pasteur also intends to contribute data on experimental human infection with RSV, obtained via in-house study (or studies) to be conducted within 24 months of the start of the project. These data are expected to be used to inform and refine the design of RSV CHIM studies in the project.

Subtopic 3

- Expertise:
 - Translational preclinical models and in vitro infection models, including organoids;

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

Subtopic 4

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

Indicative duration of the action

The indicative duration of the action is 66 months.

- Within each subtopic, it is expected that scientific activities should be completed within 60 months after project start;
- Activities related to communication, dissemination, exploitation and management (reporting) should continue for an additional 6-months (i.e. up to Month 66) to focus on communication of the results, including publications, and implementation of the sustainability plan.

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

Indicative budget

Overall budget

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

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

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

Subtopic 1 budget

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

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

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

Subtopic 2 budget

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

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

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

Subtopic 3 budget

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

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

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

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

Subtopic 4 budget

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

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

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

Financial contribution for open calls for proposals

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

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

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

Expertise and resources expected from applicants at stage 1

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

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

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

Subtopic 1

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

Subtopic 2

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

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

Subtopic 3

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

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

Subtopic 4

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

SMEs

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

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

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

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

In their stage-1 proposals applicants should:

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

Suggested architecture

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

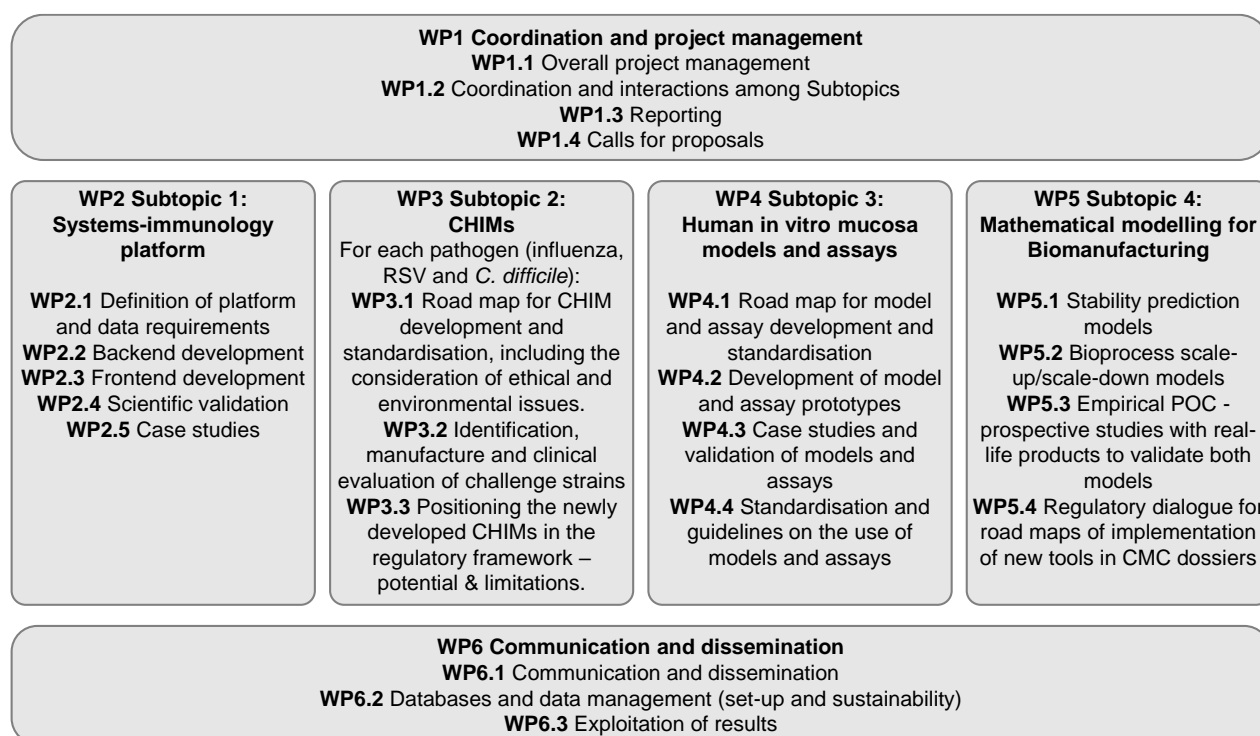


Figure 2: The project could be composed of two horizontal work packages (WPs) for project management and communication and four subtopics, each comprising several work streams.

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

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

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

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

final architecture of the full proposal will be defined by the participants in compliance with the IMI2 JU rules and with a view to the achievement of the project objectives. The allocation of a leading role within the consortium will be discussed in the course of the drafting of the full proposal to be submitted at stage 2. To facilitate the formation of the final consortium, until the roles are formally appointed through the consortium agreement, the proposed project leader from among EFPIA beneficiaries/large industrial beneficiaries shall facilitate an efficient negotiation of project content and required agreements. All beneficiaries are encouraged to discuss the project architecture and governance and the weighting of responsibilities and priorities therein.

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

Data Management

In their stage 2 proposal, applicants should give due visibility to data management including use of data standards. A full 'data management plan' (DMP) as a distinct deliverable must be delivered within the first 6 months of the project. The DMP needs to be kept up to date with the needs of the project and as such be updated as necessary during its lifetime.⁵⁰

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 project⁵¹, 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).⁵²

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.

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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

⁵¹ As an additional dissemination obligation under Article 29.1 of the IMI2 Grant Agreement will apply

⁵² <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. The challenge is compounded by a low return on investment (RoI) for the pharmaceutical sector driven largely by the lack of established reimbursement models and standard methods to express the true societal value for new technologies addressing AMR. This has subsequently led to a reduction in resources applied across the pharmaceutical industry and a decline in scientific discoveries. Overall, this situation has compromised the delivery of new options to treat and prevent resistant infections. This was highlighted in the European One Health Action Plan against Antimicrobial Resistance (for more info please visit the following link:

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

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

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

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

Overall objectives of the AMR Accelerator

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

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

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

Progression of successful assets beyond the scope of the Accelerator (pillar-dependent, see below) may occur, as appropriate, by other mechanisms. Such mechanisms might include EU funding programmes within Horizon 2020 (including SME instruments) or future framework programmes, InnovFin instruments, structural funds, venture capitals, other internal R&D funding mechanisms, etc. In addition, the applicable principles from the Davos Declaration on Antimicrobial Resistance (January 2016) or the Industry Roadmap for Progress on Combatting Antimicrobial Resistance (September 2016: <https://www.ifpma.org/wp-content/uploads/2016/09/Roadmap-for-Progress-on-AMR-FINAL.pdf>⁵³) should be taken into account.

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

AMR Accelerator programme structure

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

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

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

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

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

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

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

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

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

⁵³ For example, points 3 and 4 from the 'Roadmap for Progress'.

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

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

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

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

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

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

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

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

Consortia selected under this pillar may have a limited number of partners, and will require the participation of an EFPIA partner (e.g. 1 EFPIA partner + 1 SME/academic partner)⁵⁴. IMI2 JU Call 16, the first call under Pillar C, is divided in several topics, each dedicated to specific individual asset or research area. Additional single-stage calls, one or two per year, may be launched in the future pending budget availability. A total of at least 8-10 grant agreements are anticipated in the PBN (indicative number only).

⁵⁴ See 'Applicant consortium' section of IMI2 JU Call 16 topic text (Pillar C, "Portfolio Building Networks").

Collaboration agreements

To ensure smooth operation of the projects in the AMR Accelerator, the grant agreement of the first CBN action (COMBINE- 853967 selected under Pillar A from IMI2 JU Call 15 topic 7, and containing the coordination and support group⁵⁵) is complementary to all the grant agreements of actions selected under Pillars B and C (via IMI2 JU Call 15 topic 8, IMI2 JU Call 16 topics, IMI2 JU Call 20 topic 3 and potential future additional calls for proposals), as well as probable future grant agreements from actions selected under Pillar A. In addition, all grant agreements of actions under pillar B will be complementary between them. The respective options of Article 2, Article 31.6 and Article 41.4 of the IMI2 JU Model Grant Agreement⁵⁶ will be applied. Accordingly, the consortia selected under Pillars A, B, and C will conclude collaboration agreements with the COMBINE- 853967 consortium selected from IMI2 JU Call 15 topic 7. These collaboration agreements will provide the framework for COMBINE- 853967 to provide day-to-day support of projects in the Accelerator, and will ensure exchange of relevant information, exploration of synergies, collaboration where appropriate, and avoid duplication of efforts.

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

Need and opportunity for public-private collaborative research

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

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

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

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

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

⁵⁵ For additional details see the topic 7 "Capability Building Network" of IMI2 JU Call 15.

⁵⁶ See: https://www.imi.europa.eu/sites/default/files/uploads/documents/reference-documents/h2020-mga-imi_en_v5.pdf

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

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

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

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

Topic details

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

Specific challenges to be addressed by public-private collaborative research

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

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

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

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

Scope

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

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

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

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

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

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

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

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

Collaboration agreement(s)

The action funded under this call topic will be the second one launched under 'Pillar B TBDDN (Tuberculosis Drug Development Network),' of the AMR accelerator. Please refer to Call 15 and 16 topic texts regarding 'collaboration agreements', and 'Questions and answers'⁵⁷ associated with both calls. This topic will be complimentary to the actions funded under Pillar A and B of the AMR accelerator:

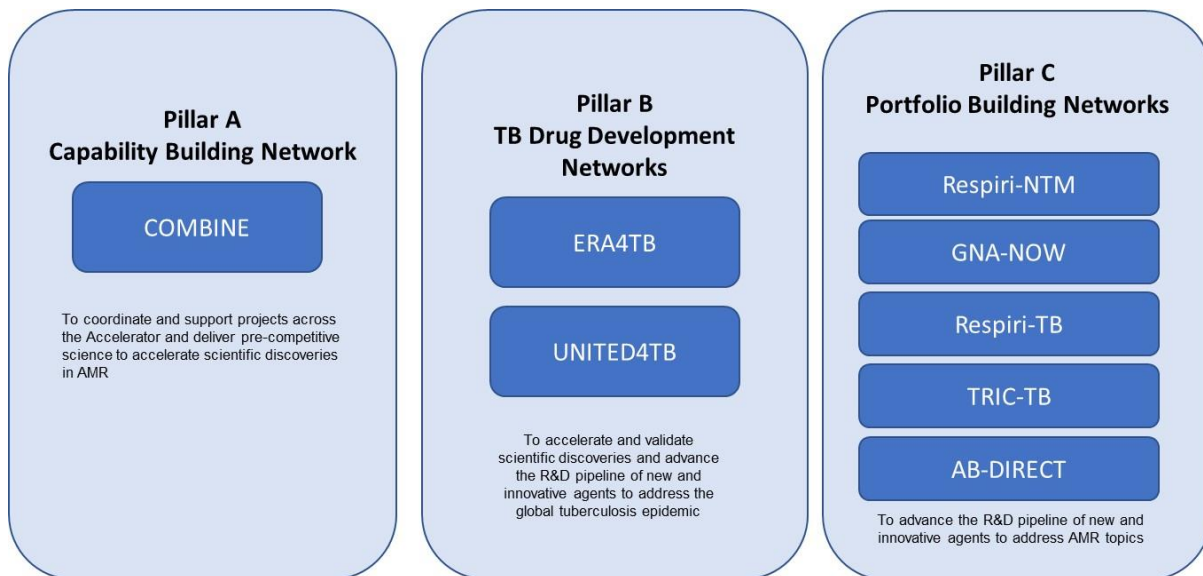


Figure 1 The structure of the AMR accelerator

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

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

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

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

⁵⁷ https://www.imi.europa.eu/sites/default/files/uploads/documents/apply-for-funding/open-calls/Questions_and_answers_on_the_AMR_accelerator_programme.pdf

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

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

Expected key deliverables

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

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

- Innovative biomarkers
 - A strategy for how published biomarkers will be prioritised and selected for evaluation and validation and subsequently implemented within ongoing trials. For the avoidance of doubt, novel biomarker development is outside the scope of this action;
 - A strategy for early scientific engagement with the EMA and FDA, prior to clinical study start, to obtain regulatory buy-in for the proposed biomarker validation framework;
 - A methodological framework to prospectively validate biomarkers to be used in adaptive trial designs to shorten drug development and expand clinical trial capacity, and ideally used as a surrogate marker of sputum culture conversion and sterilising cure;
 - Data package of prospectively validated model/panel of biomarkers to be used in clinical trials to shorten TB drug/regimen development duration, and ready for submission to the EMA and FDA for regulatory qualification.

- Pharmacogenomics
 - Pharmacogenomics strategy for exploring how host genetic variation may influence drug absorption, target exposure, clearance, and patient outcomes resulting in pharmacogenomic PKPD models for individual NCEs.

- Clinical trial simulation tool
 - Developed clinical trial simulation tool(s) incorporating AI/ML to inform trial design, facilitate in-trial adaptation and, possibly, phase 2 trial waiver.

- Digital health technologies
 - A strategy for the evaluation of the impact of these technologies on adherence, and the impact of varying treatment durations on adherence in the field
 - Technology to evaluate the impact of treatment duration on adherence. Implement and validate digital health technologies to improve adherence to TB regimens within the currently proposed studies.

- Artificial Intelligence/Machine Learning
 - A strategy for regulatory agency advice and alignment with proposed AI/ML-based models;
 - Establish models that describe the role of individual biomarkers suitable for regulatory acceptance.

- Biobank.
 - Establish a sustainable biobank to make samples with linked de-identified clinical data collected from the consortium clinical trials publicly available beyond the life of the consortium.
 - Human biological samples collected as part of the clinical studies should be banked and made available to external researchers beyond the lifetime of the consortium. Samples provided to researchers should be linked to de-identified demographic and clinical study data in a manner compliant with GDPR;
 - The applicant consortia should provide a strategy for human biological sample tracking, access and management that is compliant with relevant European legislation;
 - A strategy for granting access to samples should also be presented (e.g., an independent panel for evaluation of proposed research plans).

Expected impact

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

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

In addition, the following additional exploitation⁵⁸/dissemination⁵⁹ obligations must be considered to maximise impact: the applicant consortium is expected to have a strategy on the translation of the relevant project outputs into regulatory, clinical and healthcare practice. These strategies aim to ensure fast access and uptake in high TB burden countries to secure maximum impact on the TB epidemic.

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

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

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

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

- manage research data including use of data standards and a fully developed strategy for FAIR storage and access to data and models beyond the lifetime of the consortium;⁶⁰
- disseminate, exploit, and sustain the project results. This may involve engaging with suitable biological and medical sciences research infrastructures;⁶¹
- communicate the project activities to relevant target audiences.

⁵⁸ Article 28.1 (Additional exploitation obligations) of the IMI2 Grant Agreement will apply

⁵⁹ Article 29.1 (Additional dissemination obligations) of the IMI2 Grant Agreement will apply

⁶⁰ Guidance on data management is available at http://ec.europa.eu/research/participants/docs/h2020-funding-guide/cross-cutting-issues/open-access-data-management/data-management_en.htm

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

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 infrastructures⁶²) in order to incorporate past achievements, available data and lessons learnt where possible, thus avoiding unnecessary overlap, and duplication of efforts and funding. Applicants should specifically consider synergies with partnerships that have existing TB clinical trial networks, TB drug discovery consortia, or with relevant not-for-profit organisations in the field.

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

Industry consortium

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

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

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

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

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

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

⁶² <http://www.corbel-project.eu/about-corbel/research-infrastructures.html>

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

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

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

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

Indicative duration of the action

The indicative duration of the action is 84 months.

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

Indicative budget

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

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

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

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

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

Expertise and resources expected from applicants at stage 1

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

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

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

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

This may require mobilising, as appropriate the following expertise:

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

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

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

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

Considerations for the outline of project work plan

In their stage 1 proposals applicants should

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

Suggested architecture

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

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

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

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

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

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

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

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

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

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

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

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

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

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

Dissemination, exploitation and sustainability of results

In their stage 2 proposal, applicants must provide a draft plan for dissemination and exploitation, including sustainability of results. A full plan as a distinct deliverable must be delivered within the first 6 months of the project.⁶³, 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.

⁶³ As an additional dissemination obligation under Article 29.1 of the IMI2 Grant Agreement will apply

Sufficient resources should be foreseen for activities related to dissemination and exploitation, including the plan for the sustainability of the project results. This may involve engaging with suitable biological and medical sciences Research Infrastructures (RIs).⁶⁴

Communication

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

References

- [1] World Health Organization. *Global Tuberculosis Report 2018*. Geneva; World Health Organization (2018). <http://apps.who.int/iris>
- [2] A. H. Diacon, R. Dawson, et al. Randomized dose-ranging study of the 14-day early bactericidal activity of bedaquiline (TMC207) in patients with sputum. *Antimicrobial Agents and Chemotherapy* Volume 57, Issue 5, Pages 2199–2203 (2013). <https://doi.org/10.1128/AAC.02243-12>
- [3] S. H. Gillespie, A. M. Crook, et al. Four-month moxifloxacin-based regimens for drug-sensitive tuberculosis. *New England Journal of Medicine* Volume 371, Issue 17, Pages 1577–1587 (2014). <https://doi.org/10.1056/NEJMoa1407426>
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- [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

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

Topic 4: Tumour plasticity

Topic details

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

Specific challenges to be addressed by public-private collaborative research

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

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

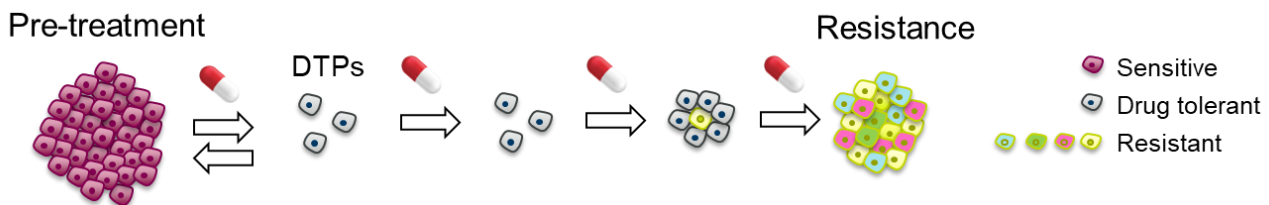


Figure 1. Diagram showing how drug tolerant persister cells (DTPs) arise from the bulk tumour following successful treatment, and ultimately contribute to the emergence of drug resistance.

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

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

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

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

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

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

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

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

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

Scope

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

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

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

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

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

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

The goals of the Call topic are:

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

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

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

Expected key deliverables

The expected key deliverables should include the following:

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

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

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

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

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

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

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

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

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

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

Expected impact

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

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

Impact for patients:

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

Impact for academia and SMEs:

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

Impact for industry:

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

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

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

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

- manage research data including use of data standards⁶⁵;
- disseminate, exploit, and sustain the project results; this may involve engaging with suitable biological and medical sciences research infrastructures⁶⁶;
- communicate the project activities to relevant target audiences.

In addition, the following additional exploitation⁶⁷/dissemination⁶⁸ obligations must be considered to maximise impact:

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

Potential synergies with existing consortia

Synergies and complementarities should be considered with relevant national, European and non-European initiatives (including suitable biological and medical sciences research infrastructures⁶⁹) in order to incorporate past achievements, available data and lessons learnt where possible, thus avoiding unnecessary overlap, and duplication of efforts and funding.

Key synergies with existing consortia that could be considered are:

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

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

⁶⁷ Article 28.1 (Additional exploitation obligations) of the IMI2 Grant Agreement will apply

⁶⁸ Article 29.1 (Additional dissemination obligations) of the IMI2 Grant Agreement will apply

⁶⁹ <http://www.corbel-project.eu/about-corbel/research-infrastructure.html>

Industry consortium

The industry consortium is composed of the following EFPIA partners:

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

The industry consortium anticipates contributing the following expertise and assets:

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

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

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

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

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

Indicative duration of the action

The indicative duration of the action is 60 months.

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

Indicative budget

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

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

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

Expertise and resources expected from applicants at stage 1

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

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

This may require mobilising, as appropriate the following expertise:

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

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

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

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

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

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

Considerations for the outline of project work plan

In their stage 1 proposals applicants should:

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

Suggested architecture

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

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

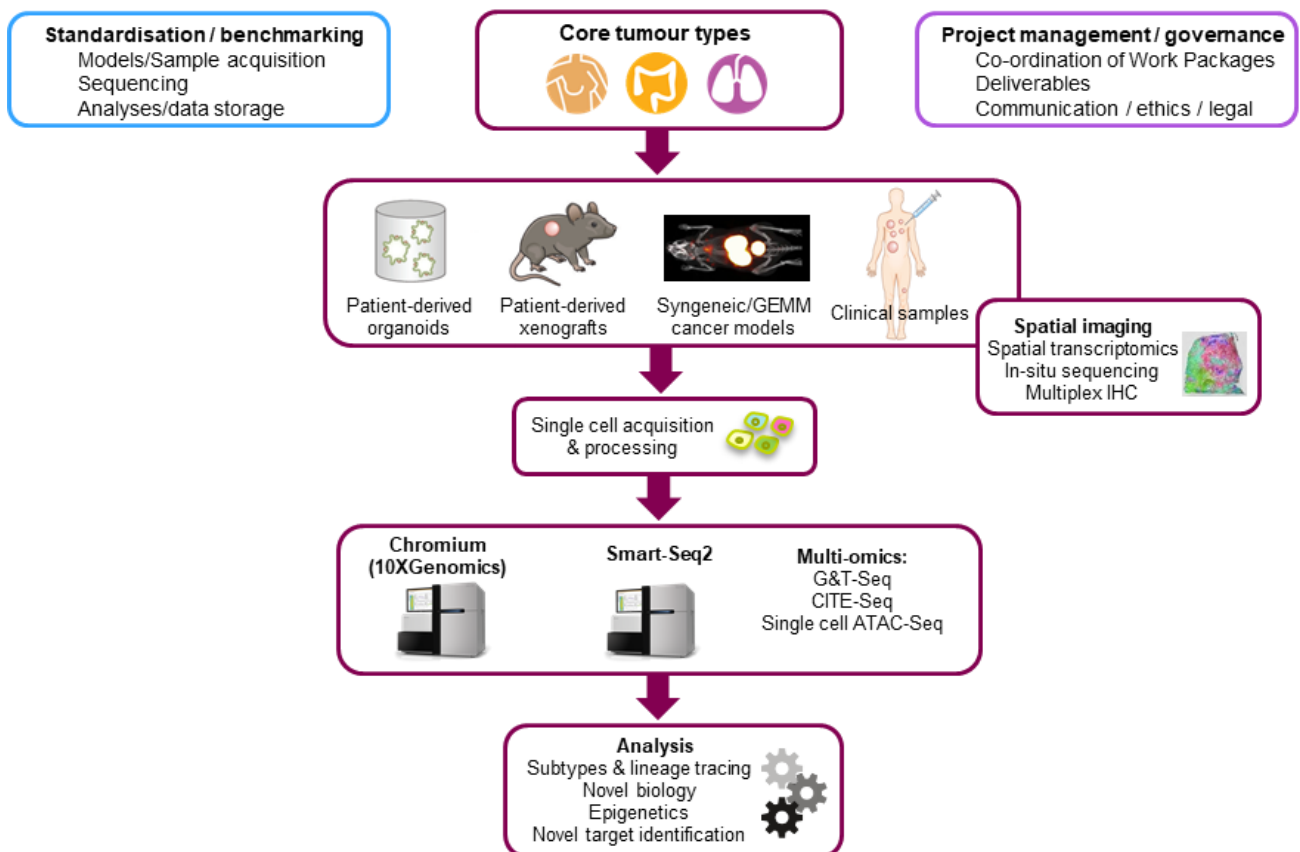


Figure 2. Work flow of the project. The various activities captured here form the basis for the 7 Work Packages detailed below.

Work Package 1 – Project management, coordination and long-term sustainability

Description: The goals of this work package are to support optimal project management in compliance with scientific and ethical standards, implement the strategy of the consortium, and ensure the appropriate dissemination of the project progress and outcomes.

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

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

Work Package 2 – Portfolio management, coordination and prioritisation

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

- **Proposed objectives:**

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

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

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

Work Package 3 – Standardisation and benchmarking of standard operating procedures

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

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

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

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

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

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

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

Work package 5 – Single-cell sequencing

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

- **Proposed objectives should include:**

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

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

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

Work package 6 – Spatial imaging technologies

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

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

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

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

Description:

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

- **Proposed objectives:**

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

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

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

Work package 8 – Communication/dissemination and ethics

Description:

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

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

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

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

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

Data management

In their stage 2 proposal, applicants should give due visibility to data management including use of data standards. A full 'data management plan' (DMP) as a distinct deliverable must be delivered within the first 6 months of the project. The DMP needs to be kept up to date with the needs of the project and as such be updated as necessary during its lifetime.⁷⁰

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 project⁷¹, 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).⁷²

⁷⁰ 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

⁷¹ As an additional dissemination obligation under Article 29.1 of the IMI2 Grant Agreement will apply

⁷² <http://www.corbel-project.eu/about-corbel/research-infrastructure.html>

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.

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

Topic details

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

Specific challenges to be addressed by public-private collaborative research

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

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

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

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

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

Scope

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

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

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

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

Expected key deliverables

To achieve the objectives, the proposed project should deliver:

- A **study protocol** for a non-blinded multi-centre randomised phase III study on a statistically significant number of oesophageal cancer patients. Patients should be treated with pre-operative concomitant chemo-radiation and randomised between irradiation to be delivered as either RT or PT. This protocol should include a rapid, clinically relevant primary endpoint to allow effectiveness to be demonstrated as early as possible.
- **Annual updates** on the progress of the study to include:
 - recruitment reports;
 - data collection reports;
- A final **dataset** collected in compliance with the FAIR principles;⁷³
- A proposal for a European methodology for multi-centric clinical trials in proton therapy;
- Publications & conference presentations on the results of the study;
- Publication and active dissemination of a **summary of results** to relevant authorities (e.g. healthcare providers, HTA bodies, payers).

⁷³ Findable, Accessible, Interoperable, Reusable, see: <https://www.force11.org/group/fairgroup/fairprinciples>

Expected impact

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

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

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

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

- Manage research data including use of data standards.⁷⁴
- Disseminate, exploit, and sustain the project results. This may involve engaging with suitable biological and medical sciences research infrastructures.⁷⁵
- 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 infrastructures⁷⁶) in order to incorporate past achievements, available data and lessons learnt where possible, thus avoiding unnecessary overlap, and duplication of efforts and funding.

Industry consortium

The industry consortium includes the following IMI2 JU Associated Partners:

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

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

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

⁷⁴ 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

⁷⁵ <http://www.corbel-project.eu/about-corbel/research-infrastructure.html>

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

Indicative duration of the action

The indicative duration of the action is 60 months.

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

Indicative budget

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

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

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

Expertise and resources expected from applicants at stage 1

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

This may require mobilising, as appropriate the following expertise:

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

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

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

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

Considerations for the outline of project work plan

In their stage 1 proposals applicants should:

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

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

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

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

Data management

In their stage 2 proposal, applicants should give due visibility to data management including use of data standards. A full 'data management plan' (DMP) as a distinct deliverable must be delivered within the first 6 months of the project. The DMP needs to be kept up to date with the needs of the project and as such be updated as necessary during its lifetime.⁷⁷

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.⁷⁸, 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.

⁷⁷ 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

⁷⁸ As an additional dissemination obligation under Article 29.1 of the IMI2 Grant Agreement will apply

Sufficient resources should be foreseen for activities related to dissemination and exploitation, including the plan for the sustainability of the project results. This may involve engaging with suitable medical sciences research infrastructures (RIs).⁷⁹

Communication

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

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⁷⁹ <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 JU Strategic Research Agenda - Axis of Research	Patient-tailored adherence programmes.
IMI2 JU Strategic Research Agenda - Health Priority	Other

Specific challenges to be addressed by public-private collaborative research

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

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

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

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

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

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

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

Scope

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

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

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

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

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

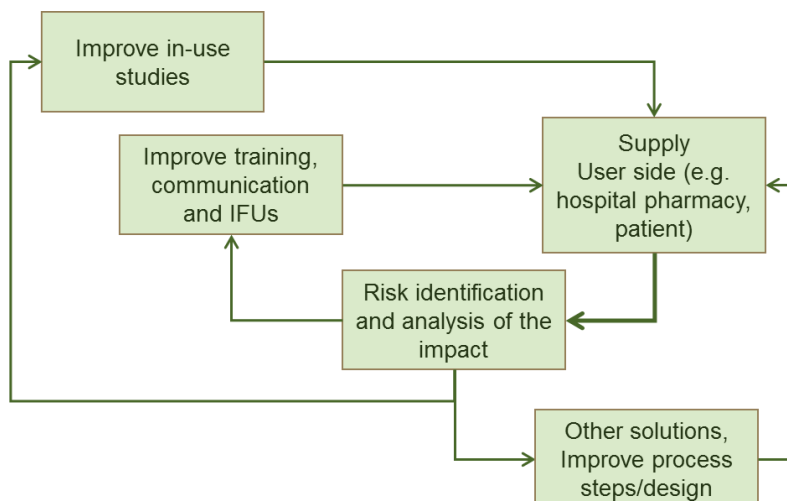


Figure 1: Good understanding of drug product handling at the user side can lead to the formulation of various solutions

Expected key deliverables

The expected deliverables from the action are the following:

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

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

Improved protein drug product development processes

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

Improved training on drug product handling

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

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

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

Expected impact

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

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

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

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

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

- manage research data, including use of data standards⁸⁰;
- Disseminate, exploit, and sustain the project results. This may involve engaging with suitable biological and medical sciences research Infrastructures⁸¹;
- 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 infrastructures⁸²) in order to incorporate

⁸⁰ 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

⁸¹ <http://www.corbel-project.eu/about-corbel/research-infrastructures.html>

⁸² <http://www.corbel-project.eu/about-corbel/research-infrastructures.html>

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

Industry consortium

The industry consortium is composed of the following EFPIA partners:

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

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

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

as well as interaction with public health stakeholders and authorities.

Indicative duration of the action

The indicative duration of the action is 48 months.

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

Indicative budget

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

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

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

Expertise and resources expected from applicants at stage 1

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

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

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

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

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

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

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

Considerations for the outline of project work plan

In their stage 1 proposals, applicants should:

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

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

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

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

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

Data Management

In their stage 2 proposal, applicants should give due visibility to data management, including the use of data standards. A full 'data management plan' (DMP) as a distinct deliverable must be delivered within the first 6 months of the project. The DMP needs to be kept up to date with the needs of the project and as such be updated as necessary during its lifetime.⁸³

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 project⁸⁴ 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).⁸⁵

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.

⁸³ 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

⁸⁴ As an additional dissemination obligation under Article 29.1 of the IMI2 Grant Agreement will apply

⁸⁵ <http://www.corbel-project.eu/about-corbel/research-infrastructures.html>

References

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

Conditions for this Call for proposals

All proposals must conform to the conditions set out in the H2020 Rules for Participation (https://ec.europa.eu/research/participants/portal/doc/call/h2020/common/1595113-h2020-rules-participation_oj_en.pdf) and the Commission Delegated Regulation with regard to IMI2 JU <http://eur-lex.europa.eu/legal-content/EN/TXT/PDF/?uri=CELEX:32014R0622&from=EN>.

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

Applicants intending to submit a Short proposal in response to the IMI2 Call 20 should read this topics text, the [IMI2 JU Manual for submission, evaluation and grant award](#) and other relevant documents (e.g. [IMI2 JU Model Grant Agreement](#)).

Call Identifier	H2020-JTI-IMI2-2020-20-two-stage
Type of actions	Research and Innovation Action (RIA)
Publication Date	21 January 2020
Stage 1 Submission start date	21 January 2020
Stage 1 Submission deadline⁸⁶	12 May 2020 (17:00:00 Brussels time)
Stage 2 Submission deadline⁸⁷	19 November 2020 (17:00:00 Brussels time)
Indicative Budget	
From EFPIA companies and IMI2 JU Associated Partners	EUR 140 209 500
From the IMI2 JU ⁸⁸	EUR 133 009 000

Call Topics

IMI2-2020-20-01 Early diagnosis, prediction of radiographic outcomes and development of rational, personalised treatment strategies to improve long-term outcomes in psoriatic arthritis	The indicative contribution from EFPIA companies is EUR 13 880 000 The financial contribution from IMI2 JU is a maximum of EUR 10 211 000	Research and Innovation Action (RIA) Two-stage submission and evaluation process. Only the applicant consortium whose proposal is ranked first at the first stage is invited for the second stage.
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⁸⁶ The IMI2 JU Executive Director may delay submission deadline by up to two months. The relevant submission deadline for each Call will be indicated in Submission Service section of the relevant topic page available under Funding & tender opportunities - Single Electronic Data Interchange Area (SEDIA).

⁸⁷ The IMI2 JU Executive Director may delay submission deadline by up to two months. The relevant submission deadline for each Call will be indicated in Submission Service section of the relevant topic page available under Funding & tender opportunities - Single Electronic Data Interchange Area (SEDIA).

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

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

Annex II - IMI2 JU Call 21 topic text

Introduction

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

The Innovative Medicines Initiative 2 Joint Undertaking (IMI2 JU) has been created⁸⁹ 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 World⁹⁰.

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 companies⁹¹, 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)⁹² is the main reference for the implementation of research priorities for IMI2 JU. The scientific priorities for 2020 for IMI2 JU have been prepared based on the SRA.

Applicant consortia are invited to submit a proposal which should address at least one of the objectives of the topic. The size and composition of each consortium should be adapted so as to respond to the scientific goals and the expected key deliverables.

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

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

⁸⁹ 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.

⁹⁰ http://www.who.int/medicines/areas/priority_medicines/en/

⁹¹ 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.

⁹² http://www.imi.europa.eu/sites/default/files/uploads/documents/About-IMI/research-agenda/IMI2_SRA_March2014.pdf

Applicant consortia shall ensure that where relevant their proposals are in compliance with the General Data Protection Regulation (EU) 2016/679⁹³ and Clinical Trial Regulation (EU) 536/2014⁹⁴ (and/or Directive 2001/20/EC⁹⁵) and any relevant legislation⁹⁶.

Before submitting a proposal, applicant consortia should familiarise themselves with all Call documents such as the IMI2 JU Manual for submission, evaluation and grant award⁹⁷, 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).

⁹³ 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.

⁹⁴ 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.

⁹⁵ [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.

⁹⁶ 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.

⁹⁷ https://www.imi.europa.eu/sites/default/files/uploads/documents/apply-for-funding/call-documents/imi2/IMI2_ManualForSubmission_v1.7_November2018.pdf

Development of therapeutics and diagnostics combatting coronavirus infections

Topic details

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

Specific challenges to be addressed by public-private collaborative research

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

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

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

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

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

Scope

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

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

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

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

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

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

Collaboration agreement(s)

To ensure the interactions between actions funded under this Call, the selected consortia are expected to cooperate with each other and share their learnings for the purpose of achieving the objectives of their respective actions, in order to maximise the impact. Therefore, all grants awarded under this Call will be complementary grants. The respective options under Article 2, Article 31.6 and Article 41.4 of the IMI2 JU Model Grant Agreement⁹⁸ will apply. Accordingly, the relevant consortia will conclude collaboration agreement(s) to ensure the exchange of relevant information, exploration of synergies, and collaboration where appropriate.

⁹⁸ See: https://www.imi.europa.eu/sites/default/files/uploads/documents/reference-documents/h2020-mga-imi_en_v5.pdf

Expected key deliverables

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

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

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

When relevant, deliverables should include:

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

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

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

Expected impact

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

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

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

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

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

In addition, considering the unknown evolution of this COVID-19 outbreak, applicants should develop strategies on how to develop their proposals and continuity plans, allocate their funds and implement

sustainability measures in the different scenarios that could occur: 1) rapid regression of the epidemic with no patients left for clinical trials, 2) pandemic, 3) seasonal reoccurrence as typically seen with influenza.

Applicants must maximise the IMI2 JU public-private partnership value by harnessing support from different stakeholders, including the mobilisation of resources through the inclusion of contributing partners⁹⁹, providing contributions (in kind and/or financial), to reflect the public-private character of IMI2 JU actions.

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

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

Potential synergies with existing consortia

Synergies and complementarities are expected with relevant national, European and non-European initiatives (including suitable biological and medical sciences research infrastructures¹⁰⁰) in order to incorporate past achievements, available data and lessons learnt where possible, thus avoiding unnecessary overlap, and duplication of efforts and funding. In particular, applicants are expected to collaborate with any relevant project or initiative targeting the current COVID-19 outbreak supported by, including but not restricting to, the European Commission (H2020 call SC1-PHE-CORONAVIRUS-2020), CEPI, Wellcome, BARDA, The Bill and Melinda Gates Foundation, GloPID-R, and others.

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

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

Indicative duration of the action

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

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

Indicative budget

Applicant consortia will be competing for the maximum total financial contribution from IMI2 JU up to EUR 72 000 000¹⁰¹.

⁹⁹ Contributing partners: EFPIA companies or organisations associated to EFPIA, and Associated Partners to IMI2 JU contributing resources to the action may report it as their in-kind or financial contribution to the IMI2 JU. If the contributing entity is not yet an affiliate or a constituent entity of an IMI2 Member other than the Union (i.e. EFPIA), or an Associated Partner at the time of the proposal submission, and the proposal is selected for funding, such a legal entity is invited to become an affiliate or a constituent entity of an IMI2 Member, other than the Union, or an Associated Partner in accordance with the IMI2 JU Statutes prior to the signature of the relevant Grant Agreement.

¹⁰⁰ <http://www.corbel-project.eu/about-corbel/research-infrastructures.html>

¹⁰¹ As modified by the IMI2 JU Governing Board decision (IMI2-GB-DEC-2020-13) adopting the second amended Annual Work Plan and Budget for 2020.

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

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

Applicant consortium

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

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

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

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

Single stage proposal

While preparing their proposal, applicants are requested to pay due attention to all the following points.

Data management

In their proposal, applicants should give due visibility to data management including use of the data standards. A full 'data management plan' (DMP) as a distinct deliverable must be delivered within the first 6 months of the action. The DMP needs to be kept up to date with the needs of the action and as such be updated as necessary during its lifetime.¹⁰²

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

Dissemination, exploitation and communication

In their proposal, applicants must provide a draft plan for the exploitation and dissemination of results. A full plan as a distinct deliverable must be delivered within the first 6 months of the project.¹⁰³ The proposed communication measures for promoting the action and its findings during the period of the grant should also be described and could include a possible public event to showcase the results of the action.

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

Sustainability

In their proposal, applicants must describe a sustainability plan beyond the end of the Grant Agreement

¹⁰² Guidance on data management is available at https://ec.europa.eu/research/participants/docs/h2020-funding-guide/cross-cutting-issues/open-access-data-management/data-management_en.htm

¹⁰³ As an additional dissemination obligation under Article 29.1 of the IMI2 JU Grant Agreement will apply

This plan may be updated during the action lifetime and could include:

- identification of results that may need sustainability solutions;
- identification of potential end-users for these results;
- a proposed sustainability roadmap.

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

Sufficient resources should be set aside for activities related to the sustainability of the project results. This may involve engaging with suitable biological and medical sciences research infrastructures (RIs).¹⁰⁴

Patient and healthcare provider engagement

Applicants are encouraged to include a strategy to engage with patients, learned societies and healthcare providers as relevant to ensure the project results impact on healthcare practices.

Regulatory strategy

Applicants are expected to have a strategy for the translation of the relevant outputs into regulatory practice to promote the uptake of the results, e.g. qualification advice, qualification opinion when relevant. A plan for interactions with regulatory agencies/health technology assessment bodies /payers, with relevant milestones and sufficient resources, should therefore be proposed.

References

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

¹⁰⁴ <http://www.corbel-project.eu/about-corbel/research-infrastructures.html>

Conditions for this Call for proposal

All proposals must conform to the conditions set out in the H2020 Rules for Participation (https://ec.europa.eu/research/participants/portal/doc/call/h2020/common/1595113-h2020-rules-participation_oj_en.pdf) and the Commission Delegated Regulation with regard to IMI2 JU <http://eur-lex.europa.eu/legal-content/EN/TXT/PDF/?uri=CELEX:32014R0622&from=EN>.

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

Applicants intending to submit a proposal in response to the IMI2 Call 21 should read this topics text, the [IMI2 JU Manual for submission, evaluation and grant award](#) and other relevant documents (e.g. [IMI2 JU Model Grant Agreement](#)).

Call Identifier	H2020-JTI-IMI2-2020-21-single-stage
Type of actions	Research and Innovation Action (RIA)
Publication Date	3 March 2020
Submission start date	3 March 2020
Submission deadline	31 March 2020
Indicative Budget	
From EFPIA companies and IMI2 JU Associated Partners	to be defined based upon selected proposals
From the IMI2 JU ¹⁰⁵	EUR 72 000 000 ¹⁰⁶

Call Topics

IMI2-2020-21-1 Development of therapeutics and diagnostics combatting coronaviruses infections	The indicative contribution from EFPIA companies is to be defined based upon selected proposals. The financial contribution from IMI2 JU is a maximum of EUR 72 000 000	Research and Innovation Action (RIA) Single stage submission and evaluation process. Proposals submitted will be evaluated and ranked in one single list. Several proposals might be invited to conclude a Grant Agreement, depending on the budget availability and their ranking.
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¹⁰⁵ In case the budget of this given line cannot be consumed (totally or partially) the corresponding budget will be allocated to the topics under the other budget lines.

¹⁰⁶ As modified by the IMI2 JU Governing Board decision (IMI2-GB-DEC-2020-13) adopting the second amended Annual Work Plan and Budget for 2020.

Annex III - IMI2 JU Call 22 topic text

Introduction

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

The Innovative Medicines Initiative 2 Joint Undertaking (IMI2 JU) has been created¹⁰⁷ 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 World¹⁰⁸.

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 companies¹⁰⁹, 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)¹¹⁰ is the main reference for the implementation of research priorities for IMI2 JU. The scientific priorities for 2020 for IMI2 JU have been prepared based on the SRA.

Applicant consortia fulfilling the specific eligibility criteria (see Conditions for this Call) are invited to submit a research and innovation action proposal to the topic of this Call and address all its aspects. The size and composition of each consortium should be adapted so to respond to the scientific goals and the expected key deliverables.

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

While preparing their proposals, applicant consortia should ensure that the needs of patients are adequately addressed. Involvement of patients, where appropriate, 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.

¹⁰⁷ 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.

¹⁰⁸ http://www.who.int/medicines/areas/priority_medicines/en/

¹⁰⁹ 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.

¹¹⁰ http://www.imi.europa.eu/sites/default/files/uploads/documents/About-IMI/research-agenda/IMI2_SRA_March2014.pdf

Applicant consortia shall ensure that where relevant their proposals are in compliance with the General Data Protection Regulation (EU) 2016/679¹¹¹ and Clinical Trial Regulation (EU) 536/2014¹¹² (and/or Directive 2001/20/EC¹¹³) and any relevant legislation¹¹⁴.

Before submitting a proposal, applicant consortia should familiarise themselves with all Call documents such as the IMI2 JU Manual for submission, evaluation and grant award¹¹⁵, 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).

¹¹¹ 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.

¹¹² 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.

¹¹³ 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.

¹¹⁴ 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.

¹¹⁵ https://www.imi.europa.eu/sites/default/files/uploads/documents/apply-for-funding/calldocuments/imi2/IMI2_ManualForSubmission_v1.7_November2018.pdf

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

Topic details

Topic code	IMI2-2020-22-01
Action type	Research and Innovation Action (RIA)
Submission and evaluation process	single stage
IMI2 Strategic Research Agenda - Axis of Research	Not applicable
IMI2 Strategic Research Agenda - Health Priority	Not applicable

Specific challenges to be addressed by public-private collaborative research

Major challenges in life sciences, in particular within the medicines development process, are the scale of the investment required, the stepwise approach, very long development timelines and the successful involvement of relevant stakeholders. A platform to facilitate close collaboration is necessary to bring together the critical mass of expertise, knowledge and resources to address these challenges.

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

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

Scope, key deliverables and applicant consortium

The scope of the restricted Call will be to support further research activities in those exceptional cases where it is necessary to enable successful consortia to build on the achievements of their initial action and move onto the next step of the challenge.

Proposals will be evaluated by experts on the basis of the award criteria 'excellence', 'impact' and 'quality and efficiency of the implementation', in line with Article 15 of the Horizon 2020 Rules for Participation (Regulation No 1290/2013). Within these criteria, the experts will focus on the points listed below and the proposals should therefore address them in detail:

- The scientific relevance for successfully addressing the IMI2 JU objectives;
- How the proposed activities relate to an area with a high-unmet need from the public health perspective and having industrial challenges (where relevant). This should also include a landscaping exercise to demonstrate that no similar initiative of the same extent is already ongoing at national, European or global level;
- The need for the proposed activities to (in a timely fashion) seamlessly build on and add value to the already remarkable results achieved in the initial action, as demonstrated and documented by the applicant consortium;
- The scope of proposed activities must fall beyond the scope of the initial action (e.g. initial objectives and its financial and temporal framework). In the event that the new action and the initial one will be running in parallel, measures should be proposed to ensure the achievement of the respective

objectives and to ensure that there is no double funding between the initial action and the new action;

- The specific circumstances justifying that only the initial consortium can carry out the follow-up activities successfully. For instance, the initial consortium represents a unique and effective partnership with the expertise, equipment, methodologies, or access to unique resources and IP rights, that are not available from another consortium; if, to cover the expertise for the newly proposed activities, some modifications of the initial partnership is needed, this would have to be justified;
- How the proposed activities build on and benefit from the strong foundations as public-private partnership established in the initial action, e.g. governance, workflows, procedures.

The applicants will also need to justify why the proposed research activities can only be carried out in public private collaboration, including substantial contributions in the project activities of i.e. EFPIA constituents and affiliated entities and, where relevant, by IMI2 JU Associated Partners¹¹⁶.

Applicants should define key specific deliverables that address the challenges identified by their proposal and enable the achievement of its objectives. They should also define deliverables that would be sustained beyond the duration of the funded action, and how this would be achieved along with any key results that would be expected to be made openly accessible.

Additional condition for participation¹¹⁷

This Call is:

- Restricted to the initial consortia of actions funded under topics published in the IMI2 JU Annual Work Plans of 2014, 2015 and 2016 since only these actions are sufficiently advanced in their implementation to be considered for follow-up activities, and;
- Limited to those actions derived from topics where the corresponding work plan already informed potential applicants about the possibility of a later restricted Call (see list of eligible actions under the Call conditions).

If the action selected under this Call starts before the end date of the initial Grant Agreement, the applicants must demonstrate in their proposal how proper collaboration between the two actions will be ensured.

Expected impact

Applicants should describe the significant impacts of their proposed activities, taking into consideration the points below. Applicants should include baseline, targets and, where relevant, metrics for measuring them:

- Improve the current drug development process by providing support for the development of tools, standards and approaches to assess efficacy, safety and quality of regulated health product;
- Benefit public health and improve the health and well-being of European citizens;
- Contribute to the EU's industrial leadership, including in relation to small and medium-sized enterprises (SMEs);
- Have an impact on regulatory and/or health technology assessment, and healthcare practices, where relevant;
- Further maximise the value of the IMI2 JU public-private partnership by harnessing support from different stakeholders, including the substantial mobilisation of funds through contributing partners

¹¹⁶ Contributing partners: EFPIA companies or organisations associated to EFPIA, and Associated Partners to IMI2 JU contributing resources to the action may report it as their in-kind or financial contribution to the IMI2 JU. If the contributing entity is not yet an affiliate or a constituent entity of an IMI2 Member other than the Union (i.e. EFPIA), or an Associated Partner at the time of the proposal submission, and the proposal is selected for funding, such a legal entity is invited to become an affiliate or a constituent entity of an IMI2 Member, other than the Union, or an Associated Partner in accordance with the IMI2 JU Statutes prior to the signature of the relevant Grant Agreement.

¹¹⁷ Article 9(5) of Regulation (EU) No 1290/2013 of the European Parliament and of the Council laying down the rules for participation and dissemination in "Horizon 2020 - the Framework Programme for Research and Innovation (2014-2020)" and repealing Regulation (EC) No 1906/2006.

(i.e. EFPIA constituents and affiliated entities and, where relevant, by IMI2 JU Associated Partners)¹¹⁸, not necessarily involved in the initial project. Reflecting the public-private character of IMI2 JU actions, applicants should demonstrate that the mobilised contributions are in addition to those already committed by any contributing partners in the initial project(s).

Indicative duration of the action

The indicative duration of the action is 24 months.

However, the consortium may propose a different duration if properly justified.

Indicative budget

Applicant consortia will be competing for a maximum total financial contribution from IMI2 JU of EUR 11,427,098.

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

Proposals above the threshold will be invited in order of ranking to prepare a Grant Agreement within the limits of the available overall budget.

Single stage proposal

While preparing their proposal, applicants are requested to pay due attention to all the following points:

Data management

In their proposal, applicants should give due visibility to data management including use of the data standards. A full 'data management plan' (DMP) as a distinct deliverable must be delivered within the first 6 months of the action. The DMP needs to be kept up to date with the needs of the action and as such be updated as necessary during its lifetime¹¹⁹.

Dissemination, exploitation and communication

In their proposal, applicants must provide a draft plan for the exploitation and dissemination of results. A full plan as a distinct deliverable must be delivered within the first 6 months of the project¹²⁰. The proposed communication measures for promoting the action and its findings during the period of the grant should also be described and could include a possible public event to showcase the results of the action.

Sustainability

In their proposal, applicants must describe a sustainability plan beyond the end of the Grant Agreement. This plan may be updated during the action lifetime and could include:

- Identification of results that may need sustainability solutions;
- Identification of potential end-users for these results;

¹¹⁸ Contributing partners: EFPIA companies or organisations associated to EFPIA, and Associated Partners to IMI2 JU contributing resources to the action may report it as their in-kind or financial contribution to the IMI2 JU. If the contributing entity is not yet an affiliate or a constituent entity of an IMI2 Member other than the Union (i.e. EFPIA), or an Associated Partner at the time of the proposal submission, and the proposal is selected for funding, such a legal entity is invited to become an affiliate or a constituent entity of an IMI2 Member, other than the Union, or an Associated Partner in accordance with the IMI2 JU Statutes prior to the signature of the relevant Grant Agreement.

¹¹⁹ Guidance on data management is available at http://ec.europa.eu/research/participants/docs/h2020-funding-guide/cross-cutting-issues/openaccess-data-management/data-management_en.htm

¹²⁰ As an additional dissemination obligation under Article 29.1 of the IMI2 JU Grant Agreement will apply.

- A proposed sustainability roadmap.

Sufficient resources should be set aside for activities related to the sustainability of the project results. This may involve engaging with suitable biological and medical sciences research infrastructures (RIs).¹²¹

Patient and healthcare provider engagement

Applicants are encouraged to include a strategy to engage with patients, learned societies and healthcare providers as relevant to ensure the project results impact on healthcare practices.

Synergies

Applicants should briefly present an environment scan of relevant existing initiatives to ensure synergies and complementarities, and avoid unnecessary overlap and duplication of efforts and include a plan on how they propose to synergise with these initiatives.

Regulatory strategy

Applicants are expected to have a strategy for the translation of the relevant outputs into the regulatory practice to promote the uptake of the results e.g. qualification advice, qualification opinion when relevant. A plan for interactions with regulatory agencies/health technology assessment bodies /payers, with relevant milestones and sufficient resources, should therefore, be proposed.

Note on the template for preparing your proposal

When using the IMI2 JU single-stage proposal template, applicants should ensure that in addition to all the information to be provided as standard in the relevant sections of the template, they also address the following points specific to this restricted Call for proposals:

Under the section **Excellence**:

Section 1.1 Objectives

- Indicate the initial action (acronym - Grant Agreement number) and the related Call topic published in the IMI2 JU Annual Work Plan of 2014, 2015 or 2016 to which their proposal relates.
- Explain how the proposal addresses the specific challenge and scope of the restricted Call for proposals (i.e. the topic text) and meet all key objectives as set out in the topic text.

Under this point, applicants should address the following:

- The scientific relevance for successfully addressing the IMI2 JU objectives;
- How the proposed activities relate to an area with a high unmet need in the context of public health and having industrial challenges (where relevant). This should also include a landscaping exercise to demonstrate that no similar initiative of the same extent is already ongoing at national, European or global level;
- The need for the proposed activities to (in a timely fashion) seamlessly build on and add value to the already remarkable results achieved in the initial action as demonstrated by the applicants. Applicants may wish to further document in an optional annex the results on which they are building the proposed activities. The annex will need to be uploaded as a separate document. There is no specific template for the annex.
- the scope of proposed activities must fall beyond the scope of the initial action (e.g. initial objectives and its financial and temporal framework);

¹²¹ <http://www.corbel-project.eu/about-corbel/research-infrastructures.html>

- the specific circumstances justifying the fact that only the initial consortium can carry out the follow-up activities successfully. For instance, the initial consortium represents a unique and effective partnership with the expertise, equipment, methodologies, or access to unique resources and IP rights, that are not available from another consortium; if some modifications of the initial partnership are needed to cover the expertise for the newly proposed activities this would have to be justified;
- how the proposed activities build on and benefit from the strong foundations as public-private partnership established in the initial action, e.g. governance, workflows, procedures.

The applicants will also need to justify why the proposed research activities can only be carried out in public private collaboration, including substantial contributions in the project activities of i.e EFPIA constituents and affiliated entities and, where relevant, by IMI2 JU Associated Partners.

Section 1.2 Concept and methodology

Define specific, important key deliverables addressing the challenges identified by their proposal and enabling the achievement of its objectives. This should include consideration for sustainability beyond the duration of the funded action and how this would be achieved, along with any key results expected to be made openly accessible.

Under the section **Impact**:

Section 2.1 Expected impact

Demonstrate how the outputs of the project will contribute to each of the expected impacts mentioned in the topic text.

Under the section **Implementation**:

Section 3.1 Project work plan — Work packages, deliverables and milestones

Provide a brief presentation of the overall structure of the project work plan; including a sound justification for the budget requested together with the contribution from EFPIA/Associated Partners. Applicants should justify the proposed total duration of the action.

Section 3.2 Management structure, milestones and procedures

If the start of the proposed action overlaps with the duration of the initial Grant Agreement, explain how the collaboration between the two actions would be ensured. In addition, in the event that the new action and the initial one will be running in parallel, measures should be proposed to ensure the proper achievement of the respective objectives;

Section 3.3 Consortium as a whole

Provide a justification in case of modifications to the initial consortium. If new members are included, applicants should justify how they bring expertise needed for the new proposed follow-up activities.

Conditions for this Call for proposals

All proposals must conform to the conditions set out in the H2020 Rules for Participation (https://ec.europa.eu/research/participants/portal/doc/call/h2020/common/1595113-h2020-rulesparticipation_oj_en.pdf) and the Commission Delegated Regulation with regard to IMI2 JU <http://eurlex.europa.eu/legal-content/EN/TXT/PDF/?uri=CELEX:32014R0622&from=EN>.

The following additional conditions shall apply to this IMI2 JU Call for proposals:

- The Call is restricted to the initial consortia of actions funded under topics published in the IMI2 JU Annual Work Plans (AWPs) of 2014, 2015 and 2016, since only these actions are sufficiently advanced in their implementation to be considered for follow-up research activities.
- In addition, it is limited to those actions derived from topics where the corresponding work plan already informed potential applicants about the possibility of a later restricted Call as listed below.

AWP year	Call	Topic number	Topic title	Project acronym	Project number	Project website
2014	1	1	Translational approaches to disease modifying therapy of type 1 diabetes Mellitus (T1DM)	INNODIA	115797	https://www.innodia.eu/
2015	3	1	RADAR-CNS	RADAR-CNS	115902	https://www.radar-cns.org/
2015	3	2	Assessing risk and progression of prediabetes and type 2 diabetes to enable disease modification	RHAPSODY	115881	https://imi-rhapsody.eu/
2015	3	3	Linking clinical neuropsychiatry and quantitative neurobiology	PRISM	115916	https://prism-project.eu/en/prism-study/
2014	4	1	Enabling platform on medicines adaptive pathways to patients	ADAPT-SMART	115890	https://www.infographic.adaptsmart.eu/
2015	5	2	Diabetic Kidney Disease Biomarkers (DKD-BM)	BEAt-DKD	115974	https://www.beat-dkd.eu/
2015	5	5	Evolving models of patient engagement and access for earlier identification of Alzheimer's disease: Phased expansion study	MOPEAD	115985	https://www.mothead.eu/
2015	6	1	Development of Quantitative System Toxicology (QST) approaches to improve the understanding of the safety of new medicines	TransQST	116030	http://transqst.org/

AWP year	Call	Topic number	Topic title	Project acronym	Project number	Project website
2015	6	2	Establishing impact of RSV infection, resultant disease and public health approach to reducing the consequences	RESCEU	116019	http://resc-eu.org/
2015	6	4	Development of an outcomes-focused data platform to empower policy makers and clinicians to optimize care for patients with hematologic malignancies	HARMONY	116026	https://www.harmony-alliance.eu/
2015	7	3	Pathological neuron-glia interactions in neuropathic pain	NGN-PET	116072	http://ngn-pet.com/
2015	7	5	A comprehensive 'paediatric preclinical POC platform' to enable clinical molecule development for children with cancer	ITCC-P4	116064	https://www.itccp4.eu/
2015	7	6	Coordination and Support Actions (CSA) for the Big Data for Better Outcomes programme	DO-IT	116055	https://bd4bo.org/
2016	9	1	Addressing the clinical burden of Clostridium difficile infection (CDI): Evaluation of the burden, current practices and set-up of a European research platform	COMBACTE-CDI	777362	https://www.combacte.com/about/combacte-cdi-understanding-of-the-epidemiology-and-clinical-impact-of-clostridium-difficile-infection/
2016	9	5	Identification and validation of biomarkers for nonalcoholic steatohepatitis (NASH) and across the spectrum of non-alcoholic fatty liver disease (NAFLD)	LITMUS	777377	https://litmus-project.eu/
2016	10	1	Understanding hypoglycaemia: the underlying mechanisms and addressing clinical determinants as well as consequences for people with diabetes by combining databases from clinical trials	Hypo-RESOLVE	777460	https://hypo-resolve.eu/
2016	10	2	How Big Data could support better diagnosis and treatment outcomes for Prostate Cancer	PIONEER	777492	https://prostate-pioneer.eu/

AWP year	Call	Topic number	Topic title	Project acronym	Project number	Project website
2016	10	4	Creation of a pan-European paediatric clinical trials network	c4c	777389	https://conect4children.org/
2016	10	6	Unlocking the solute carrier gene-family for effective new therapies (unlock SLCs)	ReSOLUTE	777372	https://re-solute.eu/
2016	10	7	Patient perspectives in medicines lifecycle	PARADIGM	777450	https://imi-paradigm.eu/

Applicants intending to submit a proposal in response to the IMI2 Call 22 should read this topic text, the [IMI2 JU Manual for submission, evaluation and grant award](#) and other relevant documents (e.g. [IMI2 JU Model Grant Agreement](#)).

Call Identifier	H2020-JTI-IMI2-2020-22-single-stage
Type of actions	Research and Innovation Action (RIA)
Publication Date	23 June 2020
Submission start date	23 June 2020
Submission deadline	29 September 2020 (17:00:00 Brussels time)
Indicative Budget	
From EFPIA companies and IMI2 JU Associated Partners to be defined based upon selected proposals	
From the IMI2 JU ¹²²	EUR 11,427,098

Call Topic

IMI2-2020-22-01 Restricted Call to maximise impact of IMI2 JU objectives and scientific priorities	The indicative contribution from EFPIA companies and IMI2 JU Associated Partners is to be defined based upon selected proposals. The financial contribution from IMI2 JU is a maximum of EUR 11,427,098	Research and Innovation Action (RIA) Single stage submission and evaluation process. Proposals submitted will be evaluated and ranked in one single list. Several proposals might be invited to conclude a Grant Agreement, depending on the budget availability and their ranking.
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¹²² In case the budget of this given line cannot be consumed (totally or partially) the corresponding budget will be allocated to the topics under the other budget lines.

Annex IV - IMI2 JU Call 23 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 created¹²³ 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 World¹²⁴.

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 companies¹²⁵, 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)¹²⁶ is the main reference for the implementation of research priorities for IMI2 JU. The scientific priorities for 2020 for IMI2 JU have been prepared based on the SRA.

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

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

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

¹²³ 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.

¹²⁴ http://www.who.int/medicines/areas/priority_medicines/en/

¹²⁵ 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.

¹²⁶ http://www.imi.europa.eu/sites/default/files/uploads/documents/About-IMI/research-agenda/IMI2_SRA_March2014.pdf

Applicant consortia shall ensure that where relevant their proposals are in compliance with the General Data Protection Regulation (EU) 2016/679¹²⁷ and Clinical Trial Regulation (EU) 536/2014¹²⁸ (and/or Directive 2001/20/EC¹²⁹) and any relevant legislation¹³⁰.

Before submitting a proposal, applicant consortia should familiarise themselves with all Call documents such as the IMI2 JU Manual for submission, evaluation and grant award¹³¹, 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).

¹²⁷ 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.

¹²⁸ 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.

¹²⁹ [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.

¹³⁰ 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.

¹³¹ https://www.imi.europa.eu/sites/default/files/uploads/documents/apply-for-funding/call-documents/imi2/IMI2_ManualForSubmission_v1.7_November2018.pdf

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

Topic details

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

Specific challenges to be addressed by public-private collaborative research

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

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

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

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

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

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

Electronic Health Record exchange format (EEHRxF) as set out in Commission Recommendation C(2019) 800¹³²;

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

Scope

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

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

To support these objectives, the project will:

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

Expected key deliverables

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

- A test version of the prototype process, agile enough to be interoperable in most countries, should be delivered by mid-term, with the final version delivered by month 42 to allow for implementation of the business plan in the final six months.
- For at least one "real" study (type and medical area to be proposed by participating EFPIA companies) the prototype process should demonstrate within a proof of concept mechanism how relevant clinical trial data can be:

¹³² <https://ec.europa.eu/digital-single-market/en/news/recommendation-european-electronic-health-record-exchange-format>

- Either integrated or interconnected with at least two existing repositories (e.g. data in national or hospital patients' EHRs or in other
- System/application directly accessible to patients); and
- Can be re-used in further medical health research or clinical studies.
- The working prototype process must be delivered alongside a robust business plan to ensure it is mature enough to pave the way for the development of a sustainable and effective platform after the end of the project.

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

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

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

Expected impact

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

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

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

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

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

- Manage research data and adhere to ethics requirements¹³³ ;
- Disseminate, exploit, and sustain the project results. This may involve engaging with suitable biological and medical sciences research infrastructures¹³⁴.
- Support the improvement of the interoperability of EHRs by aligning with the EEHRxF.

Communicate the project activities to relevant target audiences.

Potential synergies with existing consortia

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

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

- Harmonised consent forms and guidance documents for clinical trials and secondary use of data and biological samples¹ as outcomes of the IMI DO-IT decision committees;
- BBMRI Code of Conduct for health research, when available;
- ECRIN European Clinical Research Infrastructures Network;
- EUCROF Code of Conduct for clinical trials, when available;
- Relevant insights and work from the complementary Patient Data Return Initiative (PDAI) founded in 2017 by a group of Pharmaceutical companies. Though that ongoing initiative does not focus on legal or regulatory requirements of EU Member States, its progress on the data sharing process (e.g., technical insights), insights from stakeholders (such as patient groups and sponsors) on the value of returned data, and insights from completed data sharing pilots (best practices) are expected by PDAI to be available for this project by its commencement;
- Particular attention should also be paid to the initiatives piloting decentralised clinical trials, aligning clinical study data with EHRs, implementing blockchain and federated technology for secure infrastructures, aligning on data sharing with patients and/or HCPs.

Industry consortium

The industry consortium is composed of the following EFPIA partners:

- Sanofi (Lead)
- Medidata (Co-Lead)
- Abbvie
- Astra Zeneca
- Bayer
- Janssen
- Pfizer
- Servier
- Takeda

¹³³ 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

¹³⁴ <http://www.corbel-project.eu/about-corbel/research-infrastructures.html>

The industry consortium will contribute the following expertise and assets:

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

Indicative duration of the action

The indicative duration of the action is 48 months.

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

Indicative budget

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

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

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

Expertise and resources expected from applicants at stage 1

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

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

This may require mobilising, as appropriate the following expertise:

- Academic clinical trials sponsors from at least five different European Member States (including at least one central/eastern European Member State);
- Robust legal, ethics and data protection expertise (including for clinical studies);
- Proven expertise in working/collaborating with ethics committees and personal data protection authorities, as advice from various EU regulators will be essential to the success of this project and required to develop common, validated usability and privacy standards;
- Healthcare professionals;
- Participants with robust expertise in health and clinical data interoperability and secured exchanges, in EHR and in clinical trial databases, and including those operating in a commercial environment;
- Study participants and patient organisations.

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

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

Considerations for the outline of project work plan

In their stage 1 proposal applicants should:

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

Suggested architecture

Work Package 1 – Legal and Regulatory Framework

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

Work Package 2 – Standards

- The goals of this work package are to:
 - Review and elaborate upon standards and guidance documents;
 - Provide recommendations;
 - Develop new standards when necessary;
 - Submit standards (in particular regulatory ones) for approval to appropriate governing authorities/regulators.

Work Package 3 – Technology Framework

The goals of this work package are to:

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

Work Package 4 – Working Prototype process

The goals of this work package are to:

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

Work Package 5 – Communication, Dissemination & Stakeholder engagement

The goals of this work package are to:

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

Work Package 6 – Business Plan and Sustainability

The goals of this work package are to:

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

Work Package 7 – Project management and overall coordination

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

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

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

Data Management

In their stage 2 proposal, applicants should give due visibility to data management including use of data standards. A full 'data management plan' (DMP) as a distinct deliverable must be delivered within the first 6 months of the project. The DMP needs to be kept up to date with the needs of the project and as such be updated as necessary during its lifetime.¹³⁵ The DMP has to reflect on the legal, regulatory and ethical guidance from work packages 1 and 2.

¹³⁵ Guidance on data management is available at http://ec.europa.eu/research/participants/docs/h2020-funding-guide/cross-cutting-issues/open-access-data-management/data-management_en.htm

Dissemination, exploitation and sustainability of results

In their stage 2 proposal, applicants must provide a draft plan for dissemination and the exploitation, including sustainability of results. A full plan as a distinct deliverable must be delivered within the first 6 months of the project.¹³⁶, 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).¹³⁷

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.

¹³⁶ As an additional dissemination obligation under Article 29.1 of the [IMI2 Grant Agreement](#) will apply.

¹³⁷ <http://www.corbel-project.eu/about-corbel/research-infrastructures.html>

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

Background and problem statement

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

https://ec.europa.eu/health/amr/sites/health/files/antimicrobial_resistance/docs/amr_2017_action-plan.pdf.

Beyond Europe, it is of note that AMR is one of four public health concerns that has been raised to the level of discussion at the UN General Assembly (September 2016), putting it on a par with HIV and Ebola.

Additionally, drug resistant tuberculosis (TB), which is the largest single contributor to AMR health, mortality, and economic impact.

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

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

In TB, the world's leading infectious disease killer with 1.7 million deaths in 2016, (from WHO TB report 2017, Executive Summary at the following link,

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

Overall objectives of the AMR Accelerator

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

The AMR Accelerator provides, under one operational structure, a wide-ranging series of projects that addresses many of the scientific challenges in AMR. The scientific scope is broad, including prevention (vaccines, monoclonal antibodies (mAbs), immunoprophylaxis, other means) and treatment (new antibiotics, non-antibiotic alternatives, and combinations). For clarity, the term 'AMR' should be interpreted to include Gram-positive and Gram-negative bacteria, tuberculosis (TB) and non-tubercular mycobacteria (NTM). Within

this broad scope, projects in the AMR Accelerator develop new pre-clinical tools and methods, validate alternative or 'non-traditional' approaches, progress potential new treatments through phase 1-3 clinical trials, and analyse data from EFPIA-funded clinical trials to assist in the translation of preclinical data to clinical results of novel anti-infective agents and vaccines. The AMR Accelerator will also potentially generate new clinical/regulatory phase 2-3 pathways. Over the past years, IMI's New Drugs for Bad Bugs (ND4BB) programme has created a vibrant drug discovery and development network in AMR, and met important milestones. The AMR Accelerator complements and augments the capabilities of the IMI ND4BB programme¹³⁸.

Progression of successful assets beyond the scope of the AMR Accelerator (pillar-dependent, see below) may occur, as appropriate, by other mechanisms such as EU funding programmes within Horizon 2020 (including SME instruments) or future framework programmes, InnovFin instruments, Structural Funds, venture capitals, other internal R&D funding mechanisms, etc. In addition, the applicable principles from the Davos Declaration on Antimicrobial Resistance– January 2016 or the Industry Roadmap for Progress on Combatting Antimicrobial Resistance – September 2016 (<https://www.ifpma.org/wp-content/uploads/2016/09/Roadmap-for-Progress-on-AMR-FINAL.pdf>¹³⁹) should be taken into account.

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

The AMR Accelerator programme structure

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

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

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

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

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

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

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

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

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

¹³⁸ <https://www.imi.europa.eu/projects-results/project-factsheets/nd4bb>

¹³⁹ For example, points 3 and 4 from the 'Roadmap for Progress'.

The initial action in the CBN, COMBINE – 853967 selected under Pillar A from IMI2 JU Call 15 topic 7¹⁴⁰, and containing the coordination and support group¹⁴¹, implements a coordination and support group that supports the operations of all projects in the AMR Accelerator with effective management, communication, and data capture capabilities. The initial CBN action also focuses on the collection, sharing, and analysis of vaccine and/or antibacterial clinical trial data and the optimisation of animal infection models for bacterial infections.

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

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

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

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

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

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

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

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

Collaboration agreements

To ensure smooth operation of the projects in the AMR Accelerator, the grant agreement of the first CBN action (COMBINE – 853967 selected under Pillar A from IMI2 JU Call 15 topic 7, and containing the coordination and support group¹⁴²) is complementary to all the grant agreements of actions selected under

¹⁴⁰ https://www.imi.europa.eu/sites/default/files/uploads/documents/apply-for-funding/open-calls/IMI2_Call15_CallText.pdf

¹⁴¹ For additional details see the topic 7 “Capability Building Network” of [IMI2 JU Call 15](#)

¹⁴² For additional details see the topic 7 “Capability Building Network” of [IMI2 JU Call 15](#).

Pillars B and C (via IMI2 JU Call 15 topic 8, IMI2 JU Call 16 topics, IMI2 JU Call 20 topic 3 and potential future additional calls for proposals), as well as probable future grant agreements from actions selected under Pillar A. In addition, all grant agreements of actions under pillar B will be complementary between them. The respective options of Article 2, Article 31.6 and Article 41.4 of the IMI2 JU Model Grant Agreement¹⁴³ will be applied. Accordingly, the consortia selected under Pillars A, B, and C will conclude collaboration agreements with the COMBINE – 853967 consortium selected from IMI2 JU Call 15 topic 7. These collaboration agreements will provide the framework for COMBINE – 853967 to provide day-to-day support of projects in the AMR Accelerator programme, and will ensure the exchange of relevant information, exploration of synergies, collaboration where appropriate, and avoid duplication of efforts.

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

Need and opportunity for public-private collaborative research

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

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

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

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

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

¹⁴³ See: https://www.imi.europa.eu/sites/default/files/uploads/documents/reference-documents/h2020-mga-imi_en_v5.pdf

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

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

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

- **Portfolio Building Network:**
 - Provide the opportunity for SMEs and/or academic groups to partner with EFPIA companies to enable progression of promising assets or technologies to key milestones, creating value and sharing risk. There will be potential to further extend such partnerships with EFPIA companies beyond the scope of the AMR Accelerator following project completion;
 - Allow a vibrant partnering ecosystem that will benefit SMEs or academics with early stage assets based on pre-agreed conditions and milestone decision points.

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

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

Topic details

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

Specific challenges to be addressed by public-private collaborative research

Unmet medical needs

Antibiotics have greatly improved the health and life expectancy of human beings, but antimicrobial resistance (AMR) is rising, and deaths due to infections have been predicted to exceed the ones caused by cancer by 2050¹⁴⁴. The World Health Organization (WHO)¹⁴⁵ and the Centers for Disease Control and Prevention (CDC) of the United States¹⁴⁶ have recently listed the priority human pathogens with threatening drug-resistance patterns. New generation antibiotics, vaccines and antibody-based biologics can all contribute to the response to the global challenge of antimicrobial resistant pathogens.

Challenges

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

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

- 1) **Measurement of the burden of disease (BOD) and costs of AMR:** there is a need for a disaggregation of the BOD by subpopulation to compare the cost-effectiveness of targeting strategies to go beyond the work performed by Cassini et al¹⁴⁷ **Error! Reference source not found.** This would require a much more granular estimation of the burden to capture which subpopulation (e.g. migrants, elders, patients with certain comorbidities, surgery procedures, long-term care residents, etc.) are contributing most to the health burden, through which types of infection and which type of AMR. This granularity is critical to inform strategies that are most likely to reduce the AMR burden. The future burden estimations will also try to include potential incremental side effects such as increased disability, due to the fact that certain key surgery procedures will be less accessible thanks to the increased risk AMR will pose to the safety of surgeries. Once a more granular burden of disease is built, it could be possible to test which vaccine and monoclonal antibodies need to be prioritised and through which targeting strategy. As such, it requires access to multiple data sources to quantify the burden of disease and cost of AMR.

¹⁴⁴ <https://amr-review.org/Publications.html>

¹⁴⁵ <https://www.who.int/en/news-room/detail/27-02-2017-who-publishes-list-of-bacteria-for-which-new-antibiotics-are-urgently-needed>

¹⁴⁶ https://www.cdc.gov/drugresistance/biggest-threats.html?CDC_AA_refVal=https%3A%2F%2Fwww.cdc.gov%2Fdrugresistance%2Fbiggest_threats.html

¹⁴⁷ Cassini et al have estimated the BOD in the EU but they did not forecast the BOD in specific target groups and they did not adjust the models “for age-specific risks, co-infections, appropriateness of antibiotic therapy, or for type of care, assuming common transition probabilities for all subgroups”.

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

Scientific opportunity

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

Reasons for a public-private partnership

AMR has gradually depleted the antibiotic armoury and disaster will strike when the last class of antibiotics becomes ineffective. A model will have the benefit of predicting the reduction of AMR associated with novel mAb and vaccination strategies against AMR pathogens. This information should allow public health institutes and/or companies to select the right direction among several priorities. The results of the model shall then be used to better inform policy decisions which are more likely to be accepted and implemented if both the private and public sector perspectives are taken into account. Joining forces increases the chance that all points of view of the major actors feed into the analysis and produce final results that are *are more likely to be agreed upon* because they have been built through a consensus process¹⁴⁸. Whatever interventions and target groups will be prioritised, subsequent health interventions need to be financed through private and public resources and therefore it is important that both perspectives are taken into account during the modelling exercise.

¹⁴⁸ As an example, when building Disability Adjusted Life Years lost because of AMR, the industry might be more inclined to give more weight to the productive age groups while the public-health perspective might give equal weight to all age groups.

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

Scope

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

In a systematic review on AMR mathematical models, Birkegård et al [2] found that few selected studies fulfilled the TRACE modelling practice guidelines¹⁴⁹. The recommendations of the authors for future mathematical models on AMR included: “a) model the biological processes mechanistically, b) incorporate uncertainty and variability in the system using stochastic modelling, c) include a sensitivity analysis and model external and internal validation”.

The project has the following objectives:

- 1) **Evaluate the burden of disease of AMR** by estimating inpatients’ (acute care hospitals and long-term care facilities) and outpatients’ infection rates in at least 8 EU countries for which suitable data is collected and available, as well as in the US¹⁵⁰, and the relative attributable risk for morbidity, mortality and costs.
- 2) **Build a comprehensive AMR model** (i.e. model structure, parameters, assumptions) based on an analysis of the strengths and weaknesses of existing models, and a gap analysis.
- 3) **Collecting, gathering, and analysing data** from existing databases to feed the model.
- 4) **Develop and test a cost-effectiveness analysis (CEA)** to estimate the cost and benefits of covering defined target groups (e.g. 18+, 60+, surgeries) with mAbs and vaccines.
- 5) **Set up a study** to test, monitor, evaluate and improve the model.
- 6) Ensure a **public and broad access to the model**.

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

Collaboration agreement(s)

To ensure smooth operation of the projects in the AMR Accelerator, the grant agreement of the first CBN action (COMBINE – 853967 selected under Pillar A from IMI2 JU Call 15 topic 7, and containing the coordination and support group¹⁵¹) is complementary to all the grant agreements of other actions selected under Pillars A, B and C (via IMI2 JU Call 15 topic 8, IMI2 JU Call 16 topics¹⁵², IMI2 JU Call 20 topic 3¹⁵³, IMI2 JU Call 23 topic 2 and related grant agreements).

¹⁴⁹ TRACE is a general framework for documenting a model’s rationale, design, and testing. The TRACE guidelines include the following 8 elements: “1) Problem formulation (clear formulation of the objective and a description of the context of the model); 2) Model description (written description of model elements to allow readers to understand and replicate the model); 3) Data evaluation (an assessment of the quality of data used to parameterise the model); 4) Conceptual model evaluation (a list and explanation of the most important conceptual design decisions); 5) Implementation verification (internal validation of the model, testing for programming errors and assessing model performance); 6) Model output verification (external validation, testing whether the model output matches the observations); 7) Model analysis (mainly sensitivity analysis); 8) Model output corroboration (a comparison of model output with data that were not used to create the model)

¹⁵⁰ Access to data from the US will be provided by the EFPIA Partners who have licenses to databases.

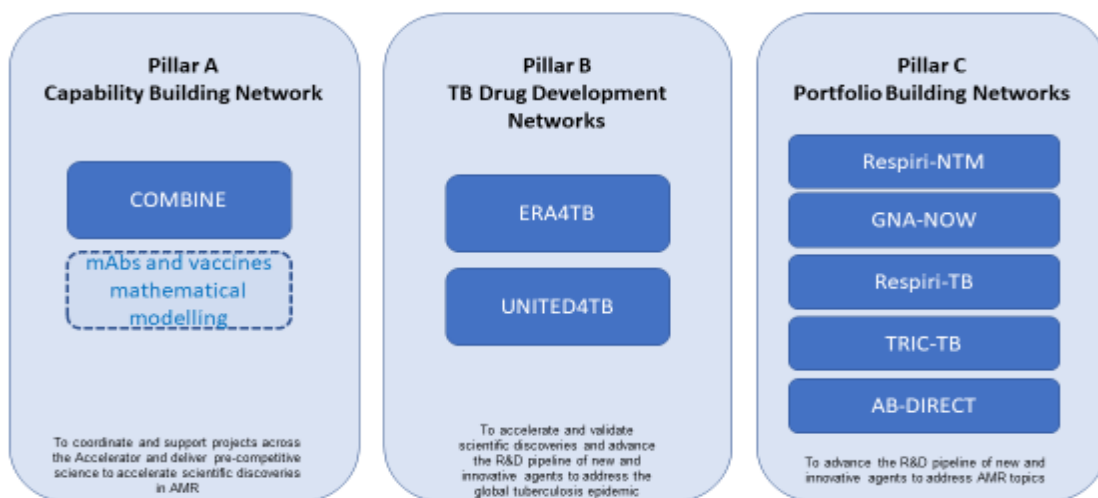
¹⁵¹ For additional details see the topic 7 “Capability Building Network” of [IMI2 JU Call 15](#).

¹⁵² https://www.imi.europa.eu/sites/default/files/uploads/documents/apply-for-funding/open-calls/IMI2_Call16_CallText.pdf

¹⁵³ https://www.imi.europa.eu/sites/default/files/uploads/documents/apply-for-funding/open-calls/IMI2_Call20_CallText.pdf

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

The AMR Accelerator



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

Expected key deliverables

- Burden of Disease caused (BOD) by AMR. The systematic review of the literature on the BOD of AMR will lead to an **epidemiological repository** of incidence, prevalence, disability (e.g. disability-adjusted life years – DALYs, quality-adjusted life year – QALYs), mortality, short- and long-term disability, consumption of antimicrobials, costs and other parameters associated with main pathogens and population groups. The repository will provide the basis for the estimation of the BOD caused by infectious disease and the contribution due to AMR. This repository will be complementary to the following existing databases:
 - In comparison with to the current ECDC database and any relevant valuable national database on AMR that is based on laboratory reporting, this repository will provide all the estimates available in the literature, with more information, for example, on incremental costs associated with AMR from case control studies.
 - Similarly, the notifications of infectious diseases of the ECDC database are very useful for surveillance, but cannot be used to estimate or infer population incidence. The project repository will provide a rich data source of the incidence of pathogens by target group derived from the literature.

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

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

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

Expected impact

The **epidemiological repository** that will be obtained in Work package 1, besides providing a transparent basis for the BOD estimation, will be made accessible through an internet database to be designed within the project. Any researcher will benefit from using the most comprehensive database on the epidemiology of infectious diseases and resource consumption associated with sensitive and resistant pathogens. Producing a reliable repository with clear description of the methods used to derive the estimates of the BOD and AMR will benefit the credibility of the results of the mathematical model. During the project, the access will be free of charge. After the end of the project, the conditions for access will depend on the operational model to ensure the maintenance and sustainability of the databases, and compliant with the IMI2 JU intellectual property policy. The ambition is to favour open access as much as possible.

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

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

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

real data, and which will be further expanded to other promising mAbs and vaccinations, with further fine-tuning.

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

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

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

- Manage research data including use of data standards¹⁵⁴;
- Disseminate, exploit, and sustain the project results. This may involve engaging with suitable biological and medical sciences research infrastructures¹⁵⁵;
- Communicate the project activities to relevant target audiences.

In addition, the following additional exploitation¹⁵⁶/dissemination¹⁵⁷ obligations must be considered to maximise impact:

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

Potential synergies with existing consortia

Synergies and complementarities should be considered with relevant national, European and non-European initiatives (including suitable biological and medical sciences research infrastructures¹⁵⁸ 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:

- GlaxoSmithKline Biologicals
- Janssen Vaccines & Prevention
- Pfizer

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

- GlaxoSmithKline Biologicals

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

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

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

¹⁵⁴ 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

¹⁵⁵ <http://www.corbel-project.eu/about-corbel/research-infrastructures.html>

¹⁵⁶ Article 28.1 (Additional exploitation obligations) of the [IMI2 Grant Agreement](#) will apply.

¹⁵⁷ Article 29.1 (Additional dissemination obligations) of the [IMI2 Grant Agreement](#) will apply.

¹⁵⁸ <http://www.corbel-project.eu/about-corbel/research-infrastructures.html>

- Janssen Vaccines & Prevention

Expertise: clinical development, market access and modelling.

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

- Pfizer

Expertise: clinical development, market access and modelling.

Indicative duration of the action

- The indicative duration of the action is 60 months.
- This duration is indicative only. At stage 2, the consortium selected at stage 1 and the predefined industry consortium may jointly agree on a different duration when submitting the stage 2 proposal.

Indicative budget

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

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

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

Expertise and resources expected from applicants at stage 1

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

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

This may require mobilising, as appropriate the following expertise:

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

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

- It is important to involve public health agencies/authorities because their expertise can substantially contribute to the scientific soundness of the study and because it is important to add their

perspective¹⁵⁹. This will ensure that the project will fully consider public health needs and is not mainly driven by pharma industry. Regulatory authorities could also have an interest to be involved in the consortia to ensure the design of the model will meet their expectations.

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

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

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

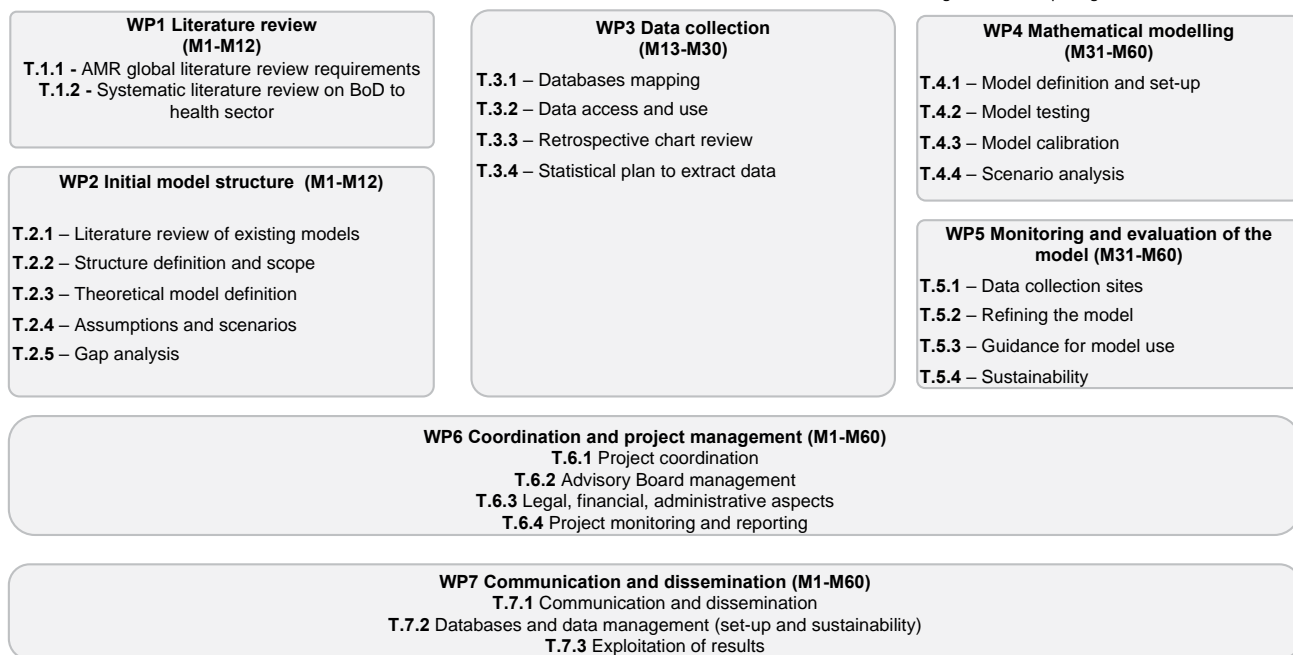
Considerations for the outline of project work plan

In their stage 1 proposals applicants should:

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

Suggested architecture

Legend: WP: workpackage T: Task



¹⁵⁹ To avoid potential conflicts of interest or issues from PHA to participate in a consortium with EFPIA partners, the applicants should propose the best and most realistic way to include these organisations.

Work Package 1 – Burden of disease due to AMR

The goals of this work package are:

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

Work Package 2 – Model structure development

These developments could include different activities such as:

- Conducting a systematic review of the models used to predict the influence of mAbs and vaccines for treatment or prevention. The review will help to clarify model structure, parameters, assumptions, strength and limitations, and gaps to be filled.
- Clarifying the scope: AMR is a universal and a complex phenomenon. Bacteria develop resistance by natural selection even without the use of antibiotics and this fraction of natural AMR is rarely taken into account. Such natural selection is speeded up when antibiotics are used for animal and human health and then antibiotics are released in the environment, ending up in the food chain. Covering all the variables influencing the complexity of AMR development in the different sectors (natural development, food production, veterinary health and health care) would be impossible, and a narrower focus is needed to make the study manageable. The model is likely to cover the health sector, leaving out the contribution of the veterinary and agricultural sectors and the natural selection of resistant strains.
- Identifying assumptions and information gaps in parameters will involve a review of the disease ecological dynamics, notably:
 - Natural history of disease for sensitive and resistant pathogens in the general population or in health care settings including asymptomatic incubation, latency, infective stage, differential probability of transmission between a susceptible and a resistant strain, fitness costs, probability of acquiring resistance if exposed;
 - AMR Diagnostics sensitivity, specificity and positive/negative predictive values;
 - Attributable outcomes by sensitive and resistance pathogen considering comorbidity, age and other confounders;
 - Type of antibiotic consumption, with a special focus on carbapenems, extended spectrum beta-lactamase, fluoroquinolones and 3rd generation cephalosporines and the probability of acquiring specific resistance if exposed to these antibiotics.

Work Package 3 – Data gathering

The goals of this work package are:

Databases already identified by industry include the Marketskan¹⁶⁰ and other claims (e.g. Kaiser Permanente) databases in the US, the NHS¹⁶¹ and GP databases¹⁶² in the UK, the Epidemiologie – France Portal Health Database¹⁶³, the health care database of the German Institute of Medical Documentation and Information¹⁶⁴, Health for All Italia¹⁶⁵. Examples of data to be collected from databases include MRSA and CRE screening and isolation carried out in US and UK hospitals, as well as similar national surveillance data from the EU Member States. This care-focused approach has the main objective of operationalising the issue of AMR by modelling different impact pathways for vaccines and mAbs while narrowing the scope of both to nosocomial transmission. This approach will also geographically focus on the EU as priority settings because data are available and screening processes are in place for priority pathogens. Besides providing a specific operational

¹⁶⁰ <https://www.ibm.com/products/marketscan-research-databases>

¹⁶¹ <https://www.nhs-database.co.uk/>

¹⁶² <https://www.cprd.com/home/>

¹⁶³ <https://epidemiologie-france.aviesan.fr/en>

¹⁶⁴ <https://www.dimdi.de/dynamic/en/further-services/health-care-data/>

¹⁶⁵ <https://www.istat.it/it/archivio/14562>

context, this focus on MRSA and CRE screening also has the advantage of being of high priority in EU countries' policy agendas.

Work Package 4 – Cost-effectiveness analysis (CEA)

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

- Which vaccines and mAbs should be included in the model. The first skeleton of the model will be based on previous assessments of the impact of existing vaccines, for example the impact of Pneumococcal Conjugate Vaccine on penicillin non-susceptible strains and the impact of influenza immunisation programmes on antibiotic prescription. This initial assessment will provide a better idea of how experience has tried to depict the patient pathways through which prevention of infection on specific bacteria and viruses can impact antibiotic consumption, AMR, health outcomes, resource consumption and costs. This initial model construction could be expanded to other vaccines and mAbs, generating several potential models and identifying common elements which could produce a core structure which could be adapted to model the impact of other vaccines and mAbs.
- Whether or not to limit the perspective to health care costs or to add social costs, too. Examples of health care costs include lengthier hospitalisation of AMR hospital infections vs the same type of infection due to sensitive bacteria. Costs will take into account the different health care systems of the EU and other countries. Cost comparability will have to consider inflation adjustment for estimates taken in different time periods, and the exchange rates of different currencies vs the reference currency (e.g. USD). An example of social costs might include lost income due to incremental length of hospitalisation and other social consequences.
- What to include in the existing standard of care (comparator). The incremental benefits of mAbs and vaccines will be compared with existing preventive strategies (e.g. Methicillin Resistant *Staphylococcus aureus* (MRSA) screening and isolation), stewardship for the correct antibiotic prescription, and similar existing activities.
- The patients' pathways by type of health care setting. This includes the various steps patients go through between admission and discharge (e.g. carbapenem resistant screening and isolation) to capture all the costs due to resource consumption and the transmission dynamics (e.g. in the case of not complying with screening and isolation).
- The strategic options will be evidence-based, through the selection of interventions on the basis of their demonstrated efficacy in clinical trials, their feasibility and operational effectiveness in clinical settings, and their targeting strategies to provide the most health gains and economic savings.
- Predict potential impact of novel vaccines and mAbs against AMR in reducing the emergence of resistance.

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

Work Package 5 – Evaluation

The goals of this work package are:

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

Work Package 6 – Coordination and Management

The goals of this work package are:

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

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

Work Package 7 – Communication and Dissemination.

The goals of this work package are:

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

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

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

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

Data Management

In their stage 2 proposal, applicants should give due visibility to data management including use of data standards. A full 'data management plan' (DMP) as a distinct deliverable must be delivered within the first 6 months of the project. The DMP needs to be kept up to date with the needs of the project and as such be updated as necessary during its lifetime.¹⁶⁶

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 project¹⁶⁷, 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

¹⁶⁶ 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

¹⁶⁷ As an additional dissemination obligation under Article 29.1 of the [IMI2 Grant Agreement](#) will apply.

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).¹⁶⁸

Communication

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

References

- [1] Cassini A, Högberg LD, Plachouras D, Quattrocchi A, Hoxha A, Simonsen GS, et al. Attributable deaths and disability-adjusted life-years caused by infections with antibiotic-resistant bacteria in the EU and the European Economic Area in 2015: a population-level modelling analysis. *Lancet Infect Dis* 2019; 19 (1): 56–66. [https://doi.org/10.1016/S1473-3099\(18\)30605-4](https://doi.org/10.1016/S1473-3099(18)30605-4)
- [2] Birkegård AC, Halasa T, Toft N, Folkesson A and Græsbøll K. Send more data: a systematic review of mathematical models of antimicrobial resistance. *Antimicrob Resist Infect Control* 2018; 7:117. <https://doi.org/10.1186/s13756-018-0406-1>
- [3] Magiorakos AP, Burns K, Rodríguez Baño J, Borg M, Daikos G, Dumpis U, et al. Infection prevention and control measures and tools for the prevention of entry of carbapenem-resistant Enterobacteriaceae into healthcare settings: guidance from the European Centre for Disease Prevention and Control. *Antimicrob Resist Infect Control* 2017; 6: 113. <https://doi.org/10.1186/s13756-017-0259-z>

¹⁶⁸ <http://www.corbel-project.eu/about-corbel/research-infrastructures.html>

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

Topic details

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

Specific challenges to be addressed by public-private collaborative research

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

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

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

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

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

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

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

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

Scope

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

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

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

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

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

Applicants need to be aware that activities related to building a biorepository or data management and sharing platform from scratch are **out of scope** for this topic. Instead, they must build upon existing resources (including ongoing longitudinal cohorts or studies), knowledge and infrastructures to deliver a novel solution able to seamlessly incorporate existing retrospective samples and data with prospective samples and data collections. The industry consortium will make available a data platform (e.g., Alzheimer's Disease (AD) Workbench¹⁶⁹ via the Alzheimer's Disease Data Initiative), which will soon start. The AD Workbench provides not just for storage but also for computational needs, tools, and a virtual analytics environment, among others.

¹⁶⁹ To register as a user of the Alzheimer's Disease Workbench please go to the following web site : <https://portal.addi.ad-datainitiative.org/> and follow the steps in this guide: <https://knowledgebase.aridhia.io/article/registering-for-a-workspaces-account/>

Thus, applicants are expected to propose solutions for adapting AD Workbench to create an instance of the data platform in Europe to achieve the objectives of the topic. Any data platform to be used in addition to and/or in combination with the AD Workbench must be open source and fully interoperable.

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

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

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

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

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

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

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

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

- the amyloid-tau-neurodegeneration (ATN) system, which has been proposed as a very suitable staging and prediction system, but whose measurement still relies on complex markers which do not lend themselves easily to screening and testing of large numbers of elderly people;
- the complement pathway, which is a specific component of the inflammation response that is now recognised as a key factor in a wide range of chronic neurodegenerative conditions and has been genetically linked to Alzheimer's disease; furthermore, there continues to be increasing attention towards digital biomarkers (see point 3);
- digital biomarkers with the potential for monitoring neurodegenerative diseases given the ubiquitous nature of consumer electronics and powerful computational platforms.

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

Applicants have to include the well substantiated description of:

- cohorts with early Alzheimer's disease, which will allow the evaluation of the ATN system, comparing more complex and expensive markers like cerebrospinal fluid amyloid β ($A\beta$) & tau, amyloid-positron emission tomography (PET) and magnetic resonance imaging (MRI) with potential liquid biopsy (blood, saliva,..) markers as alternate biomarkers and;
- cohorts with Parkinson's disease to investigate the impact/relation of the complement system on diagnosis, severity and progression. This should be especially in light of new classes of minimally invasive neurodegenerative disease biomarkers (e.g. autoantibodies, DNA methylation, exosomes) and sample matrices (e.g. saliva).

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

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

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

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

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

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

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

Applicants need to present a strategy and plan of activities to further grow the platform and ensure steady sample availability by attracting and integrating data and samples from novel cohorts and clinical trials beyond those provided by consortium members. The plans need to be documented by previous record of success. These plans need to be based on a thorough analysis of both blocking factors and success ingredients for making the platform attractive to the donors of data and samples. These latter should/could also be the end-users, to create a virtuous self-sustaining cycle. Starting from multiple neurodegeneration cohorts (in

Alzheimer's disease and Parkinson's disease) the potential for future expansion to other indications (e.g. other tauopathies), beyond the funding period, should be considered. Applicants should also demonstrate the suitability of the platform for integrating unusual samples (e.g. faeces, saliva) and unusual data sets (e.g. dietary surveys, microbiota profiles).

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

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

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

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

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

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

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

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

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

Expected key deliverables

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

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

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

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

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

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

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

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

Associated with objective 4) Test the above with case studies

- Produce reports on the performed case studies testing the established network, and demonstrating the utility of the data, biomarkers and biorepository. These need to appraise the value of leveraging samples and data towards:
 1. demonstration of utility of samples with a standardised assay of current neurodegenerative disease biomarkers;
 2. new biomarker identification and analysis interrogating the complement system for neurodegenerative diseases. This needs to include an appraisal on the utility in the regulatory context considering as relevant e.g. Innovation Task Force and Scientific Advice.¹⁷⁰
- Case studies:
 - Evaluate the ATN (amyloid-tau-neurodegeneration) system in cohorts with early Alzheimer's disease, to allow comparison of the more complex and expensive markers like cerebro-spinal fluid (CSF) amyloid β (A β) & tau, amyloid-PET and MRI with potential liquid biopsy (blood, saliva,..) markers as alternate biomarkers;
 - Interrogate the complement pathway biomarkers across a panel of neurodegenerative diseases. This could start potentially using first a discovery stage complement proteomics unbiased approach, that could be followed by confirmatory studies with standard lab-based assays on larger sample panel, in order to identify potential patient subgroups. This needs to include regulatory advice, e.g. from EMA Innovation Task Force¹⁷¹;
 - Include at least one cohort with longitudinally collected digital biomarkers.
- Generation of harmonised sample and datasets: Novel, prospective samples and datasets must be incorporated in the platform and must be harmonised and interoperable with data resources already included from the start of the operation.

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

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

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

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

¹⁷⁰ <https://www.ema.europa.eu/en/human-regulatory/research-development/scientific-advice-protocol-assistance/qualification-novel-methodologies-medicine-development>

¹⁷¹ [https://www.ema.europa.eu/en/human-regulatory/research-development/innovation-medicines#ema's-innovation-task-force-\(itf\)-section](https://www.ema.europa.eu/en/human-regulatory/research-development/innovation-medicines#ema's-innovation-task-force-(itf)-section)

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

Expected impact

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

In particular, short proposals must address:

- how the self-sustainable network platform composed of a European biobank operation, and accompanying data platform, will positively fuel and impact basic research and development and drug development campaigns;
- how the public-private partnership providing infrastructure to enable worldwide sample and data sharing will have a substantial impact on the development and regulatory validation of biomarkers/diagnostics, and how in turn this would likely have a cascading effect on accelerating therapeutic development.

In their proposals, applicants need to outline how the project plans to leverage the public-private partnership model to maximise impact on innovation, research & development; regulatory, clinical and healthcare practices, as relevant. This could include a strategy for the engagement with patients, healthcare professional associations, healthcare providers, regulators, HTA agencies, payers etc., where relevant. A clear plan on how to involve the public and patients in the project from the beginning until the end of the project, as well as a demonstration of their involvement in the formulation of the proposal (short and full proposal) is a requirement and has to be included in the proposal. This is especially important given the need to engage ongoing cohorts for this project to be successful.

In addition, applicants need to describe how the project will impact on competitiveness and growth of companies including SMEs.

In their proposals, applicants must outline how the project will:

- manage research data including use of data standards¹⁷²;
- disseminate, exploit, and sustain the project results - this may involve engaging with suitable biological and medical sciences research Infrastructures¹⁷³;
- communicate the project activities to relevant target audiences.

In addition, the following additional dissemination¹⁷⁴ obligations must be considered to maximise impact.

Dissemination needs to include (1) publication and actively engaging the stakeholder community to implement the agreed principles for data/sample sharing and access; and (2) demonstrating the value of the platform (key to support its sustainability) as impact of the enabled data/sample usage.

Potential synergies with existing consortia

Synergies and complementarities must be considered with relevant national, European and non-European initiatives (including suitable biological and medical sciences research infrastructures) in order to incorporate resources, past achievements, available data and lessons learnt where possible, thus avoiding unnecessary overlap, and duplication of efforts and funding.

¹⁷² 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

¹⁷³ <http://www.corbel-project.eu/about-corbel/research-infrastructures.html>

¹⁷⁴ Article 29.1 (Additional dissemination obligations) of the [IMI2 Grant Agreement](#) will apply

Industry consortium

The industry consortium is composed of the following EFPIA partners:

- Gates Venture (co-lead)
- UCB (co-lead)
- Janssen
- Novartis
- Roche
- Sanofi
- SVAR Lifescience
- Takeda

The industry consortium will contribute the following expertise:

- Project leadership, governance and project management resource and capabilities.
- The identification and transfer of samples into the biorepository will be supported, including accompanying patient / participant data.
- Provide the necessary scope of legal, technical, and other required resources (Full Time Employees) to enable successful transfer of samples and subsequent utility of the platform for users.
- Testing of the consistency and quality of sample handling, storage, and distribution using some of the now standard biomarkers used in the field such as A β 40, A β 42, Tau, phosphorylated Tau (p-Tau), synuclein, neurofilaments (NFL) etc.
- Interaction to ensure banking of samples will aid in disease understanding and modelling. For example, existing sample collections from previous clinical trials entertained by EFPIA-companies may be used to:
 - define and refine criteria to incorporate, use, distribute samples and return obtained data back into the database for further use by third parties;
 - refine legal requirements and documents (inform consent forms, etc) to standardise how samples will be retrieved in future trials to be incorporated in such repositories.
- Support for research activities focusing on the utility of the biorepository to identify biosignatures related to the dysregulation of as-yet under-researched mechanisms in neurodegeneration, e.g. the complement system (see case studies appraising biobank operational scheme).
- Supporting validation of biomarkers to accelerate the development of diagnostics.
- Supporting development of sample collection, quality assurance/quality control, sample storage and handling protocols.
- Facilitation of transfer of capabilities and knowledge to reach the ultimate goal of self-sustainability of the biobanking entity.

The industry consortium plans to contribute the following assets:

- Existing samples from clinical trials including accompanying data and information. The transfer of such samples into the biorepository will be supported.
- Assays, standard operating procedures, and necessary material (e.g. antibodies) to perform diagnostics.
- Research assay with CSF and plasma markers of neurodegeneration and neuroinflammation including but not limited to:
 - CSF: A β 42, total Tau (tTau), (pTau), A β 40, neurofilaments (NFL), soluble triggering receptor expressed on myeloid cells 2 (STREM2), tyrosine (Y), lysine (K) and leucine (L)-40 glycoprotein

(YKL40), glial fibrillary acidic protein (GFAP), Alpha Synuclein, Neurogranin, interleukin-6 (IL-6), S100b;

- plasma/ serum: A β 42 high sensitivity, A β 40, tTau, NFL, STREMB2, YKL40, IL-6, S100b, GFAP, brain derived neurotrophic factor (BDNF), growth differentiation factor-15 (GDF-15), insulin like growth factor binding protein 7 (IGFBP7), neuron-specific enolase (NSE).

These assays are high-performance, non-commercial assays, and would be made available for service at a contract research organisation (Covance) and would require advance planning to ensure capacity and availability (> 6 Months).

- Diagnostic assays to evaluate the function of the patient's complement system via classical, alternative and lectin pathway in serum.
- Contribute datasets from retrospective (and ongoing) interventional and/or observational studies to the data platform.
- AD Work bench – access and leverage AD Work bench data platform for the project.
- In addition, the Gates Ventures will provide synergy and point of contacts with its other funded initiatives including Diagnostics Accelerator¹⁷⁵, Dementia Discovery Fund¹⁷⁶, Early Detection of Neurodegenerative diseases¹⁷⁷, and a yet to be publicly announced initiative on data sharing and interoperability (Alzheimer's Disease Data Initiative) for the benefit of the Alzheimer's disease patients. The AD Data Initiative has developed a set of solutions to enable interoperability across a representative sample of data platforms.

Indicative duration of the action

The indicative duration of the action is 60 months.

This duration is indicative only. At stage 2, the consortium selected at stage 1 and the predefined industry consortium may jointly agree on a different duration when submitting the stage 2 proposal.

Indicative budget

The financial contribution from IMI2 JU is a maximum of EUR 9 680 000.

The indicative in-kind and financial contribution from EFPIA partners is EUR 9 720 000.

The total financial contribution available from the EFPIA partners for the activities in relation to the objectives of this action is EUR 3 000 000.

The allocation of the EUR 3 000 000 financial contribution will be decided by the full consortium at stage 2 when preparing the stage 2 proposal.

Due to the global nature of the participating industry partners it is anticipated that some elements of the contributions will be non-EU/H2020 Associated Countries in-kind contributions.

Expertise and resources expected from applicants at stage 1

The applicant consortium will be selected on the basis of the submitted short proposals.

The stage 1 applicant consortium is expected, in the submitted short proposal, to address all the objectives and key deliverables of the topic, taking into account the expected contribution from the industry consortium which will join at stage 2 to form the full consortium.

¹⁷⁵ <https://www.alzdiscovery.org/research-and-grants/diagnostics-accelerator>

¹⁷⁶ <https://theddfund.com/>

¹⁷⁷ <https://edon-initiative.org/>

This may require mobilising, as appropriate the following expertise.

All relevant areas of expertise that are necessary to deliver on all of the project deliverables. This needs to include entities with a proven track record of successful experience in the following or equivalent areas of experience, including key considerations of SMEs.

- Technology and solid understanding of technical architectures for biobanks and bio-repository know-how for long-term collection, storage and distribution of large numbers of samples, including:
 - capacity to allow online identification and ordering of samples including infrastructure to accept, add, and retrieve data obtained with and attached to samples; this includes modalities for covering handling, maintenance, and distribution costs of the repository which will support the transformation of the action into a self-sustainable operation in a European and worldwide context;
 - legal expertise;
 - data / information technology infrastructure expertise;
 - expertise and networks to procure samples through existing or (clinical) networks that are to be established;
 - experience in standardisation procedures (e.g. via European Committee for Standardisation (CEN)) including QC of samples;
 - experience with federated and/or centralised laboratory information management system (LIMS) architecture, security and standards to monitor the status of the repository and maintain and amend information available to each specimen.
- Expertise regarding establishing and managing a data platform that:
 - utilises requisite standards and common data models;
 - facilitates data access;
 - can incorporate new data generated using samples from the repository;
 - with appropriate protections and security to protect sensitive healthcare data;
 - is suitable for a public-private partnership context.
- Knowledge in establishing and maintaining a harmonised online data portal / interface that:
 - can interrogate available datasets and samples via federated approaches to unify available clinical datasets;
 - is interoperable between biobanks, clinical data systems, and across the biorepository network involved in the action, including requesting samples for analysis.
- Experience relevant to biomarker discovery and validation, ideally including the expertise below to ensure the success of the described pilot case studies:
 - experience with early AD biomarkers;
 - experience in complement pathway biomarker analysis, both unbiased (such as large-scale targeted proteomics), and more standard biomarker assays for large-scale analysis of larger case panels;
 - experience in digital biomarkers and digital signatures via connected devices and wearables e.g. for early detection and/or disease progression.
- EU & worldwide legal, ethical and regulatory expertise pertaining to:
 - legal requirements specifically to sharing, access and usage of health data in Europe at a minimum;
 - the use of human samples (sampling, storage, distribution across regions), bio-banking and patient consent/secondary use / ethics;
 - data sharing, access and consent related to sensitive health-related data and their secondary use;
 - regulatory expertise in how to engage and influence outcomes with regulators in line with targeted project deliverables.

- Business, financial, and economics experience to transform the bio-sample repository into a self-sustainable business:
 - experience and expertise in developing a strategy for ensuring the translation of the project results / bio-sample analysis to drug development, regulatory / health technology assessment (HTA) settings (e.g. through scientific advice/ qualification advice /opinion, etc.), clinical and healthcare practices and/or decision-making processes;
 - general project management (ability to consistently set and achieve milestones on time and within budget; managing varying interests of multiple stakeholders) and professional communication expertise (expertise in communication tools and systems for project management purposes).

Applicants are also encouraged to consider having a patient group involvement within the consortium to ensure that the input of patients is covered, including not limited to, but including consent and other aspects e.g. 'Henrietta Lacks' representation (<https://www.nature.com/news/deal-done-over-hela-cell-line-1.13511>).

The size of the consortium should be proportionate to the objectives of the topic while ensuring its manageability.

It may also require mobilising, as appropriate, the following resources:

- A pre-existing and functional sample repository, preferentially with a background in the neurodegenerative disease therapeutic area (Alzheimer's disease and related tauopathies, Parkinson's disease), that could already be made available for distribution at the beginning of the action;
- Active cohorts with early stage neurodegenerative disease (e.g. Alzheimer's disease and Parkinson's disease);
- An established distribution pipeline to deliver samples to customers and be operational at within first year of the action;
- Existing sample and data sets (provided e.g. from industry partners or provided by third parties) that will be contributed to this network.

Considerations for the outline of the project work plan

In their stage 1 proposals, applicants need to:

- Give due visibility on data management; dissemination, exploitation and sustainability; and communication activities. This must include the allocation of sufficient resources for these tasks which will be further developed in stage 2 proposal.
- Propose a work plan that efficiently enables the implementation of activities following the two Phases as in the Scope section.
- Consider including a strategy for ensuring the translation of the projects results to drug development, regulatory/HTA settings (e.g. through scientific advice/ qualification advice /opinion, etc.), clinical and healthcare practices and/or decision-making processes.

Suggested architecture

Please consider a work plan that includes all activities and elements related to scope and deliverables.

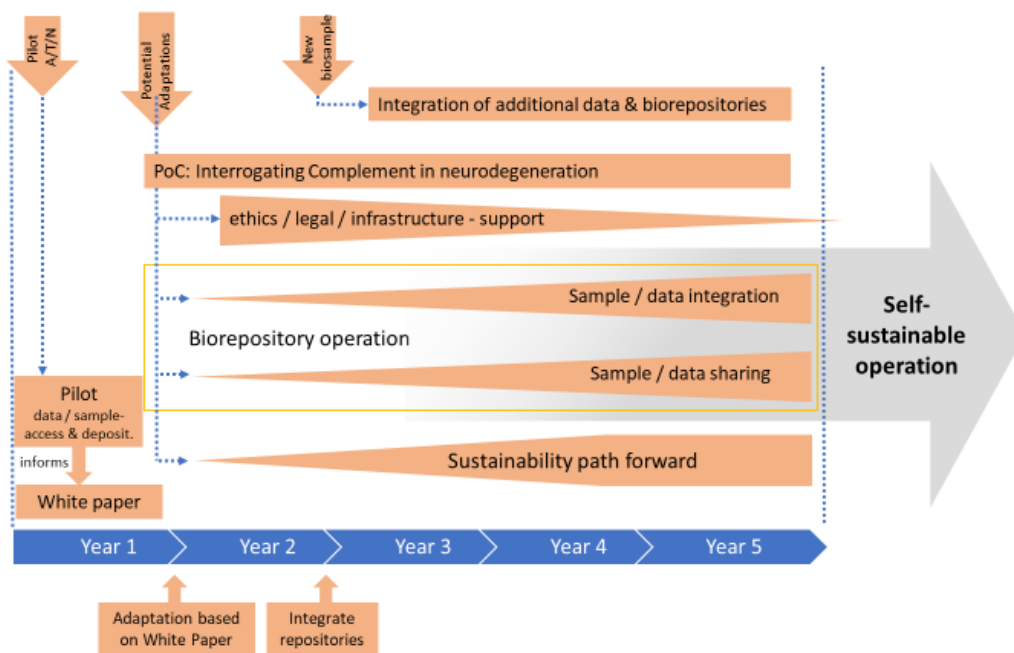


Figure 1 – draft structure of activities

Additional considerations to be taken into account at the stage 2 full proposal

At stage 2 of the IMI review process, the consortium selected at stage 1 and the predefined industry consortium jointly submit the full proposal developed in partnership. The full proposal is based upon the selected short proposal at stage 1.

In the spirit of the partnership, and to reflect how IMI2 JU call topics are built on identified scientific priorities agreed together with EFPIA beneficiaries/large industrial beneficiaries, these beneficiaries intend to significantly contribute to the programme and project leadership as well as project financial management. The final architecture of the full proposal will be defined by the participants in compliance with the IMI2 JU rules and with a view to the achievement of the project objectives. The allocation of a leading role within the consortium will be discussed in the course of the drafting of the full proposal to be submitted at stage 2. To facilitate the formation of the final consortium, until the roles are formally appointed through the consortium agreement, the proposed project leader from among EFPIA beneficiaries/large industrial beneficiaries shall facilitate an efficient negotiation of project content and required agreements. All beneficiaries are encouraged to discuss the project architecture and governance and the weighting of responsibilities and priorities therein.

Data Management

In their stage 2 proposal, applicants must give due visibility to data management including use of data standards. A full 'data management plan' (DMP) as a distinct deliverable must be delivered within the first 6

months of the project. The DMP needs to be kept up to date with the needs of the project and as such be updated as necessary during its lifetime.¹⁷⁸

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.¹⁷⁹, and updated during the project lifetime and could include identification of:

- Different types of exploitable results;
- Potential end-users of the results;
- Results that may need sustainability and proposed sustainability roadmap solutions.

Sufficient resources need to be foreseen for activities related to dissemination and exploitation, including the plan for the sustainability of the project results. This may involve engaging with suitable biological and medical sciences research infrastructures (RIs).¹⁸⁰

Communication

The proposed communication measures for promoting the project and its findings during the period of the grant must also be described and could include a possible public event to showcase the results of the project.

¹⁷⁸ 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

¹⁷⁹ As an additional dissemination obligation under Article 29.1 of the [IMI2 Grant Agreement](#) will apply.

¹⁸⁰ <http://www.corbel-project.eu/about-corbel/research-infrastructures.html>

Topic 4: Optimal treatment for patients with solid tumours in Europe through Artificial Intelligence

Topic details

Topic code	IMI2-2020-23-04
Action type	Research and Innovation Action (RIA)
Submission and evaluation process	2 stages
IMI2 Strategic Research Agenda - Axis of Research	Adoption of innovative clinical trial paradigms
IMI2 Strategic Research Agenda - Health Priority	Cancer

Specific challenges to be addressed by public-private collaborative research

Demands of cancer care in Europe continue to increase significantly, with the number of incident cancer cases in Europe projected to increase by 14.1% by 2030¹⁸¹. This leads to a growing demand for innovative cancer treatments among patients, payers, physicians, and society. At the same time, the understanding of the complex biology of cancer is growing, and as a result, pharmaceutical companies are developing a multitude of new therapeutic agents. These include, but are not limited to, novel kinase inhibitors, immunotherapy combinations, and cell therapies.

This trend for new, effective therapies creates more treatment options for patients. However, it confronts physicians with an increasingly expanding number of potential therapeutic options, which each need to be understood and adopted effectively. Numerous factors such as genetic analysis, specific tumour biology, and biomarkers have a growing influence on clinical decision-making. To become familiar with the huge volume of available information, physicians need to learn continuously about medical guideline changes and marketed treatments. In conclusion, future decision-making processes will become ever-more complex, with the potential outcome of sub-optimal or even incorrect treatment choices being made. Furthermore, some patients have disease characteristics for which evidence of guideline recommendations is scarce and physicians lack information about real-world treatment outcomes. Hence, the challenges to be addressed are assisted guideline-based decision-making and the discovery of knowledge about treatment outcomes in real-world settings. As the latter challenge requires analysis of large data sets, the application of Artificial Intelligence (AI) will be a key technology.

To ensure the challenges can be properly addressed, and ensure the innovations reach the physicians and patients, a public-private partnership is necessary, including the following actors:

- **patient organisations and regulatory authorities** to specify the requirements and boundaries of AI-driven data processing, data security and privacy as well as individual data ownership
- **medical societies** to provide the network of participating in- and out-patient clinics to enable data access
- **medical experts/institutions** to specify AI approaches, validate the decision support and set the requirements for general acceptance
- **life-science companies** to contribute study data for the evaluation of therapeutic approaches, as well as expertise in data mining and data-set merging
- **SMEs** for infrastructure set-up, data management and data security, AI-driven data processing and merging of unstructured information, visualisation and user experience design.

¹⁸¹ <https://gco.iarc.fr/tomorrow/home>

Scope

The scope of this call topic is to establish guideline-based decision support and platform solutions to generate knowledge discovery for breast, lung and prostate cancer with applicability to other indications, in several European (EU member states and H2020 associated countries) 'model' regions. The model regions serve as platforms to show general feasibility of the decision-support tool and lay the foundation for further expansion to other European regions. The results obtained from these model regions are expected to be of relevance to countries with different socioeconomic backgrounds. The funded action will focus only on breast, lung and prostate cancer. These indications show a high number of cases per year, a high, unmet medical need, multiple available therapeutic options and a fast-evolving treatment environment. Expansion to other indications is not part of the funded action but a proposed solution should allow for expansion afterwards. The three core objectives of this call topic are as follows:

Objective 1: Establish a guideline-based decision support for prioritised indications

Development of a decision-support tool that automatically extracts relevant clinical information from electronic health records (EHRs) and facilitates guideline-compliant treatment approaches for the defined solid tumours.

Objective 2: Establish a structured and interoperable data platform to unlock real-world-data potential in an oncology network

A major requirement for the provision of patient-specific treatment is the availability and the harmonisation of extensive patient data across in-patient (e.g. academic centres, teaching hospitals) and out-patient (community and private practices) settings - stored in a structured format, ready to be used and interoperable. The successful consortium should address this need by involving relevant and available regional/national networks of in-/out-patient clinics providing access to their data, for instance with the inclusion of medical societies.

Easy-to-use new platforms that enable the gathering and granular storage of clinical data to offer a foundation for data analysis and knowledge discovery need to be established. The real-world data platforms should include prospective data from electronic health records, structured data from (non)interventional studies provided by members of the pre-identified industry consortium as well as potentially registry data.

Objective 3: Leverage the real-world-data gathered by the action to establish an AI-knowledge base and support treatment decisions for prioritized indications

The funded action will develop a disease-specific (breast, lung and prostate cancer) AI system that facilitates the discovery of novel medical knowledge. This includes hypothesis generation about optimal treatment sequences for patients and prognostic features that can be validated in clinical research. The output will strongly support building the European health data space and improve the quality and acceptance of AI-generated evidence in decision making in research and healthcare delivery. It will also set the foundation for explainable AI approaches necessary for personalised treatment.

During the funded action, members of the industry consortium plan to contribute scientifically relevant pre-existing data and/or data from prospective studies including activities for generating such data that are part of broader industry clinical studies and making such data fit for purpose.

Expected key deliverables

In order to address the call topic challenges, the selected action must ensure that current medical knowledge is quickly translated into clinical practice. It must deal with patients who do not fully match the reasoning paths of guidelines due to certain characteristics for which evidence is limited. Finally, it must be able to decipher how current treatment approaches affect patient outcomes in the real world.

The collaborative public-private consortium is expected to address these challenges in a three-step process. First, a guideline-based decision-making tool that automatically extracts and validates relevant clinical information from EHRs needs to be developed. Second, a database for real-world treatment outcomes needs to be created. Third, AI-technology is to be applied to analyse the data and facilitate novel knowledge discovery.

Overarching considerations:

- Ensure adherence to existing regulatory guidelines and (e.g. GDPR, Convention on Human Rights and Biomedicine (Oviedo Convention), WMA Declaration of Helsinki: Ethical Principles for Medical Research Involving Human Subjects, WMA Declaration of Taipei on Ethical Considerations regarding Health Databases and Biobanks);
- Patient informed consent for data collection and data sharing;
- Real-world data must be provided from identified countries having access to cancer treatments suggested by treatment guidelines;
- A business model for a platform that is 'sustainable by design' for public health applicability;
- Provision of a detailed concept for its sustainability, maintenance and commercialisation;
- Present concepts and strategies about how their respective proposals will have an impact on competitiveness and industrial leadership of Europe in a sustainable way, e.g. via SME engagement.

A guideline-based decision-support tool:

- Develop a decision model based on national and/or international clinical guidelines for the three indications; breast, lung and prostate cancer;
- Implement the decision model and integrate into existing IT infrastructures;
- Establish methods to acquire and process decision-relevant clinical information automatically from EHRs;
- Include mechanisms to quickly adapt guideline changes or updates, and scale to incorporate guidelines from additional countries after the project ends.

Data platform:

- Integration of multi-language user frontends;
- Implementation of secure and interoperable cloud-based data storage;
- Integration into existing clinical IT infrastructures across various geographies to address socioeconomic barriers and IT infrastructure differences;
- Integration of system mechanics that address individual data ownership and transferable data access and usage permissions via extended rights;
- Consideration of different viewpoints on the data based on the stakeholder group:
 - Physicians; a transparent decision-support and intuitive result visualisations;
 - Patients; data ownership and permission management;
 - Patient organisations patient-centric viewpoints;
 - SMEs; programming interfaces.
- Relevant data sources can be derived from electronic health records, (non)Interventional study data or registry data and may include, for example:
 - Patient demographics;
 - Lab panel;
 - Pathological cancer classification;
 - Genomic data;
 - Treatment sequences;
 - Radiology and nuclear medicine reports.
- Documentation of outcomes data like progression-free survival, overall survival, quality of life and adverse events;
- A description of how generated data will be shared with other institutions to further evaluate the generated results and enable transnational comparison throughout the different healthcare systems;

- Applicants are allowed to bring in an existing platform that is then tailored to the needs of the project.

Deliverables of the AI-supported knowledge discovery:

- Healthcare providers should be able to monitor the impact of the solutions regarding personalised medical treatment as well as the associated cost and outcome;
- Integration of verified knowledge (e.g. outcomes data such as progression-free survival, overall survival, quality of life and adverse events) into the indication-specific knowledge base;
- Process of knowledge discovery needs to be guided by a scientific review committee;
- Consortium members and third parties must be able to request data analyses after approval of the scientific review committee;
- Integration of simulation features based on the knowledge base, e.g. to simulate therapy response, side-effects, quality of life or other outcome-related factors based on prediction modelling on top of the retrospective case data.

Expected impact

In their proposals, applicants should describe how the outputs of the project will contribute to the following impacts and include wherever possible baseline, targets and metrics to measure impact.

- An explainable AI-based knowledge discovery platform should enable the development of data-driven solutions with the goal to sustainably improve oncologic treatments throughout the EU and beyond;
- The results obtained from these model regions are expected to be of relevance to countries with different socioeconomic backgrounds;
- The platform should allow oncologists to save valuable time due to the automatic data gathering and facilitated guideline-based assessment;
- In addition, physician-patient communication and shared decision making should be supported which might improve proactive therapy involvement to accomplish increases in individual quality of life as well as overall patient satisfaction;
- The platform may also allow research questions from various stakeholders to be answered through data analysis and data pooling as well as data extraction. Besides overall survival, this could include real-world quality of life (QoL) and safety evaluations of new therapies as well as novel combinations under real world conditions. This can potentially contribute to value-based healthcare assessments at EU level;
- The solutions provided by a public-private consortium will significantly benefit European society: patients receive optimal personalised treatment; physicians are supported in complex decision-making processes; and payers as well as pharmaceutical companies receive information about real world treatment outcomes as a foundation for value-based healthcare approaches;
- The topic is well aligned with the EU Commission's strategy to develop a European Health Data Space and Europe's Beating Cancer Plan.

In their proposals, applicants should outline how the project plans to leverage the public-private partnership model to maximise impact on innovation, research & development, as well as regulatory, clinical and healthcare practices, where relevant. This could include a strategy for engagement with patients, healthcare professional associations, healthcare providers, regulators, Health Technology Assessment (HTA) agencies, payers etc., where relevant.

In addition, applicants should describe how the project will impact the competitiveness and growth of companies including SMEs.

In their proposals, applicants should outline how the project will:

- Manage research data including use of data standards¹⁸²;

¹⁸² 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 Infrastructures¹⁸³;
- Communicate the project activities to relevant target audiences.

Potential synergies with existing consortia

Synergies and complementarities should be considered with relevant national, European and non-European initiatives (including suitable biological and medical sciences research infrastructures) in order to incorporate past achievements, available data and lessons learnt where possible, thus avoiding unnecessary overlap, and duplication of efforts and funding.

Industry consortium

The industry consortium is composed of the following EFPIA partners:

- Pfizer (lead)
- Abbvie
- Amgen
- Bayer
- Roche

The industry consortium plan to contribute the following expertise and assets:

- Personnel with expertise in oncology solid tumours, AI algorithm implementation, real-world data;
- Real-world data from (non)interventional studies supplementing the public partner cohorts. Relevant data may include, for example, outcome results like progression-free survival, overall survival, quality of life and adverse events as well as patient demographics and treatment sequences.

Indicative duration of the action

The indicative duration of the action is 60 months.

This duration is indicative only. At stage 2, the consortium selected at stage 1 and the predefined industry consortium may jointly agree on a different duration when submitting the stage 2 proposal.

Indicative budget

The financial contribution from IMI2 JU is a maximum of EUR 10 460 000.

The indicative in-kind contribution from EFPIA partners is EUR 11 400 000.

The EFPIA contribution includes EUR 3 500 000 financial contribution. The allocation of this financial contribution will be decided by the full consortium at stage 2 when preparing the full proposal.

Due to the global nature of the participating industry partners and IMI2 JU Associated Partners, it is anticipated that some elements of the contributions will be non-EU/H2020 Associated Countries in-kind contributions.

¹⁸³ <http://www.corbel-project.eu/about-corbel/research-infrastructures.html>

Expertise and resources expected from applicants at stage 1

The stage 1 applicant consortium is expected, in the submitted short proposal, to address all the objectives and key deliverables of the topic, taking into account the expected contribution from the industry consortium which will join at stage 2 to form the full consortium.

The stage 1 submitted short proposals should include suggestions for creating a full proposal architecture which could be in line with the suggested architecture described below, though this architecture is only a suggestion.

This may require mobilising, as appropriate the following expertise:

- Expertise in medical oncology with a special focus on the three prioritised indications: breast, lung and prostate cancer;
- Expertise from patient organisations as well as regulatory expertise to address data security and privacy as well as individual data ownership and AI-driven data processing;
- Large-scale medical data management and processing expertise to ensure proper data modelling according to current technical and infrastructural standards;
- Expertise in interoperable IT system design e.g. implementing Health Level 7 Fast Healthcare Interoperability Resources (HL7 FHIR);
- Expertise in technical interface development regarding current clinical technologies and systems such as EHR, Picture Archiving and Communication Systems (PACS) or Laboratory Information Management Systems (LIMS);
- Advanced database and transfer security, client- and server-side encryption (E2E), system threat modelling and prevention;
- User experience design and accessibility considering the broad spectrum of potential users;
- Application development for different server- and client-side systems (e.g. web applications and mobile operating systems);
- Big data analysis;
- Strategies to deal with unstructured data;
- Strategies for handling unfavourable data sets (e.g. incomplete or missing data);
- Methodologies of proper semantic and contextual modelling of patient and disease characteristics;
- Unification, pre-processing, and validation of multimodal clinical data sources.

The size of the consortium should be proportionate to the objectives of the topic while ensuring its manageability.

Furthermore, at stage 1, the applicant consortium should also provide a strategy for allocating the amount of EFPIA Financial contribution – mentioned under indicative budget. The allocation will be decided by the full consortium at stage 2 when preparing the full proposal.

It may also require mobilising, as appropriate, the following resources:

Considering the development of AI-supported data analysis and knowledge modelling, applicants will need to provide extended competences regarding:

- Network of clinics (in- and/or out-patient) with access to patient level electronic health records.

Considerations for the outline of project work plan

In their stage 1 proposals applicants should:

- Give due visibility on data management, dissemination, exploitation and sustainability, and communication activities. This should include the allocation of enough resources for these tasks which will be further developed in stage 2 proposal;

- Consider including a strategy for ensuring the translation of the projects results to drug development, regulatory/ Health Technology Assessment (HTA) settings (e.g. through scientific advice / qualification advice / opinion, etc.), clinical and healthcare practices, and/or decision-making processes.

Suggested architecture

The project challenges are summarized in Figure 1.

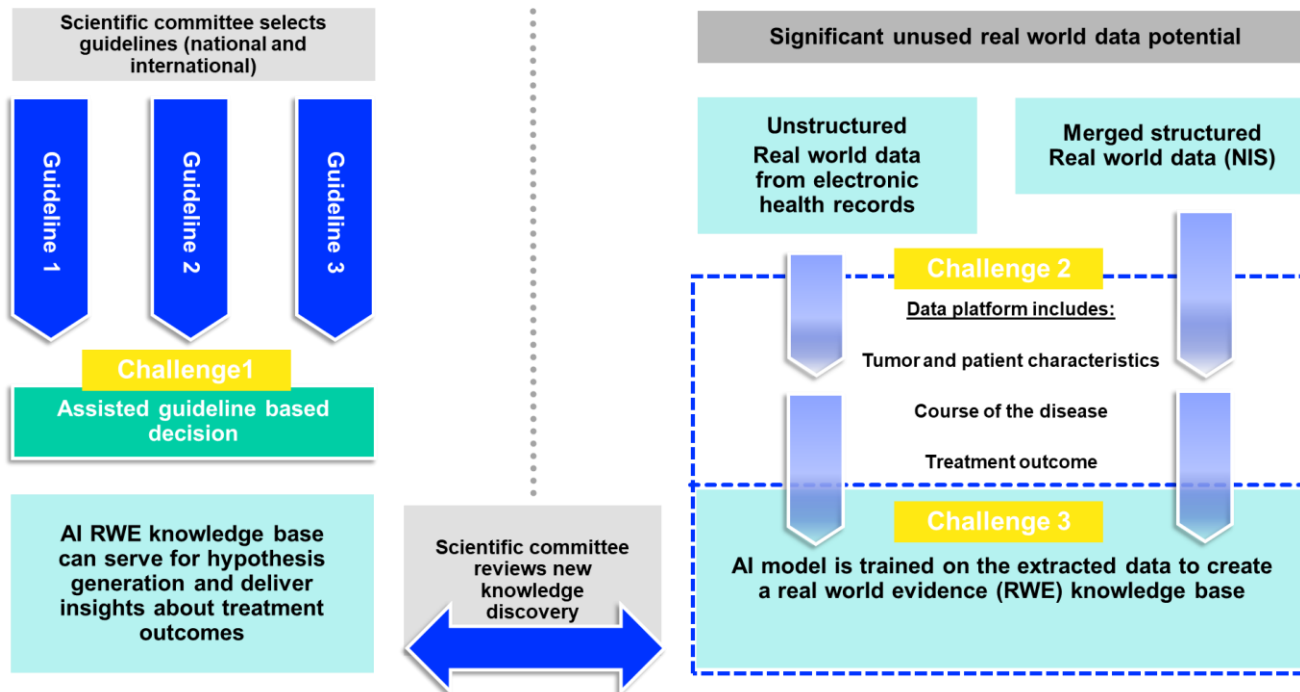


Figure 2 – Overview of project challenges.

Work package 1 – Project management

The goals of this work package are to:

- Ensure alignment between the beneficiaries as well as smooth internal and external communication;
- Monitor compliance with the work plan;
- Monitor planned resources and time schedule;
- Coordinate fulfilment of all administrative milestones;
- Ensure legal and data privacy requirements are met during the project lifetime.

The expected applicant consortium contribution should include project management, ensuring the implementation of the coordinating tasks and running the day-to-day operation, such as project tracking and reporting, meetings, internal communication, website creation, budget management, etc.

Work package 2 – Informed consent, general requirement analysis, governance, and regulation

The goals of this work package are to:

- Obtain patient informed consent;
- Technical and medical requirement analyses to specify the clinical need and required technical infrastructure;
- Design of governance principles for both data platform and AI component including legal structures in participating countries and sites;

- Definition of ethical principles towards the application of AI in a medical context;
- Conceptualisation of long-term operation and monetisation strategies;
- Requirements for data privacy adherence (e.g. GDPR).

Work package 3 – Guideline-based decision support tool

The goals of this work package are:

- Identification of relevant treatment guidelines for the targeted indications by a scientific committee;
- Development of model-based representations of those guidelines;
- Allowing instantiation of the decision models with real-world patient data;
- Integration of automatic reasoning methods for the individual patient case;
- Integration of an automatic or assisted evaluation pipeline for model updates and adjustments.

Work package 4 – Platform technical and infrastructural requirement analysis

The goals of this work package are:

- Specification of the technical platform infrastructure;
- Consideration of necessary tools for data analysis and knowledge discovery;
- Specification of all necessary technical interfaces;
- Evaluation of data storage and management strategies;
- Establishment of a resource plan including strategies for resource scaling;
- Development of a data and operations security framework.

Work package 5 – Platform implementation and evaluation

The goals of this work package are:

- Generation of user personas based on the relevant platform stakeholders;
- Integration of data analysis tools or integration of compatibility features for external applications;
- Development of automated testing and deployment pipelines;
- Conduction of a user study to evaluate visual and functional platform components accordingly to the generated personas;
- Platform and interface documentation for users and third-party developers.

Work package 6 – (Non)interventional study data and real-world data gathering, preparation and integration

The goals of this work package are:

- Aggregation and evaluation of available study data sources;
- Consideration of all legal and ethical aspects relating to the data sets;
- Assessment of gathered data pools regarding quality and impact of the contained data;
- Quality assurance in terms of data preparation;
- Establishment of a processing pipeline for unstructured entities;
- Strategies to deal with inconsistent or missing information.

Work package 7 – Artificial Intelligence knowledge base implementation

The goals of this work package are:

- Development of a suitable knowledge representation scheme;

- Development of pre-processing features for data integration (e.g. validation);
- Integration of explainability and traceability mechanisms that allow for linking individual discoveries to the respective evidence and its derivation;
- Integration of system-assisted validation features for a committee of experts (e.g. peer-review) that verifies individual findings before knowledge base integration.

Work package 8 – Dissemination and communication

Work package 9 – Exploitation and sustainability of the results

Additional considerations to be taken into account at the stage 2 full proposal

At stage 2, the consortium selected at stage 1 and the predefined industry consortium jointly submit the full proposal developed in partnership. The full proposal is based upon the selected short proposal at stage 1.

In the spirit of the partnership, and to reflect how IMI2 JU call topics are built on identified scientific priorities agreed together with EFPIA beneficiaries/large industrial beneficiaries, these beneficiaries intend to significantly contribute to the programme and project leadership as well as project financial management. The final architecture of the full proposal will be defined by the participants in compliance with the IMI2 JU rules and with a view to the achievement of the project objectives. The allocation of a leading role within the consortium will be discussed in the course of the drafting of the full proposal to be submitted at stage 2. To facilitate the formation of the final consortium, until the roles are formally appointed through the consortium agreement, the proposed project leader from among EFPIA beneficiaries/large industrial beneficiaries shall facilitate an efficient negotiation of project content and required agreements. All beneficiaries are encouraged to discuss the project architecture and governance and the weighting of responsibilities and priorities therein.

Data Management

In their stage 2 proposal, applicants should give due visibility to data management including use of data standards. A full 'data management plan' (DMP) as a distinct deliverable must be delivered within the first 6 months of the project. The DMP needs to be kept up to date with the needs of the project and as such be **updated as necessary during its lifetime**.¹⁸⁴

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 project¹⁸⁵, 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).¹⁸⁶

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.

¹⁸⁴ 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

¹⁸⁵ As an additional dissemination obligation under Article 29.1 of the [IMI2 Grant Agreement](#) will apply.

¹⁸⁶ <http://www.corbel-project.eu/about-corbel/research-infrastructures.html>

Topic 5: Shortening the path to rare disease diagnosis by using newborn genetic screening and digital technologies

Topic details

Topic code	IMI2-2020-23-05
Action type	Research and Innovation Action (RIA)
Submission and evaluation process	2 stages
IMI2 Strategic Research Agenda - Axis of Research	Innovative medicines
IMI2 Strategic Research Agenda - Health Priority	Rare/orphan diseases

Specific challenges to be addressed by public-private collaborative research

Unmet medical need:

Approximately 5,000-8,000 distinct rare diseases (RD) affect 6-8% of the EU population i.e. between 27 and 36 million people¹⁸⁷; 263-446 million people are affected globally [1]. Considerable public funding has been invested in research for rare diseases for more than 12 years, with a significant share coming from the EU framework programmes¹⁸⁸. However, despite scientific advances, in Europe, the fact remains that fewer than 10% of RD patients receive treatment and only 1% are managed using an approved treatment¹⁸⁹. Delivering effective treatments to RD patients where the prevalence is low has been described as one of the major global health challenges of the 21st century. There is a need for a strategic approach to address some of the major challenges faced by the RD Community, endorsed by IMI2 JU.

Challenges:

Even though RDs span a plethora of multisystemic syndromes, involving virtually every single organ or physiological function, most RD patients face common problems. These major hurdles can be summarised as delayed diagnosis, lack of R&D, and lack of access to or reimbursement of innovative medicines¹⁹⁰.

One of the main challenges for RDs is related to diagnosis because RDs are characterised by a broad diversity of syndromic disorders and symptoms that vary from disease to disease and from patient to patient suffering from the same disease. In isolation, these symptoms can be very common, leading to misdiagnosis. Altogether, this leads to a lengthy and burdensome path to diagnosis that can take, on average, take eight years¹⁹¹, often involving pointless treatments, creating a heavy human and societal burden that could be avoided by earlier diagnosis.

Benefit to Public Health:

Early detection of rare genetic diseases would enable early intervention (when available), follow-up, and genetic counselling (such as family planning). This would result in improved clinical and patient oriented outcomes. Overall, this project will increase public understanding around RDs, and therefore foster rare disease R&D. A better understanding of rare diseases would also potentially lead to better rare disease policies, as well as reduced healthcare inefficiencies & disparities.

¹⁸⁷ https://ec.europa.eu/health/non_communicable_diseases/rare_diseases_en

¹⁸⁸ https://ec.europa.eu/health/ern_en

¹⁸⁹ <https://www.eurordis.org/about-rare-diseases>

¹⁹⁰ https://www.eurordis.org/sites/default/files/publications/Fact_Sheet_RD.pdf

¹⁹¹ <http://download2.eurordis.org.s3.amazonaws.com/documents/pdf/Undiagnosed-International-Joint-Recommendations.pdf>

Public Funding:

Strategic collaboration with public partners is required as this programme is central at the cusp of public health policy. To address the challenges and undertake a project of such a transformational nature, an active partnership from a range of contributors across the public and private sectors is necessary. A project of this nature and scope requires a synergistic effort across academia, industry partners and other relevant stakeholders, in order to potentially positively impact the lives of up to 30 million RD patients in the EU and their families. As mentioned above, RDs are diverse and complex, which calls for a vast and diverse group of collaborators to leverage the required spectrum of knowledge, expertise, and network, as detailed in the section entitled "Expertise and resources expected from applicants at stage 1". Positive results will lead the consortium to make recommendations with regards to wider government run programme(s). Perspectives from Public Partners will ensure that proposed solutions are fit-for-purpose, and truly value-added for all stakeholders. The establishment of a public-private partnership offers a unique mechanism for all parties to engage in delivering the range of input and expertise necessary for achieving the project aims and ensuring that a practical and long-term sustainable plan follows this action.

Scope

It has been recently estimated that between 3.5 to 5.9 % of the general population has a RD (excluding rare cancers) and 72% of those RDs have an identified genetic origin [1]. Therefore, RD genetic screening might yield significant results. In addition, 70% of those RD patients are children [1], which points towards newborn screening¹⁹². In 2003, the cost of sequencing a human genome was a billion dollars. Today, it is under a thousand dollars and falling. With the advent of gene / genome sequencing, along with the ever-increasing availability of digital tools enhancing ways to collect, store, process and interpret massive amounts of data ("big data"), there is an unprecedented opportunity to transform the landscape of RD diagnosis as it is today.

In order to address the RD conundrum, the overall objective of this call topic is to shorten the path to RD diagnosis by using newborn / paediatric (infants during their first weeks of life) genetic screening; and, via application of advanced digital technologies that enable rare disease diagnosis / identification. The latter might require consolidation of existing fragmented efforts.

The specific objectives are:

1. Assessment and development of a comprehensive, strategic overview of existing converging RD resources e.g. databases, registries (such as the EU RD platform¹⁹³), natural history projects, platforms, reference networks, rare disease academic centers of excellence (e.g. European Reference Networks (ERNs)¹⁹⁴), and initiatives for evaluation / identification of potential collaboration and synergies;
2. Federation of available RD databases into a RD metadata repository amenable to machine learning or other advanced digital tools;
3. Co-creating a sustainable strategy for newborn genetic screening and pilot it. This could start directly after achieving objective 1;
4. Based on the output of objectives 1 & 2:
 - a) Repurposing of pre-existing diagnosis AI algorithm to identify early onset RD patients in electronic health records (EHRs). This will include at least 3 pilots in better-known rare diseases (with the understanding that solutions and algorithms developed or adapted should be amenable or made amenable to be emulated for larger sets of better-known RDs) where more robust data is available to train and test the AI algorithm(s), and / or;
 - b) Design and development of new AI algorithm(s) to achieve the above goal.
5. Based on insights generated by objectives 1, 2 & 4, either repurposing or development of a broad AI RD diagnosis "symptom checker" to help undiagnosed RD patients going from one health care provider (HCP)

¹⁹² <https://www.eurordis.org/sites/default/files/publications/fact-sheet-new-born-screening.pdf>

¹⁹³ <https://eu-rd-platform.jrc.ec.europa.eu/en>

¹⁹⁴ https://ec.europa.eu/health/ern_en

to another. In addition, exploration of further viable options to implement the symptom checker in actionable solutions for HCPs and patients.

Expected key deliverables

The consortium would have the following role:

- Responsible for making it possible to interconnect all the different sources of data;
- Curate data to make it interoperable and reusable; the applicants should follow the data standards developed by the European Joint Programme on Rare Diseases (EJP RD)¹⁹⁵ and the EU RD platform for research and registries data, as well as use European Patient Identifiers (EUPID) to track the diagnosis history and involvement in clinical studies;
- Ensure the algorithms are compliant with existing/emergent governance and validation policies;
- Ensure the algorithms are compliant with the Guidelines for Trustworthy Artificial Intelligence adopted by the High-Level Expert Group on AI¹⁹⁶
- Make the algorithms available to the hospitals to run on their existing systems and, at the same time, use the data generated by the algorithms to improve diagnosis (through prediction and identification of potential new diagnostic/predictive/monitoring biomarkers).

The key deliverables are as follows:

- 1. Addressing objective 1:** All listed deliverables are required in order to perform the subsequent “steps”, must include GDPR / data ethics considerations, and follow FAIR principles:
 - Comprehensive landscape analysis of ongoing relevant initiatives and pre-existing resources with strategic recommendations about potential for collaboration. This includes a Cochrane systemic literature review, or equivalent;
 - Landscape analysis of relevant available data sources with analysis of usability readiness (data integrity, validity, re-consenting requirements, etc.) within the timeframe and budget scope of this project;
 - Definition of a pre-competitive business model to access rare disease data to purchase, license, or negotiate data sharing agreements. The consortium should be able to either bring the data or ensure access to data in a sustainable way with a long-term plan. For the data, as for all background brought into the project, access rights (according to IMI2 JU’s intellectual property (IP) policy¹⁹⁷) should be respected during and after the project (access rights of other beneficiaries and of third parties);
 - Analysis of regulatory, ethics and data privacy dimension requirements with strategic recommendations for subsequent work packages.
- 2. Addressing objective 2:**
 - Federating of available RD databases into a RD metadata repository amenable to machine learning or other advanced digital tools;
 - Co-creating new or identify available pre-existing optimal AI approach / platforms (considering access rights etc.), able to identify early-onset rare disease patients. Access rights should be considered not only during but also after the project, as per IMI2 JU IP policy;
 - Integration of platforms with de-identified data and control of access rights for each data point to improve the use of big data analytics by several partners;
 - Ensuring platform interoperability: readiness to integrate and aggregate new data from different sources or operate with other platforms, e.g. patient-reported outcomes or biobank databases;
 - Ensuring adoptability and acceptance of such tools from the public, regulators and HCPs by engaging in dialogue with relevant stakeholders.

¹⁹⁵ <https://www.ejprarediseases.org/>

¹⁹⁶ <https://ec.europa.eu/digital-single-market/en/news/ethics-guidelines-trustworthy-ai>

¹⁹⁷ <https://www.imi.europa.eu/apply-funding/general-overview/intellectual-property>

3. Addressing objective 3:

- RD gene panel for the purpose of newborn screening (NBS): List of criteria for inclusion / exclusion in the panel (scientific, technical, sustainable, and ethical) aligned with the overarching goals of action;
- Fully developed RD genetic NBS protocol (and / or kit), tested and validated, with post-diagnosis planning recommendations (genetic counselling, referral, etc.);
- As a complementary approach, development of a whole exome sequencing (WES) implementation protocol (with criteria) for infants (up to 1-2 months old) with unexplained symptoms, including all considerations mentioned in the deliverables above. These two sequential approaches should be strategically mapped for feasibility and acceptability, according to the opinions of all stakeholders, but also on a case-by-case basis, driven by family decision (both approaches in b and c should be developed);
- Post-pilot metrics and data on feasibility, health economics, scalability, improved outcomes for patients; benefits to patients & families. This will contribute to the input that feeds into health policy and ethics discussions.

4. Addressing objective 4:

- Repurposing and / or development of digital diagnosis algorithms trained on the RD metadata repository to be used in electronic health records to continuously screen for patients with early signs of better-known RDs and facilitate referral for genetic testing or further testing;
- This algorithm should be tested; based on this pilot, recommendations should be formulated for public health authorities.

5. Addressing objective 5:

- Review and analysis of options for a potential artificial intelligence phenotypic recognition tool (digital “clinical symptom checker” support tool) trained on the federated RD database to help RD patients cycling through HCPs. The intent is that the tool(s) will be publicly available afterwards, open source, with the associated HCP training curriculum. The tool should be designed in such a way that it would be used by both HCPs and patients;
- In addition, generation of a strategic report regarding potential further viable options to implement the symptom checker in actionable solutions for HCPs and patients. This could include mapping further potential functionalities within the symptom checker and / or other avenues to leverage the symptom checker capabilities.

6. Overall output:

- Publication plan, data dissemination and communication plan, recommendations to public health governing bodies, multi-stakeholder engagement strategy that includes the EMA, FDA and other regulatory bodies.

Expected impact

In their proposals, applicants should describe how the outputs of the project will contribute to the following impacts and include, wherever possible, baseline, targets and metrics to measure impact.

The Rare Disease conundrum:

Despite the recent rise in RD research and development, most RDs remain under-studied, and therefore under-treated / cared for. This can be attributed for the most part to:

- Patients are not identified / diagnosed;
- Lack of epidemiological data;
- No natural history of disease data;
- No validated endpoint / patient-reported-outcomes (PROs);
- Patient are rare, experts are even rarer.

This has the pernicious additional effect of blunting interest in diagnosis / screening initiatives, as it would lead to patients being diagnosed with no concrete medical or clinical option. This poses an ethical challenge, which unfortunately feeds the conundrum. This has been identified as a major problem for the rare disease community.

This Call topic anticipates the following benefits:

- For patients:
 - Decreased time to the right diagnosis;
 - Improved patient journey;
 - Better healthcare;
 - Increased quality of life;
 - Decreased irreversible organ damage;
 - Access to their own healthcare data.
- For healthcare
 - Implementation of digital transformation in healthcare;
 - Paradigm change in rare disease diagnosis;
 - Improved diagnostic tools;
 - Improved understanding of disease;
 - Higher accuracy in clinical decisions;
 - Better care delivery;
 - Integrated care among different specialties.
- For research
 - Advances in utilisation of digital technologies;
 - Increased disease knowledge for future research;
 - Improved data availability for future research.
- For society
 - Decreased burden for family and carers;
 - Increased trust in the healthcare system;
 - Better use of data for public health;
 - Improved value-based healthcare.

In their proposals, applicants should outline how the project plans to leverage the public-private partnership model to maximise impact on innovation, research & development; regulatory, clinical and healthcare practices, as relevant. This could include a strategy for engagement with patients, healthcare professional associations, healthcare providers, regulators, health technology assessment (HTA) agencies, payers etc., where relevant.

In addition, applicants should describe how the project will impact the competitiveness and growth of companies including SMEs.

In their proposals, applicants should outline how the project will:

- Manage research data including use of data standards¹⁹⁸ and, to the extent relevant, the data standards developed by the European Joint Programme on Rare diseases¹⁹⁹ (EJP RD) and the EU RD platform for research and registries data respectively, as well as the use of EUPID;
- Disseminate, exploit, and sustain the project results. This may involve engaging with suitable biological and medical sciences research infrastructures;²⁰⁰
- Communicate the project activities to relevant target audiences.

Potential synergies with existing consortia

Synergies and complementarities should be considered with relevant national, European and non-European initiatives (including suitable biological and medical sciences research infrastructures) in order to incorporate past achievements, available data and lessons learnt where possible, thus avoiding unnecessary overlap, and duplication of efforts and funding.

Industry consortium

The industry consortium is composed of the following EFPIA partners:

- Pfizer (lead)
- Illumina
- Lysogene
- Novartis / Avexis
- Novo Nordisk
- ProQR
- Roche
- Sanofi
- Takeda

The industry consortium plans to contribute the following expertise and assets:

- Project leadership and programme oversight, genetic research, medical affairs, data science / analytics & AI, epidemiology, regulatory, public relations / policy, commercial innovation;
- Scientific affairs, innovation, PPP management support, medical affairs, public affairs;
- Genetic diseases / digital medical innovation, newborn screening, diagnostics, personalised medicine / healthcare, public policy, immunodeficiency

One of the foreseeable rate-limiting factors for the success of this project is the availability of robust disease natural history data, of high enough quality that it can be used for machine learning (training data sets). Therefore, during the funded action, members of the industry consortium plan to contribute scientifically relevant activities for generating data in prospective activities that are part of broader industry clinical studies. Namely, data provided by members of the industry consortium will include (but will not be limited to) rare disease clinical trial data. This data will be either control data (such a placebo) or baseline data. For the purpose of this project, such data will serve as “natural history data”, to be used for machine learning covered by objectives 2, 4, and 5.

The relevant activities will be included in the project’s Description of the Action and are necessary for achieving its objectives. The introduction of the data constitutes an in-kind contribution which entails access

¹⁹⁸ 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

¹⁹⁹ <https://www.ejprarediseases.org/>

²⁰⁰ <http://www.corbel-project.eu/about-corbel/research-infrastructures.html>

rights to these project results in line with IMI2 JU intellectual property (IP) rules. The estimated in-kind contribution for the prospective activities to generate these data and samples is EUR 3 500 000.

Indicative duration of the action

The indicative duration of the action is 60 months.

This duration is indicative only. At stage 2, the consortium selected at stage 1 and the predefined industry consortium may jointly agree on a different duration when submitting the stage 2 proposal.

Indicative budget

The financial contribution from IMI2 JU is a maximum of EUR 11 940 000.

The indicative in-kind contribution from EFPIA partners is EUR 12 600 000.

The EFPIA contribution includes EUR 1 000 000 financial contribution; the allocation of this financial contribution will be decided by the full consortium at stage 2 when preparing the full proposal.

Due to the global nature of the participating industry partners it is anticipated that some elements of the contributions will be non-EU/H2020 Associated Countries in-kind contributions.

Expertise and resources expected from applicants at stage 1

The stage 1 applicant consortium is expected, in the submitted short proposal, to address all the objectives and key deliverables of the topic, taking into account the expected contribution from the industry consortium which will join at stage 2 to form the full consortium.

The stage 1 submitted short proposals should include suggestions for creating a full proposal architecture, which could be in line with the suggested architecture described below, though this architecture is only a suggestion.

This may require mobilising, as appropriate the following expertise:

The consortium should include (but not limited to) the following key stakeholders:

- Patient Organization, Academia, SMEs, Public Health Decision Makers, Regulators.

The consortium should mobilise the following expertise:

- In order to achieve objective 1 and to deliver associated deliverables, the consortium should have the required expertise and capabilities to networking with EU, local Healthcare & Data Protection Regulators. Expertise will be needed in the fields of regulatory affairs, policy and politics, health economics, HTA / pharmaco-economy, regulatory sciences, legal / IP / licensing, rare disease expertise, international rare disease Patient Advocacy, patient journey, Innovation, public health, expertise in high & low-income EU health systems, public health systems Implementation.
- In order to attain goals described for objective 2, 4 & 5 and to deliver associated deliverables, the consortium should have the required following expertise and capabilities: Data Exchange & Building Digital Infrastructure, User experience, Data security and Data Anonymisation, Methodology development, Data Management, Data Science, Data standards, Data translation, Pharmaco-epidemiology, Biostatistics, Bioinformatics, Software Engineering, Data stewardship, Business and governance model development (Including sustainability), Medical, Legal General Data Protection Regulation (GDPR) Compliance, Data ethics, Privacy, Medical Insurance, Medical Training, Data Quality assurance, IT, Cyber security, Federated data
- In order to attain goals described for objective 3 and to deliver associated deliverables, the consortium should have the required following expertise and capabilities: Genetics, Genomics, Molecular Biology, Whole Exome and Whole genome Sequencing (WES / WGS), Gene panel, In silico panel, Bioethics, Genetic Counseling;

- In addition, the following general expertise / capabilities will be required: Project Management, Study / Trial Operation Manager, Medical / Scientific Writing, Communications, Public Outreach.

It may also require mobilising, as appropriate, the following resources:

- Ideally, the consortium should welcome the participation of partners who could and would be willing to contribute RD phenotypic data that could be integrated in the meta-data repository that would train the AI algorithm(s), as well as partners able to contribute pre-developed rare disease recognition algorithm(s).

Considerations for the outline of project work plan

In their stage 1 proposals applicants should:

- Give due visibility on data management; dissemination, exploitation and sustainability; and communication activities. This should include the allocation of sufficient resources for these tasks which will be further developed in stage 2 proposal;
- Consider including a strategy for ensuring the translation of the projects results to drug development, regulatory/ HTA settings (e.g. through scientific advice/ qualification advice /opinion, etc.), clinical and healthcare practices and/or decision-making processes.

Suggested architecture

Work packages:

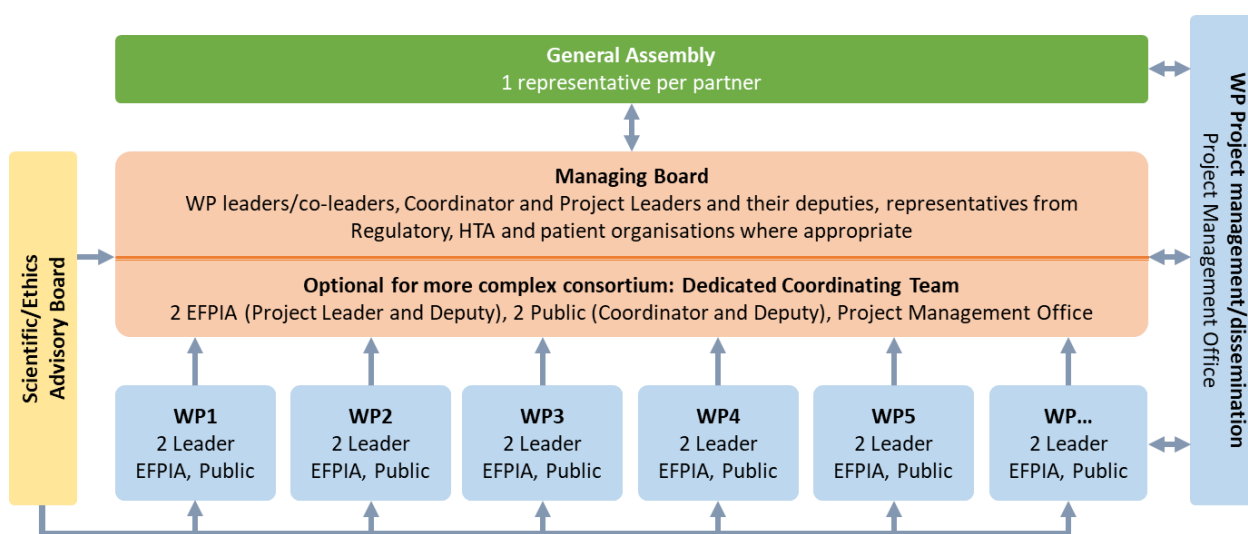
It is suggested that each of the 5 objectives described under section “SCOPE” (with associated goals and deliverable) becomes a work package (WP).

In addition, consideration should be given to a project management WP that would:

- Ensure alignment between the participants as well as smooth internal and external communication;
- Monitor compliance with the work plan;
- Monitor planned resources and time schedule;
- Coordinate fulfilment of all administrative milestones;
- Ensure legal and data privacy requirements are met during the project lifetime.

Applicant consortium is expected to contribute to project management, ensuring the implementation of the coordinating tasks and running the day-to-day operation, such as project tracking and reporting, meetings, internal communication, website creation, budget management, etc.

Example Architecture:



Additional considerations to be taken into account at the stage 2 full proposal

At stage 2, the consortium selected at stage 1 and the predefined industry consortium jointly submit the full proposal developed in partnership. The full proposal is based upon the selected short proposal at stage 1.

In the spirit of the partnership, and to reflect how IMI2 JU call topics are built on identified scientific priorities agreed together with EFPIA beneficiaries/large industrial beneficiaries, these beneficiaries intend to significantly contribute to the programme and project leadership as well as project financial management. The final architecture of the full proposal will be defined by the participants in compliance with the IMI2 JU rules and with a view to the achievement of the project objectives. The allocation of a leading role within the consortium will be discussed in the course of the drafting of the full proposal to be submitted at stage 2. To facilitate the formation of the final consortium, until the roles are formally appointed through the consortium agreement, the proposed project leader from among EFPIA beneficiaries/large industrial beneficiaries shall facilitate an efficient negotiation of project content and required agreements. All beneficiaries are encouraged to discuss the project architecture and governance and the weighting of responsibilities and priorities therein.

Data management

In their stage 2 proposal, applicants should give due visibility to data management including use of data standards. A full 'data management plan' (DMP) as a distinct deliverable must be delivered within the first 6 months of the project. The DMP needs to be kept up to date with the needs of the project and as such be updated as necessary during its lifetime.²⁰¹

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 project²⁰², 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).²⁰³

Communication

The proposed communication measures for promoting the project and its findings during the period of the grant should also be described and could include a possible public event to showcase the results of the project.

References

- [1] Nguengang Wakap, S., et al., Estimating cumulative point prevalence of rare diseases: analysis of the Orphanet database. *Eur J Hum Genet*, 2020. 28(2): p. 165-173.

²⁰¹ 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

²⁰² As an additional dissemination obligation under Article 29.1 of the [IMI2 Grant Agreement](#) will apply

²⁰³ <http://www.corbel-project.eu/about-corbel/research-infrastructures.html>

Topic 6: Behavioural Model of Factors Affecting Patient Adherence

Topic details

Topic code	IMI2-2020-23-06
Action type	Research and Innovation Action (RIA)
Submission and evaluation process	2 stages
IMI2 Strategic Research Agenda - Axis of Research	Patient-tailored adherence programmes.
IMI2 Strategic Research Agenda - Health Priority	Other

Specific challenges to be addressed by public-private collaborative research

Patient non-adherence to prescribed treatment is an issue that affects patient health outcomes and healthcare system costs worldwide. It is estimated that it contributes to 200 000 premature deaths in the EU each year [1]. The annual costs in Europe of avoidable hospitalisations, emergency care and adult outpatient visits are assessed at EUR 125 billion¹ and there are similar figures in the US [2]. In addition, poor patient outcomes and resulting lower productivity affect the wider society, estimated in the US as 2.3 times direct healthcare costs [2]. Addressing the issues of adherence would significantly improve both individual patient outcomes and reduce societal costs.

Reported adherence rates for on-market drug products vary from 7% to 87% [3] and average 50% [4]. Non-adherence may also include non-pharmaceutical treatments (e.g. digital therapeutics, non-pharmaceutical respiratory devices, lifestyle changes) and over-use of medication, for example, patients are known to increase their intake of pain relief medication above their prescribed dose [5].

Many researchers have approached the topic of adherence³ but insights have necessarily been limited to specific sub-topics due to the breadth of the field. Consequently, whilst there are pockets of knowledge, both published and unpublished, there are also areas and interactions that are not fully understood. Although a number of app-based solutions for non-adherence have been developed, their effectiveness is highly variable [6]. Unless the underlying problem is well-defined and understood, the probability of developing effective solutions with broad and consistent impact is low. In addition, for a solution to be effective, it must be used. Therefore, the patient burden must be minimised and the solution must be simple to apply to ensure broad implementation. An optimised solution is required balancing personalisation (complexity) and simplicity of use. This may include population segmentation according to behavioural phenotypes [7].

A disease-agnostic solution has the potential to achieve the necessary simplicity. Although there are some factors which appear to be disease-specific (e.g. stigma of the disease) these may exist more generally in the population and merely be weighted more strongly in specific conditions. There are also many significant factors which are not associated with any single disease state and which vary minimally between them, such as a patient's health beliefs, need for control, social environment or education level. This indicates the potential for a disease-agnostic baseline model.

Consequently, there is a need to generate a more comprehensive theoretical and empirical understanding of the underlying causes of these patient behaviours and any interactions. This topic proposes the creation of a generalised model, grounded in behavioural theory, which integrates significant factors affecting non-adherent behaviour. Factors should include patient motivation, which is critical to adherence [8], and is particularly under-represented in the literature compared to more quantitative factors such as education level. This would provide a robust definition of the problem – a foundation for understanding and predicting patient behaviour – and guidance to develop and implement cost-effective tools and solutions for patients, healthcare professionals (HCPs) and other healthcare stakeholders which directly target the causes of non-adherence and, ultimately, improve patient outcomes and reduce health system costs.

As medication adherence includes three distinct elements: 1) initiation of therapy, 2) implementation of the dosing regimen, and 3) persistence with treatment [Error! Reference source not found.](#), it is anticipated that these three issues can be addressed by the proposed model.

Creating the necessary understanding for an effective model will require broad engagement and skills, particularly since we are targeting a disease agnostic model. The perspectives of patients, healthcare providers, academic experts, behavioural scientists, digital and data analytics experts and regulatory bodies will be essential to maximise the benefits and ensure all sectors of society are well served.

The establishment of a public-private partnership offers the opportunity to generate the necessary breadth of data and bring together the breadth of expertise needed to address these challenges.

Scope

The aims of the Call topic are to:

- develop a comprehensive understanding of the factors which affect patient needs and adherence, independently from the therapeutic area (i.e. generic or disease-agnostic), in a real-world context (as opposed to clinical setting);
- identify the most significant factors;
- evaluate existing models and then either create an open access behavioural model or further develop an existing model;
- collect additional real-world data to refine the model;
- provide tools that will enable healthcare stakeholders to cost-effectively develop and implement solutions to address patient needs and improve adherence rates.

The project will require a phased approach as the results of earlier activities may influence the focus and definition of later stages.

The scope of the project will include a definition of adherence and collate the factors affecting adherence. The relative impact and significance of factors shall be assessed and a gap analysis performed against theory to identify areas for research during the project. The review stage should therefore include an evaluation of available models of non-adherence behaviour. One potential model identified during the development of this text is the Subjective Experienced Health Methodology (SEHM) [10]. The evaluation of models should consider the extent to which significant factors are included and the applicability and availability of models for ongoing development to achieve the project aims.

Based on this research, a behavioural model will be created or selected and refined. In parallel, adherence modules will be added to existing patient studies to fill identified gaps in the data.

While disease-agnostic, the model should be able to increase the prediction power and accuracy when applying additional, disease-specific inputs. The model should be sufficiently flexible to allow future development as population needs change.

It is envisaged that there will be a strong data analysis component (e.g. through Machine Learning (ML) or Artificial Intelligence (AI), if applicable) in the evaluation of data and generation of tools to assess the proposed model. This will identify any factors not demonstrated in the literature and identify patterns within the data. The model should clearly indicate the primary causes of patient motivations and should provide guidance for aligning patient needs with solutions. Feedback from this activity will be used to develop and optimise the model.

Given the quantity of data that will be collected or generated, consideration will be required for data storage and management solutions.

Once developed or refined, the model will be validated for multiple ages (including paediatric), ethnicities and conditions. It is anticipated that this shall be achieved using the following therapeutic areas, dependent on access to patients provided by members of the consortium:

- Cardiovascular;
- Oncology;

- Immunology;
- Neurology;
- Endocrinology and
- Rare Disease.

It should be noted that this list is not exhaustive. Where opportunities arise to validate in other additional therapeutic areas, these should be explored. The objective of this phase is to demonstrate the consistency and effectiveness of identifying patient needs and predicting adherence rates.

Finally, an implementation strategy of this model will be determined (e.g. guidelines for use, Application Programming Interface or API approach). To ensure that any future tools generate genuine benefit for both patients and HCPs, a phase of work is required to assess how the interface could be simplified for patients, potentially sharing common data between companies or a common interface framework to engage with patients in a single location.

The implementation of stand-alone, patient-facing solutions (e.g. digital platforms) is out of scope of this Call topic. Modelling the behaviour of HCPs is also out of scope.

During the funded action, members of the industry consortium plan to contribute scientifically relevant pre-existing data and/or data from prospective studies including activities for generating such data that are part of broader industry clinical trials and/or patient studies and making such data fit for purpose.

Expected key deliverables

- Searchable database of published and available (to the consortium) unpublished sources of data on treatment adherence causes;
- Definition of adherence and methodology for assessing data, including consideration of bias;
- Statistical analysis and prioritisation of relative significance of factors on treatment adherence and persistence;
- Evaluation of available treatment adherence models, assessing strengths and weaknesses of selected models, considering the balance between personalisation and simplicity of implementation. This deliverable will then be used by the consortium to choose one model to refine/build a new model for validation;
- Methods to measure key factors and adherence levels which can feasibly be used with patients, considering minimum burden to patient;
- Disease-agnostic model of patient behaviour considering all factors identified above;
- Development of tools to collect data from patients and to quantify behavioural factors, for use in validating the model and in future applications of the model;
- Evaluation of trends within the data which indicate population sub-groupings with similar causes of non-adherent behaviour, and which could be used to cost-effectively identify suitable support types for patients;
- Model validation to demonstrate effective understanding of patient needs and prediction of adherence rates;
- Guidance on applying the model to develop solutions to address patient needs and, hence, adherence rates;
- Educational tools for patient organisations and support groups, pharmacies and healthcare providers;
- Requirements assessment for data-sharing solutions to minimise patient burden and data entry duplication. Potential proof-of-concept solution to demonstrate how a single patient input can be shared with multiple companies.

Expected impact

The model and supporting guidance developed under the project have the potential to transform the way healthcare stakeholders engage with patients to optimise their understanding of their condition and their adherence levels throughout their healthcare journey.

In their proposals, applicants should describe how the outputs of the project will contribute to the following impacts and include wherever possible baselines, targets and metrics to measure impact:

- Positive impact on healthcare at a societal level through enhanced adherence, targeted use of resources, and improved overall patient outcomes;
- Validated foundation to compile and understand factors affecting patient non-adherence to treatment regimens and the relative weighting of these factors;
- Identification of sub-groups of the population with similar causes of non-adherent behaviour such that solutions can be tailored to population needs and applied in a cost-effective manner to multiple treatment conditions;
- Model for the basis of a consistent approach to non-adherence across the industry; a framework for future development of patient-centric solutions, with the capacity for the model to evolve with the future needs of patient populations;
- Guidance, based on the validated model, for identifying patient needs and tailoring support tools for patients and HCPs which most closely address patient adherence needs and improve patient outcomes and quality of life;
- The data collected during the project will provide a broad and deep resource for future understanding of adherence.

The model and associated tools and guidance will provide open access resources that healthcare stakeholders can use to independently:

- Collect a minimum dataset from patients e.g. via questionnaire or online tool;
- Use data and the model to estimate risk of patient non-adherence;
- Use data and the model to identify patient needs for good adherence – potentially linked to a sub-group of similar patients;
- Use as a baseline to create their own specific toolkits;
- Create support solutions for delivery to patients or patient sub-groups, based on patient needs e.g. patient education, practical tools such as dose histories, links to HCPs or patient groups for emotional support. Potential to create multiple tools or resources but only deliver those that are most valuable to the individual patient;
- Repeat assessments to identify changing patient attitudes and needs

In their proposals, applicants should outline how the project plans to leverage the public-private partnership model to maximise impact on innovation, research & development, as well as regulatory, clinical and healthcare practices, where relevant. This could include a strategy for engagement with patients, healthcare professional associations, healthcare providers, regulators, Health Technology Assessment (HTA) agencies, payers etc., where relevant.

In addition, applicants should describe how the project will impact the competitiveness and growth of companies including SMEs.

In their proposals, applicants should outline how the project will:

- Manage research data including use of data standards;²⁰⁴
- Disseminate, exploit, and sustain the project results. This may involve engaging with suitable biological and medical sciences Research Infrastructures;²⁰⁵

²⁰⁴ 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

²⁰⁵ <http://www.corbel-project.eu/about-corbel/research-infrastructures.html>

- Communicate the project activities to relevant target audiences.

In addition, the following additional exploitation²⁰⁶/dissemination²⁰⁷ obligations must be considered to maximise impact:

It is expected that the model, guidance and any development tools will be made available through an open source process to achieve the aims of maximising the number of patients receiving support.

Potential synergies with existing consortia

Synergies and complementarities should be considered with relevant national, European and non-European initiatives (including suitable biological and medical sciences research infrastructures²⁰⁰) in order to incorporate past achievements, available data and lessons learnt where possible, thus avoiding unnecessary overlap, and duplication of efforts and funding.

Industry consortium

The industry consortium is composed of the following EFPIA partners:

- Pfizer (lead)
- Astellas
- Janssen
- Merck KGaA
- Novonordisk
- Resmed
- Servier
- Takeda

In addition, the industry consortium includes the following IMI2 JU Associated Partner:

- Link2Trials

The industry consortium (EFPIA and Associated Partner) plan to contribute the following expertise and assets as in-kind contributions:

- Curation and re-analysis of existing in-house study data or data summaries to show adherence rates and links to causes of non-adherence;
- Expertise in behavioural science to support model development/refinement;
- Development of methods to collect and assess treatment adherence rates;
- Study design, planning and management experience;
- Access to planned patient studies for data generation, model development, testing and validation activities. Identification of planned industry-sponsored phase 4 or other planned real-world studies to which an adherence module could be appended. Industry studies will provide access to patients for the selected medical conditions as a minimum. Further assessment areas may be added depending on the availability of suitable studies. Studies will be sponsored and funded by the respective company including the cost of full-time equivalents (FTEs) and other expenses to run the studies, including but not limited to contract research organisations (CRO) and investigator costs;
- Data analysis, including statistical analysis of study results and advanced analytics/machine learning expertise to identify trends;
- Project leadership and programme oversight;
- Regulatory, General Data Protection Regulation (GDPR), legal and medical expertise.

²⁰⁶ Article 28.1 (Additional exploitation obligations) of the [IMI2 Grant Agreement](#) will apply

²⁰⁷ Article 29.1 (Additional dissemination obligations) of the [IMI2 Grant Agreement](#) will apply

Indicative duration of the action

The indicative duration of the action is 60 months.

This duration is indicative only. At stage 2, the consortium selected at stage 1 and the predefined industry consortium may jointly agree on a different duration when submitting the stage 2 proposal.

Indicative budget

The financial contribution from IMI2 JU is a maximum of EUR 5 950 000.

The indicative in-kind contribution from EFPIA partners and IMI2 JU Associated Partner is EUR 5 950 000. This contribution comprises an indicative EFPIA in-kind contribution of EUR 5 700 000 and an indicative IMI2 JU Associated Partner in-kind contribution EUR 250 000.

Due to the global nature of the participating industry partners and IMI2 Associated Partner it is anticipated that some elements of the contributions will be non-EU/H2020 Associated Countries in-kind contributions.

Expertise and resources expected from applicants at stage 1

The stage 1 applicant consortium is expected, in the submitted short proposal, to address all the objectives and key deliverables of the topic, taking into account the expected contribution from the industry consortium, which will join at stage 2 to form the full consortium.

The stage 1 submitted short proposals should include suggestions for creating a full proposal architecture (which could be in line with the suggested architecture described below, though this architecture is only a suggestion.)

This may require mobilising, as appropriate the following expertise:

- Published expertise in patient experience, factors which affect treatment adherence, e.g. scientific and research organisations;
- Expertise to provide insight across countries and therapeutic areas as well as insight from different HCPs (e.g. physicians, pharmacists, nurses) and stakeholders (e.g. patients, healthcare providers, healthcare policy makers, and pharmaceutical researchers);
- Academic and commercial expertise in building and evaluating behavioural models and frameworks and the factors which drive treatment adherence behaviour;
- Reporting capabilities in agreement with the ABC taxonomy and the EMERGE guidelines;
- Study design and management expertise;
- Expertise in the use and analysis of real-world data on treatment adherence to contribute to and validate the model, including machine learning to identify data patterns and trends;
- SMEs with implemented solutions (i.e. hardware and software) to measure and manage medication adherence, ideally with own datasets and published evidence;
- Experience of patient communication, patient interfaces and app development for individualisation of therapies and patient empowerment;
- Legal and data privacy (e.g. GDPR) expertise;
- Access to health authorities, healthcare professionals, patients, patient advocacy groups and policy makers for their input into the implementation of the model, either as partner of the consortium or seeking advice;
- Information technology, data management, website management expertise;
- Expertise in clinical compliance/ICH GCP (International Council for Harmonisation – Good Clinical Practice) aspects;
- Project management, project administration/coordination, budget management and communication expertise;

N.B. It is not a requirement that public partners recruit patients unless it is for patient studies to which they have access.

It may also require mobilising, as appropriate, the following resources:

- Evidence-based digital tools to systematically collect adherence factors and dosing rate data from all participants included in studies and to identify relevant patterns in the adherence data.

Considerations for the outline of project work plan:

In their stage 1 proposals applicants should

- Give due visibility to data management; dissemination, exploitation and sustainability; and communication activities. This should include the allocation of sufficient resources for these tasks which will be further developed in stage 2 proposal;
- Consider including a strategy for ensuring the translation of the project results to drug development, regulatory/ HTA settings (e.g. through scientific advice/qualification advice/opinion, etc.), clinical and healthcare practices and/or decision-making processes.

Suggested architecture

Work package 1 – Review of existing data and state of the art

The goals of this work package are to:

- Agree on a definition of adherence;
- Collate published adherence work and unpublished data from members of the consortium demonstrating significant factors that impact patient behaviour with respect to treatment adherence. The work should consider medical, psychological and social factors, variation during the patient journey, and both over- and under-utilisation;
- Create a searchable database of data on treatment adherence causes;
- Carry out statistical analysis and prioritisation of relative significance of factors on treatment adherence and persistence;
- Identify published and unpublished models of patient behaviour with respect to treatment adherence and adherence levels;
- Evaluate available adherence models, assessing strengths and weaknesses of selected models. This deliverable will then be used by the consortium to choose one model to refine/build a new model for validation;
- Perform gap analysis against behavioural theories to identify factors that are missing or not well substantiated.

Work package 2 – Model Development / Model Refinement

The goals of this work package are to:

- Develop a disease-agnostic model of patient behaviour considering all factors identified in WP1;
- Refine the model using the additional data collected in WP3 and any data analysis techniques to identify trends, patient groupings or surrogate measures for adherence;
- Develop methods to measure key factors and adherence levels that can feasibly be used with patients, considering minimum burden to patient.

Work package 3 – Generation of additional data

The goals of this work package are to:

- Generate additional data to fill the gaps identified in WP1 and contribute to WP2 for the model refinement;
- Develop tools to collect data from patients and to quantify behavioural factors and potential solution types, for use in refining and validating the model and future model implementation;
- Use existing industry-sponsored real-world studies and append a module on adherence factors and measurement to generate a breadth of data across different conditions.

Work package 4 – Model validation

The goals of this work package are to:

- Identify suitable studies (e.g. existing Phase 4 clinical studies, real-world studies) to test the model predictions of patient needs and adherence rates;
- Validate the behavioural model for at least six therapeutic areas covering the most significant medical, psychological and social factors identified in WP1;
- Develop prototype solutions as required to support validation activities.

Work package 5 – Implementation strategy

The goals of this work package are to:

- Develop guidance on how to apply the model to develop solutions to address patient needs and, hence, adherence rates, for use by industry partners, academia or healthcare practitioners;
- Consider how patients with multiple conditions may interact with likely adherence solutions. Consider concepts for future tools that could share data or interfaces to minimise the burden on the patient. Determine the requirements for such tools, including the needs of patients, healthcare providers, regulators and industry;
- Prepare a proof of concept of such tools.

Work package 6 – Project management, incl. sustainability plan, regulatory, legal & data privacy

The goals of this work package are to:

- Ensure alignment between the beneficiaries as well as smooth internal and external communication;
- Monitor compliance with the work plan;
- Monitor planned resources and time schedule;
- Coordinate fulfilment of all administrative milestones;
- Prepare a sustainability plan for the deliverables that shall be maintained and/or developed after the completion of the project. The plan shall be produced in parallel with model development;
- Ensure legal and data privacy requirements are met during the project lifetime.

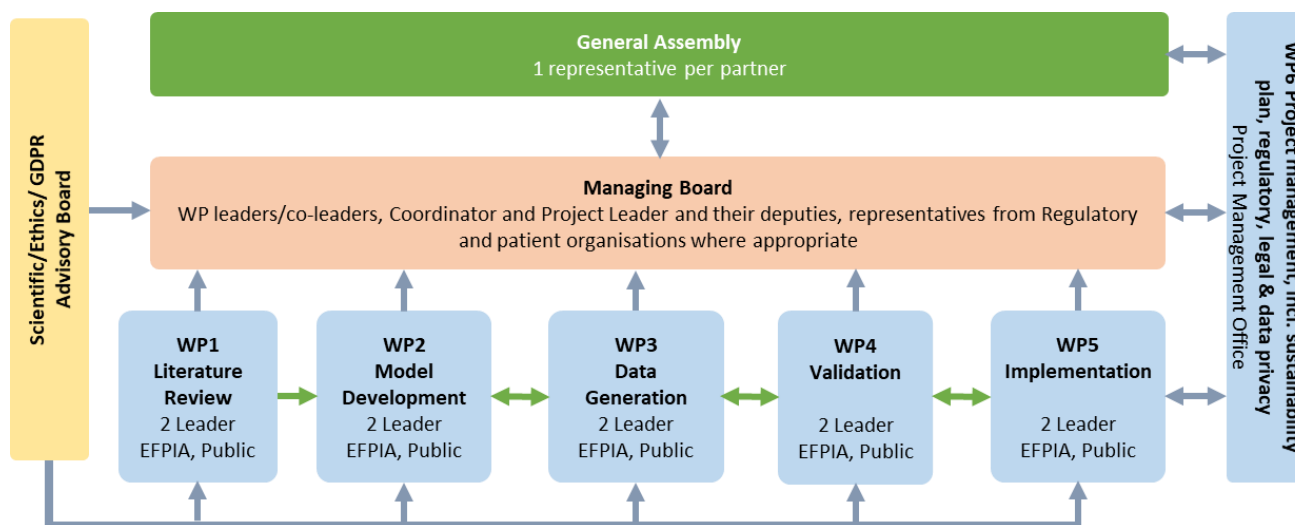


Figure 1 – Suggested WP architecture

Additional considerations to be taken into account at the stage 2 full proposal

At stage 2, the consortium selected at stage 1 and the predefined industry consortium jointly submit the full proposal developed in partnership. The full proposal is based upon the selected short proposal at stage 1.

In the spirit of the partnership, and to reflect how IMI2 JU call topics are built on identified scientific priorities agreed together with EFPIA beneficiaries/large industrial beneficiaries, these beneficiaries intend to

significantly contribute to the programme and project leadership as well as project financial management. The final architecture of the full proposal will be defined by the participants in compliance with the IMI2 JU rules and with a view to the achievement of the project objectives. The allocation of a leading role within the consortium will be discussed in the course of the drafting of the full proposal to be submitted at stage 2. To facilitate the formation of the final consortium, until the roles are formally appointed through the consortium agreement, the proposed project leader from among EFPIA beneficiaries/large industrial beneficiaries shall facilitate an efficient negotiation of project content and required agreements. All beneficiaries are encouraged to discuss the project architecture and governance and the weighting of responsibilities and priorities therein.

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 six 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.²⁰⁸

Dissemination, exploitation and sustainability of results

In their stage 2 proposal, applicants must provide a draft plan for dissemination and the exploitation, including sustainability of results. A full plan as a distinct deliverable must be delivered within the first six months of the project.²⁰⁹, 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).²¹⁰

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.

²⁰⁸ 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

²⁰⁹ As an additional dissemination obligation under Article 29.1 of the [IMI2 Grant Agreement](#) will apply

²¹⁰ <http://www.corbel-project.eu/about-corbel/research-infrastructures.html>

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Conditions for this Call for proposals

All proposals must conform to the conditions set out in the H2020 Rules for Participation (https://ec.europa.eu/research/participants/portal/doc/call/h2020/common/1595113-h2020-rules-participation_oj_en.pdf) and the Commission Delegated Regulation with regard to IMI2 JU <http://eur-lex.europa.eu/legal-content/EN/TXT/PDF/?uri=CELEX:32014R0622&from=EN>.

The following conditions shall apply to this IMI2 JU Call for Proposals:

Applicants intending to submit a Short proposal in response to the IMI2 Call 23 should read this topics text, the [IMI2 JU Manual for submission, evaluation and grant award](#) and other relevant documents (e.g. [IMI2 JU Model Grant Agreement](#)).

Call Identifier	H2020-JTI-IMI2-2020-23-two-stage
Type of actions	Research and Innovation Action (RIA)
Publication Date	23 June 2020
Stage 1 Submission start date	23 June 2020
Stage 1 Submission deadline	29 September 2020 (17:00:00 Brussels time)
Stage 2 Submission deadline	17 March 2021 (17:00:00 Brussels time)
Indicative Budget	
From EFPIA companies and IMI2 JU Associated Partners	47 360 000 EUR
From the IMI2 JU ²¹¹	47 790 000 EUR

Call Topics

IMI2-2020-23-01 Returning Clinical Trial Data to Study Participants within a GDPR compliant and approved ethical framework	The indicative contribution from EFPIA companies is EUR 4 930 000 The financial contribution from IMI2 JU is a maximum of EUR 3 260 000	Research and Innovation Action (RIA) Two-stage submission and evaluation process. Only the applicant consortium whose proposal is ranked first at the first stage is invited for the second stage.
IMI2-2020-23-02 Modelling the impact of monoclonal antibodies and vaccines on the reduction of antimicrobial resistance	The indicative contribution from EFPIA companies is EUR 2 760 000 The financial contribution from IMI2 JU is a maximum of EUR 6 500 000	Research and Innovation Action (RIA) Two-stage submission and evaluation process. Only the applicant consortium whose proposal is ranked first at the first stage is invited for the second stage.

²¹¹ In case the budget of this given line cannot be consumed (totally or partially) the corresponding budget will be allocated to the topics under the other budget lines.

<p>IMI2-2020-23-03</p> <p>A platform for accelerating biomarker discovery and validation to support therapeutics development for neurodegenerative diseases</p>	<p>The indicative contribution from EFPIA companies is EUR 9 720 000</p> <p>The financial contribution from IMI2 JU is a maximum of EUR 9 680 000</p>	<p>Research and Innovation Action (RIA)</p> <p>Two-stage submission and evaluation process.</p> <p>Only the applicant consortium whose proposal is ranked first at the first stage is invited for the second stage.</p>
<p>IMI2-2020-23-04</p> <p>Optimal treatment for patients with solid tumours in Europe through Artificial Intelligence</p>	<p>The indicative contribution from EFPIA companies is EUR 11 400 000</p> <p>The financial contribution from IMI2 JU is a maximum of EUR 10 460 000</p>	<p>Research and Innovation Action (RIA)</p> <p>Two-stage submission and evaluation process.</p> <p>Only the applicant consortium whose proposal is ranked first at the first stage is invited for the second stage.</p>
<p>IMI2-2020-23-05</p> <p>Shortening the path to rare disease diagnosis by using newborn genetic screening and digital technologies</p>	<p>The indicative contribution from EFPIA companies is EUR 12 600 000</p> <p>The financial contribution from IMI2 JU is a maximum of EUR 11 940 000</p>	<p>Research and Innovation Action (RIA)</p> <p>Two-stage submission and evaluation process.</p> <p>Only the applicant consortium whose proposal is ranked first at the first stage is invited for the second stage.</p>
<p>IMI2-2020-23-06</p> <p>Behavioural Model of Factors Affecting Patient Adherence</p>	<p>The indicative contribution from EFPIA companies is EUR 5 700 000</p> <p>The indicative IMI2 JU Associated Partners contribution is EUR 250 000</p> <p>The financial contribution from IMI2 JU is a maximum of EUR 5 950 000</p>	<p>Research and Innovation Action (RIA)</p> <p>Two-stage submission and evaluation process.</p> <p>Only the applicant consortium whose proposal is ranked first at the first stage is invited for the second stage.</p>

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
AIDS	Acquired immune deficiency syndrome
AMR	Antimicrobial Resistance
AP	IMI2 JU Associated Partner
API	active pharmaceutical ingredient
API	Application Programming Interface
AST	Assistant
ATN	Amyloid-Tau-Neurodegeneration
AWP	Annual Work Plan
A β	Amyloid beta
BDNF	Brain Derived Neurotrophic Factor
BOD	Burden of Disease
CA (Budget)	Commitment Appropriation
CA (HR)	Contractual Agent
CASPAR	Classification Criteria For Psoriatic Arthritis
CBN	Capability Building Network
CDC	Centers for Disease Control and Prevention
CDISC	Clinical Data Interchange Standards Consortium
CEA	Cost-Effectiveness Analysis
CEN/TS	European Committee For Standardization / Technical Specification
CEOi	Global CEO Initiative
CFAST	Coalition for Accelerating Standards and Therapies
cfDNA	Circulating Free DNA
CFS	Certificates on Financial Statements
CHIM	Controlled Human Infection Model
Chromium	Single-Cell RNA Sequencing Platform (10xgenomics) – Reads 3' End Of Transcript
CMC	Chemistry, Manufacturing, And Control
CoV	Coronaviruses
COVID-19	Coronavirus disease 2019
C-Path	Critical Path Institute
CPD	Continuing professional development
CPDL	Clinical Practice Data Linkage
CPE	Carbapenemase Producing Enterobacteriaceae
CPRD	Clinical Practice Data Linkage
CPTR	Critical Path To Tb Drug Regimens
CRE	Carbapenem Resistant Enterobacteriaceae
CRO	Contract research organisation
CROSS	ChemoRadiotherapy for Oesophageal Cancer Followed by Surgery Study
CSA	Coordination and Support Action
CSC	Common Support Centre
CSF	Cerebro-spinal fluid
CSTD	Closed System Drug Transfer Devices
CT	Computer Tomography
ctDNA	Circulating Tumour DNA
CTR	Clinical Trial Regulation
CUA	Cost-Utility Analysis

Acronym	Meaning
CV	Cardiovascular
CyTOF	Mass cytometry by time-of-flight.
DALYs	disability-adjusted life years
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)
DKD-BM	Diabetic Kidney Disease Biomarkers
DMP	Data Management Plan
DNA	Deoxyribonucleic acid
DP	Drug Product
DPA	Data Protection Authority
DPH	Drug Product Handling
DPO	Data protection officer
DSUR	Developmental Safety Update Report
DTPs	Drug Tolerant Persister Cells
DZIF	German Centre For Infection Research
E&T	Education & Training
E2E	Client- and Server-side Encryption
EBA	Early Bactericidal Activity
EBiSC	European induced pluripotent stem cell
EC	European Commission
ECs	Ethics Committee
ECA	European Court of Auditors
ECDC	European Centre for Disease prevention and Control
EDPB	European Data Protection Board
EDPS	European Data Protection Supervisor
EEG	Electroencephalograph
EFPIA	European Federation of Pharmaceutical Industries and Associations
EGFR	Epidermal Growth Factor Receptor
EHR	Electronic Health Record
EEHRxF	European Electronic Health Record Exchange Format
EMA	European Medicines Agency
EMBL	European Molecular Biology Laboratory
EQAs	External Quality Assessment Schemes
ERA	environmental risk assessment
ESFRI	European Strategy Forum on Research Infrastructures
EU	European Union
EUCROF	European Contract Research Organisation Federation
EUPID	European Patient Identifiers
EUR	Euros
ExPEC	Extra-Intestinal Pathogenic Escherichia Coli
FAIR	Findable, Accessible, Interoperable, Reusable
FDA	Food and Drug Administration
FG	Function Group
FHIR	Fast Healthcare Interoperability Resources
fNIH	Foundation for the National Institute of Health
FP	Full Proposal
FP7	Seventh Framework Programme
FTE	Full-Time Equivalent
FWC	Framework Contract
GA	Grant Agreement

Acronym	Meaning
GAP	Global Alzheimer's Platform
Gates MRI	Gates Medical Research Institute
GB	Governing Board
GCP	Good Clinical Practice
GDF-15	Growth Differentiation Factor-15
GDPR	General Data Protection Regulation
GEMM	Genetically Engineered Mouse Models
GFAP	Glial Fibrillary Acidic Protein
GLP	Good Laboratory Practice
GMP	Good Manufacturing Practice
GP	General Practitioner
GPCRs	G-protein-coupled receptors
GRAPPA	Group For Research And Assessment Of Psoriasis And Psoriatic Arthritis
GSK	Glaxosmithkline
H2020	<p>Horizon 2020 is the biggest EU Research and Innovation programme ever with nearly EUR 80 billion of funding available over 7 years (2014 to 2020) – in addition to the private investment that this money will attract. It promises more breakthroughs, discoveries and world-firsts by taking great ideas from the lab to the market.</p> <p>Horizon 2020 is the financial instrument implementing the Innovation Union, a Europe 2020 flagship initiative aimed at securing Europe's global competitiveness. For more information, click here: http://ec.europa.eu/programmes/horizon2020/en/what-horizon-2020</p>
HCA	Human Cell Atlas
HCP	Healthcare Professional
HCT	Human challenge trials
Helmsley Charitable Trust	Leona M. and Harry B. Helmsley Charitable Trust
HIV	Human immunodeficiency viruses
HL7	Health Level 7
HR	Human resources
HTA	Health Technology Assessment
HTS	High-throughput screening
IAC	Internal Audit Capability
IAPO	International Alliance of Patients' Organisations
IARC	International Agency for Research on Cancer
IAS	Internal Audit Service of the European Commission
ICC	Internal Control Coordinator
ICF	Informed Consent Form
ICH	International Conference On Harmonisation Of Technical Requirements For Registration Of Pharmaceuticals For Human Use
ICH-GCP	International Council for Harmonisation – Good Clinical Practice
ICI	Immune Checkpoint Inhibitor
ICS	Internal Control Standards
ICT	Information Communications Technology
IGFBP7	Insulin like Growth Factor Binding Protein 7
IL-6	Interleukin-6
ILG	Industry Liaison Group
IMI JU	Innovative Medicines Initiative Joint Undertaking
IMI2 JU	Innovative Medicines Initiative 2 Joint Undertaking
IMI2 JU AP	IMI2 JU Associated Partner
IMPD	Investigational Medicinal Product Dossier
iMRM	Immuno-Multiple Reaction Monitoring
IMRT	Intensity-Modulated Radiation Therapy
INDSR	Investigational New Drug Study Report
IP	Intellectual property

Acronym	Meaning
IPD	Individual Patient Data
iPS	Induced Pluripotent Stem
iPS cells	Induced pluripotent stem cells
IRB	International Review Board
IRP	Integrated Research Platform
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.
LIMS	Laboratory Information Management System
mAb	Monocolonal Antibodies
MAPPs	Medicines adaptive pathways to patients
MDR	Multi-drug Resistant
MDR-TB	Multidrug Resistant-Tuberculosis
MEP	Member of the European Parliament
MERS-CoV	Middle East respiratory syndrome coronavirus
ML	Machine Learning
MOA	mechanisms-of-action
MRD	Minimal Residual Disease
MRI	Magnetic resonance imaging
MRSA	Methicillin Resistant Staphylococcus aureus
MS	Multiple sclerosis
MTA	Material transfer agreement
MTB	Mycobacterium Tuberculosis
NBS	New-born Screening
NCE	New Chemical Entity (A Candidate Medicine Or Drug)
ND4BB	New Drugs for Bad Bugs
NFL	Neurofilaments
NGS	Next Generation Sequencing
NIMH	National Institute of Mental Health
NSCLC	Non-Small Cell Lung Cancer
NSE	Neuron-Specific Enolase
NTM	Non-tubercular mycobacteria
OAC	Obesity Action Coalition
OECD	Organisation for Economic Co-operation and Development
OLAF	European Anti-Fraud Office
PA	Payment Appropriation
PACS	Picture Archiving and Communications System
PBNs	Company-specific Portfolio Building Networks
pCR	Pathological Complete Response
PCR	Polymerase Chain Reaction
PDAI	Patient Data Return Initiative
PDO	Patient-Derived Organoid
PD	Parkinson's disease
PDX	Patient-Derived Xenograft
PEC	Predicted Environmental Concentration
PET	Positron emission tomography

Acronym	Meaning
PBT	persistent, bioaccumulative and toxic
PHE	Public Health England
PI	Principal Investigator
PIC	Patient Informed Consent
PiE	pharmaceuticals in the environment
PKPD	Pharmacokinetic-Pharmacodynamic
PM	Person/month
PMDA	Pharmaceuticals and Medical Devices Agency
POC	Proof of concept
PPP	Public-private partnership
PRO	Patient reported outcomes
PsA	Psoriatic Arthritis
PsO	Psoriasis
PSRI	Periodic Safety Reports For Investigators
PT	Proton Therapy
pTau	Phosphorylated Tau
QA/QC	Quality Assurance/Quality Control
QALYs	quality-adjusted life year
QoL	Quality of life
QST	Quantitative sensory testing
QST	Quantitative System Toxicology
R&D	Research and development
RA	Rheumatoid arthritis
RAE	Risk assessment exercise
RCSA	Risk and control self-assessment
RD[s]	Rare Disease[s]
RECIST	Response Evaluation Criteria In Solid Tumours
RepER	Representative error rate
ResER	Residual error rate
RI	Research Infrastructure
RIA	Research and Innovation Action
RIs	Research infrastructures
RNA	Ribonucleic Acid
Rol	Return on Investment
RP	Reporting Period
RSV	Respiratory Syncytial Virus
RT	Radiotherapy with photons
RTOs	Research and Technology Organisations
SAICM	Strategic Approach to International Chemicals Management
SARS-CoV	Severe acute respiratory syndrome
SARS-CoV-2	Severe acute respiratory syndrome coronavirus 2
SC	Scientific Committee
scRNA-seq	Single-Cell RNA-Sequencing – Expression Of The Transcriptome Per Single Cell
SEHM	Subjective Experienced Health Methodology
SEND	CDISC SEND Controlled Terminology
SGGs	IMI2 JU Strategic Governing Groups
SLC	Solute carriers
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
SOFIA	Submission of Information Application
SOP	Standard operating procedure
SP	Short Proposal

Acronym	Meaning
SRA	Strategic Research Agenda
SRG	States Representatives Group
STREM2	Soluble Triggering Receptor Expressed on Myeloid cells 2
SUSAR	Suspected Unexpected Serious Adverse Reaction
T1D	Type 1 diabetes
T1DM	Type 1 diabetes Mellitus
T2D	Type 2 diabetes
TA	Temporary Agent
TB	Tuberculosis
TBDA	TB Drug Accelerator
TBDDN	Tuberculosis Drug Development Network
TDTDC	Tuberculosis Drug Treatment Development Consortium
tTau	Total Tau
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
WES	Whole Exome Sequencing
WGS	Whole Genome Sequencing
WHO	World Health Organisation
WP(s)	Work Package(s)
XDR-TB	Extensively Drug Resistant-Tuberculosis
YLK40	tyrosine (Y), lysine (K) and leucine (L)-40 glycoprotein

