Second amended Annual Work Plan and Budget for 2018

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In accordance with Article 16 of the Statutes of the IMI2 JU annexed to Council Regulation (EU) No 557/2014 of 6 May 2014 and with Article 31 of the Financial Rules of the IMI2 JU.

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

Annex to the Decision of IMI2 JU Governing Board No. IMI2-GB-DEC-15-adopted on 12.06.2018

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Chronology and list of reviews

Version	Date of Governing Board approval	Items
Version 1.0 (Annual Work Plan and Budget for 2018)	15.12.2017	Annual Work Plan and Budget for 2018
Version 2.0 (the first amended Annual Work Plan and Budget for 2018)	09.03.2018	IMI2 States Representatives Group and Scientific Committee consultation carried out from 09 January to 30 January 2018 Update of the following sections: ▪ IMI2 Key Performance Indicators ▪ 2.2.2 Scientific priorities for 2018 Insertion of Annex I
Version 3.0 (the second amended Annual Work Plan and Budget 2018)	12.06.2018	Update of the following sections: ▪ 2.2.2 Scientific priorities for 2018 - Budget ▪ 4. Budget

2　Introduction

The year 2018 will mark the 10th anniversary of the launch of the very first Innovative Medicines Initiative (IMI) Call for proposals. As such, it is an excellent opportunity for IMI2 JU to assess and communicate on how far it has come and stimulate a discussion on IMI2 JU's current activities and future direction.

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

In addition, as the results of the interim review of the IMI2 programme have been made public in October 2017, in 2018 IMI2 JU will focus on reviewing and implementing the recommendations made by the reviewers.

We have already started putting in place systems to address these recommendations. For example, a new set of relevant, accepted, credible, easy and robust key performance indicators is being defined. We have also developed a strategy to attract more small and medium-sized enterprises (SMEs) to IMI2 JU. We are also putting greater efforts into identifying our projects' most important outputs and communicating on them to a wider audience.

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

Throughout the year, the IMI2 JU Programme Office will strive to deliver work of the highest quality, following strict ethical standards, adhering to the principle of sound financial management and using appropriate checks and balances.

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

Pierre Meulien

Executive Director

3 Annual Work Plan Year 2018

3.1 Executive Summary

The main goals of IMI2 JU in 2018 are set out as follows:

- Launching two new Calls for proposals based on scientific priorities set out in section 2.2.2.
- Successfully manage and connect a growing portfolio of projects, under both the Seventh Framework Programme for Research (FP7) and Horizon 2020 (H2020).
- Expand the basis of external collaborations and partnerships to best meet the challenges of the biopharmaceutical environment and optimise the innovation framework.
- Implement an ambitious communication strategy to demonstrate, in a spirit of openness and transparency, the added value of the partnership to EU citizens. The results of the socio-economic impact study on completed IMI1 projects will also contribute to meeting this objective.
- Implement the recommendations of the interim evaluation of IMI2 JU (completed on 30 June 2017, with conclusions and observations published on 9 October 2017).
- Improve and upgrade various aspects of our operating systems, including implementation of the Call management process under Horizon 2020, effective transition to the Horizon 2020 IT tools, review of the risk assessment and internal control framework, and reorganisation of IMI2 JU Programme Office towards enhanced efficiency and cost effectiveness.
- Carry out and implement audits and controls over beneficiaries that receive of IMI2 JU funding and companies' in-kind contributions.

3.2 Operations

3.2.1 Objectives & indicators - risks & mitigations

The key objectives for IMI2 JU operations in 2018 are identified by the Governing Board in the Annual Work Plan and by the Management at operational level.

Key operational objectives for 2018 are as follows:

- Initiate competitive calls for proposals within the Strategic Research Agenda priorities bringing together the different stakeholders involved in drug development (including SMEs, regulators and patient organisations) and foster cross-project collaboration through proactive outreach strategies and conducive call design;
- Ensure sound budget implementation through the efficient management of calls for proposals, grant award process and close monitoring of ongoing projects, ensuring the completion and close-out;
- Demonstrate the EU added value of IMI2 JU through assertive communication to target audiences of the openness, transparency, relevance, effectiveness, efficiency and coherence of IMI2 JU activities;
- Involve industry from related sectors other than the pharmaceutical industry (diagnostics, medical technologies industry, imaging, digital industry, etc.) in IMI2 JU projects through proactive outreach strategies;
- Ensure IMI2 JU internationalisation and build productive linkages to major international efforts to address Global Challenges (AMR, Alzheimer's, autism, cancer, emerging infectious diseases, etc.).

IMI2 Key performance indicators (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 2018 and beyond.

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

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

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

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

KPI	Definition	Comment	Relates to	Baseline	Target
8	New tools and processes generated by IMI2 projects that have been implemented by the industry participants of IMI projects.	- New tools and processes: e.g. animal models, standards, biomarkers, SOPs, use of screening platforms and clinical trial networks. - Expressed as net figure. - Complemented by the number and budget of grant agreements that delivered them. - Assessment based on yearly reporting by industrial partners until the project close-out meetings.	IMI2 Regulation objective a, b2 and b6: a: "to support… the development and implementation of pre-competitive research and of innovation activities of strategic importance to the Union's competitiveness and industrial leadership…" b2: "reduce the time to reach clinical proof of concept in medicine development" b6: "improve the current drug development process by providing the support for the development of tools, standards and approaches to assess efficacy, safety and quality of regulated health products"	0	50
9	Share of projects involving patient organisations and healthcare professionals' associations (as consortium partners, members of advisory boards, members of stakeholder groups etc).	- Complemented by the number and budget of grant agreements that delivered them.	IMI2 Regulation objective a, and b1: a: "to support… the development and implementation of pre-competitive research and of innovation activities of strategic importance to the Union's competitiveness and industrial leadership…" b1: "increase the success rate in clinical trials of priority medicines identified by the WHO"	Share of IMI 1 projects involving patient organisations: (participants /advisory boards etc. 40%)	80%

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

Risks & mitigations

Risks are a strategic element of planning activities as their identification enables management to customise their objectives and corresponding actions. That further enables the prioritisation of actions to reduce the risks to an acceptable level. This section gives an overview of the risks and corresponding mitigating actions identified by the IMI2 JU Programme Office to support the achievement of the strategic goals and objectives set out above.

The risk assessment on the objectives and actions planned for 2018 shows in particular that some strategic risks identified are associated with IMI2 JU mission and have therefore to be accepted as such thus the IMI2 JU has planned appropriate mitigating measures to control any possible adverse effects This is typically the case of:

- Insufficient participation of non-pharma industry and SMEs as well as limited leverage effect of private contributions.

  - Control measures planned aim at developing new partnerships and promoting IMI2 JU visibility at international level through targeted actions by area and in collaboration with projects. This will ensure that the IMI2 JU brand is enhanced by the international strategy and relationship. In addition, joint IMI-EFPIA events are planned at regional and national level involving industry and policymakers. Furthermore, the IMI website is promoting different ways of contributing to IMI projects as Associated Partners and Partners in Research. Finally, on the specific issue of SME participation IMI2 JU and EFPIA are exploring new initiatives (such as incubator models) and potential call topics targeting SMEs (focusing on areas of new technology where standardisation and interaction between SMEs and large pharma companies could accelerate the development of innovative solutions such as sensors or organ-on-a-chip platforms).

- In addition, the IMI2 JU programme may be affected adversely by factors such as delay in defining the annual scientific priorities and call topics, insufficient comprehensibility of the participation process, low budget execution and postponement of project conclusion. The risk is that IMI2 JU may be perceived as unable to meet the needs of patients and the scientific community losing scientific attractiveness and stakeholders' (especially SME) involvement, resulting in low participation to calls and unsatisfactory programme implementation.

  - In view of ensuring efficient management of the grant award process and optimal budget implementation on ongoing projects, the IMI2 JU Programme Office is reinforcing its monitoring activities in liaison with all project coordinators in order to:
    - reassess the project needs and the work plan;
    - thoroughly review the overall need for payments appropriations in 2018 as the basis for a revised forecast;
    - enhance interactions between science and finance operations;
    - closer monitoring of the high-risk projects.

  - Furthermore, IMI2 JU will continue i) to implement the reengineered Call topic definition process reinforcing the Strategic Governing Groups (SGG) as thematic platforms addressing defined areas under the umbrella of the IMI2 JU SRA and ii) to search the advice of patients through the Patient Advisory Committee (PAC).

- Unbalance – at the end of the programme – between the EU financial contribution and the in-kind contribution provided by industry.

  - Measures to control and mitigate this risk are the systematic monitoring of projects' financial management made by the IMI2 JU Programme Office on the periodic report received from coordinators associated with ex-post control of costs incurred in indirect actions by industry and associated partners planned according to a risk-based plan.

- Finally, the risks of negative external perception at political level due to inaccurate comments about IMI in the press and other public fora have been identified.

  - IMI is promoting an ambitious communication strategy to demonstrate, in a spirit of openness and transparency, the results achieved by the partnership. To that end, the IMI2 JU will be proactive in identifying and promoting stories that highlight IMI's successes. The Programme Office shall also maintain close relationships with key decision-makers to ensure they have an informed view of how IMI works and its successes.

Concerning risks related to the performance of the Programme Office and operations, particular attention will be given to the organisational structure and staff allocation, especially as regards project management activities, the efficiency of which is dependent upon a sound interaction between science and finance. This is considered crucial by the management in order to ensure that the structure and resources of the JU continue to meet evolving organisational objectives and needs. Moreover, management will ensure that annual targets and objectives as well as key performance indicators are updated and coordinated with responsibilities and tasks are also revised to reflect changing strategic priorities. In turn, continuous measures are to be taken to strengthen both IMI2 JU operational procedures, increasing the resources available in some specific areas, improving the approach used for topic development, project monitoring and reporting as well as for IT management.

Finally, as UK stakeholders have largely contributed to the IMI success and the consequences of Brexit remain unpredictable, the IMI2 Governing Board will continue to monitor within the EU's broader political agenda the potential impact of Brexit on its strategy and programme implementation.

3.2.2   Scientific priorities for 2018

The IMI2 JU activities for 2018 are fully in line with the objectives as set out in Article 2 of the IMI2 JU Regulation. In particular, they aim at the development and implementation of pre-competitive research and innovation activities of strategic importance to the EU's competitiveness and industrial leadership, and address specific H2020 societal challenges, in particular improving European citizens' health and well-being.

These activities will be developed within the general framework of the Scientific Research Agenda (SRA) for IMI2 (see http://www.imi.europa.eu/about-imi/strategic-research-agenda). The SRA identifies a set of scientific priorities where IMI attempts to pilot new ideas in a real-life, safe-harbour environment that 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 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. Additionally, it identifies education and training, and excellence in clinical trial implementation as key implementation strategies.

In order to achieve its objectives, IMI 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 2018 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.

Small- and medium-sized enterprises (SMEs) have an important role in strengthening the competitiveness and industrial leadership in the European Union. 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 IMI2 in 2018 will increase its efforts for engaging SMEs in all its activities and encouraging their involvement in applicant consortia.

IMI has identified eight scientific priorities, broken down into several topics, for 2018, taking into account the advice provided by Strategic Governing Groups 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 2018 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 2018 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 2018 would then be updated accordingly.

To implement the 2018 priorities, IMI2 JU will initiate two competitive Calls for proposals, each covering several topics (see table at the end of this section), with indicative predefined launch dates foreseen for Q1 and Q3 in 2018.[1]

Topics launched on the basis of this Annual Work Plan 2018 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.

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

A. Diabetes/Metabolic disorders

The activities in this priority area should seek progress towards novel diagnostic and treatment paradigms for the mechanisms being involved and triggering the early onset and progression of (type 1 and type 2) diabetes/metabolic disorders and their complications.

This should aim to enable an early diagnosis with predictive biomarkers, to allow the development of experimental medicine approaches to safe and efficacious treatments, considering also health system sustainability of treatment intervention.

Activities in 2018 will address the following topic:

1) **The role of the gut Microbiome as modulator of type 1 Diabetes: Need for a systematic and integrated approach.** In the past years, major scientific interest has grown to elucidate the possible role of the microbiome in health and disease. The relevance for understanding the role of the microbiome in complex diseases like cancer, Parkinson´s disease or T2D is high but strongly hampered by the heterogeneity of these disease populations and the complexity of their disease mechanisms. Therefore, a systematic approach to study the microbiome in a more homogeneous disease like type 1 diabetes (T1D) with careful clinical phenotyping and deep-dive analysis of immune, genetic, ß-cell and 'omics`-biomarker could be the first step in elucidating the role of the gut microbiome in maintenance of health. A better understanding of the complex interactions between the intestinal microbiota and several functional systems of the body like the immune system, intestinal integrity and function, intermediary metabolism, ß-cell function and others may provide new and scientifically rational approaches for diagnosis, prediction and therapeutic options to prevent the decline of pancreatic ß-cells and the development of type 1 diabetes. The objective of this topic is the systematic elucidation of the gut microbiome in T1D individuals, already recruited and deep phenotyped, with integration of functional and taxonomic microbiome results with clinical phenotyping and immune, genetic, ß-cell and broad 'omic`-analysis. The IMI2 INNODIA project has created a unique European clinical infrastructure for recruiting, deep-dive phenotyping and biosampling newly diagnosed T1D subjects and at-risk relatives (around 5000 individuals), which represents an extremely valuable resource to build on and tackle this challenge in a timely way.

2) **Optimising future obesity treatment**. The overall aim is to optimize future obesity treatment by identifying pathophysiological and clinically meaningful subgroups and increase our understanding of how weight management can best be implemented in these subgroups to prevent or treat the complications of obesity. Activities covered may be: 1) establishing and analysing database(s) of relevant pharma sponsored- and/or academic trials or observational cohorts of high validity including enough clinical phenotyping and multi-omics data to address the heterogeneity of obesity; 2) re-addressing biomarkers in relevant animal models that translate to the clinic and can be used to monitor and predict weight loss progress in distinct patient subgroups; 3) developing novel innovative diagnostic packages for sub-classification and effect evaluation; 4) developing a health economic model including health care utilisation and economic consequences in subgroups of people with obesity; 5) raising awareness of obesity and weight management by using multiple channels to make public the data and knowledge obtained.

Expected impact:
- Facilitating the design and interpretation of rationally designed stratified clinical trials via the better understanding and scientific base of the diabetes, metabolic disorders and obese population.
- A faster evaluation of the benefit, and benefit/risk relationship of novel treatment options.
- Identification of key contributing pathways involving the microbiome with the potential to find efficacious and causative therapeutic options to treat and/or prevent diabetes and metabolic disorders.
- Potential high impact on future guidelines to treat diabetic and obese individuals.
- Potential high impact on public health regarding population morbidity and mortality, and public healthcare costs.
- Increased awareness of obesity as a chronic disease and of the effect of weight loss on a broad range of obesity related complications.
- Demonstration of the value of weight loss to people with obesity and to society.
- Increased number of people with obesity being able to lose and maintain weight

Type of actions:
Research and Innovation Actions

B. Neurodegeneration and other Neuroscience Priorities

The priority area neurodegeneration aims to address the high-unmet medical need for effective disease modifying and improved symptomatic interventions, as well as relevant companion diagnostics, for neurodegenerative disorders in general and Alzheimer's disease (AD) in particular. The priority area addresses the following themes: 1) increasing disease aetiology understanding for new drug target identification & validation as well as predictive animal models; 2) development of translational model systems and identification/validation of biomarkers; 4) improving clinical trial capabilities and methodologies including primary/secondary prevention; 5) better patient access.

Furthermore, there is still a high-unmet need in the areas of understanding, treating and managing pain, thus in 2018 pain will continue to be in the scope of this area.

Activities in 2018 will address the following topics:

3) **Synaptic plasticity**. The topic supports activities for the development of predictable animal models and predictive early translational clinical models or biomarkers, such as a physiological marker of synaptic dysfunction, which for example is altered in early AD (at very least in prodromal subjects, preferably in pre-symptomatic subjects). These should be sensitive enough to detect both abnormalities versus healthy controls and pharmacological intervention.

4) **Premotor Parkinson's disease.** The topic objective is to develop new approaches towards pre-motor status definition and validation of Parkinson's disease including interaction with regulators. This topic may be launched separately or as part of a platform initiative jointly with topic number 5.

5) **Personalised treatment for Parkinson's disease patients.** The topic supports activities to enable the development of innovative personalised treatments for Parkinson's disease using a biomarker approach. This topic may be launched separately or as part of a platform initiative jointly with topic number 4.

6) Identification and validation of novel disease-modifying pain targets and clinically relevant biomarkers for intractable chronic pain: The topic supports activities for the analysis of tissue samples from pain patients using omics-scale technologies to increase disease understanding, to identify clinically relevant biomarkers, and for the development of new platforms to facilitate future drug screening.

Expected impact:
▪ Validation of tools and platforms for discovery of new biological insights into neurodegenerative disease understanding.
▪ Enabling of the development of more personalised treatments for patients with neurodegenerative diseases.
▪ Enabling the development of new approaches to disease interception for neurodegenerative diseases.
▪ Improved understanding of pain mechanisms, identification of biomarkers and increased feasibility for drug development paving the way to new disease-modifying treatment options.

Type of actions:
Research and Innovation Actions

C. Immunology

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. Respiratory diseases in particular are relevant here. Within this remit, activities should seek progress towards novel diagnostic, monitoring and treatment paradigms for the mechanisms being involved in triggering the early onset, remission and progression of early lung diseases in particular, bronchiectasis, asthma, Chronic Obstructive Pulmonary Disease (COPD) and Idiopathic Pulmonary Fibrosis (IPF).

The proposed work will focus on a key set of immune mediated diseases or on disease mechanisms where working in partnership will benefit the knowledge base and accelerate delivery of drug treatments to patients. The proposed work will build on the knowledge base and infrastructure present within the European Union and the H2020 Associated Countries. This include achievements from ongoing research-based initiatives which together have aggregated substantive information on disease phenotypes, biomarkers and other factors associated with disease progression in many autoimmune disorders in order to guide better patient treatments. This should aim to enable identification of potential targets for therapeutic intervention and early diagnosis of disease with predictive biomarkers, eHealth, digital or telemedicine tools, to allow the development of experimental medicine approaches to safe and efficacious treatments, considering also health system sustainability of treatment intervention.

Activities in 2018 will address the following topics:

7) **Targeted immune intervention for the management of non-response and relapse.** The aim of this topic is to identify novel biomarkers predictive of clinical disease behaviour and response. This should be achieved by applying state of the art molecular and immune technologies and sophisticated informatics approaches on highly annotated pre- and post-therapy bio-samples obtained from patients with Systemic Lupus Erythematosus (SLE), Rheumatoid Arthritis (RA), Multiple Sclerosis (MS), Ulcerative Colitis (UC), Crohn's Disease (CD), Asthma, and Chronic Obstructive Pulmonary Disease (COPD). A major aim beyond studying an individual disease is the discovery of cross-disease biomarkers with relevance to a group of immune-mediated inflammatory diseases.

8) **Non-invasive clinical molecular imaging of immune cells.** Current pharmacodynamic assessments of immune cells are based on peripheral blood biomarkers, or on biopsies acquired by invasive procedures, while current imaging tracers provide limited information on disease-relevant immune cell subtypes, or measures of direct engagement of immune targets. The topic objective is to study how immunotracers designed to bind specific immune cell biomarkers may enable the clinical imaging of immune cell subtypes and immune markers of disease. Activities supported are those that will provide in vivo insights into effects of immunomodulatory therapies at disease sites (organs/tissues), improve knowledge about the pathophysiology of various immune-mediated diseases, and enable patient stratification based on immune signatures. The overall objective is to develop and validate a quantitative, non-invasive, immune-cell-imaging platform, which includes (novel) molecular imaging agents, (hybrid) imaging modalities, and image processing algorithms. The final objective is to extend the current markers and validate them extensively for clinical use.

9) **Characterization of human immunology mechanisms**. This topic focuses on the role of the interplay and crosstalk of tissue and immune system for progression / remission of immune diseases.

   This should lead to the discovery of disease-relevant actionable parameters in tissue and identify "circulating signatures" in blood ("liquid biopsies") to improve and enable human target validation, model system selection, patient stratification, informative POC endpoints and overall to develop more effective and safer therapies in multiple therapeutic areas. This topic also explores in this context the correlation of patient reported outcomes to biosensors measurements.

10) **Early disease interception of immune-dependent disease**. This topic focuses on activities to enable earlier diagnosis of an immune disease, enable early disease interception and more effective patient treatment to improve quality of life (incl. potential Atopic March aspects). Activities aim among others to deconstruct the pathways leading to manifestation of immune diseases via genomic or disease biomarker analysis that will ultimately lead to the identification of a series of key targets within

the disease area. The topic is envisaged to lead to the precompetitive identification of new drug targets and cellular understanding within key disease areas including, but not limited to, type 1 diabetes / ABCD (autoimmune beta cell disease), rheumatoid arthritis / CSA (clinically suspected arthritis) and coeliac disease. The topic objective is also to develop ways to prosecute newly identified targets via the use of tool molecules, or drug repositioning with clinical trial cohorts and test their clinical validity.

11) **Emerging technologies & tools for interrogating human immuno-biology**.
The overall objective is to enable the development of novel classes of immuno-modulatory medicines of high safety. To this end the topic supports activities for 1) the development of a predictive safety assessment for immuno-modulatory drugs; 2) the establishing and validating non-clinical tools i.e. technologies for in-situ molecular profiling of immune cells and ex-vivo technologies for recapitulating in vivo human immuno-biology.

Expected Impact
- Generation of tools and capabilities required to support precision medicine.
- Increase the efficiency of the drug discovery and clinical development process.
- 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.
- Advance the understanding of disease mechanisms including epigenetics of immune and inflammatory disease for disease interception at the earliest stage, for progression, relapse, or during drug treatment, and potentially the identification of new drug targets.
- Expanding our current knowledge will give rise to more precise, targeted treatments that can yield long-lived reductions in disease and improved patient quality of life, fulfilling unmet medical needs in patient care.
- Options for improved treatment of respiratory patients to decrease their risk for morbidity and mortality, via a better understanding of disease progression, remission and the identification of reliable markers for its diagnosis and risk.
- Facilitating the design and interpretation of rationally designed stratified clinical trials via the better understanding and scientific base of the early respiratory disease population.
- Potential high impact on future guidelines to treat patients with respiratory diseases.

Type of actions:
Research and Innovation Actions

D. Infection control including vaccines

Infection control including vaccines is a key priority of IMI. The aim is to support the development of new platforms that facilitate rapid deliveries of novel and improved diagnostics, vaccines and treatments for infections, including emerging and re-emerging ones.

Antimicrobial resistance (AMR) continues to be a major global public health threat. The clinical burden is associated with soaring treatment and societal costs with a cost of AMR being estimated at around 1.5 billion Euros per year only in Europe. Despite the recognised need for new antimicrobials the reality is that as a society we are faced with the potential situation where prescribers could have few, if any, therapeutic options to treat certain bacterial infections. Continued efforts will focus on overcoming the barriers to the discovery, development and delivery of effective antibiotics; furthermore work on novel, resistance-breaking antibiotics should be supported.

Because of their low unit cost for individuals (albeit high societal cost) and improved clinical outcome, antibiotics were overused in the past century which resulted in the pandemic spread of highly resistant bacterial clones. Because of the increased bacterial resistance we need a paradigm shift in the way we deliver care and prescribe antibiotics. Personalised medicine based on novel and rapid diagnostic strategies should help in achieving this paradigm shift by identifying those patients who really need antibiotics, and by helping to select the appropriate and most effective antibiotic.

Activities in 2018 will address the following topics:

12) **Sustainable European antibacterial clinical trial network.** Over the past decade, significant efforts were made to establish a clinical trial network in Europe to support antibiotic drug development. This includes IMI's New Drugs for Bad Bugs (ND4BB) programme with its clinical investigator network CLIN-Net, associated laboratory network LAB-Net, and statistics and epidemiology expertise (STAT-Net and EPI-Net). CLIN-Net includes more than 800 clinical investigator sites across more than 40 countries. The sites are GCP certified and ready to be included in clinical trials with new antibiotics against multi-drug resistant pathogens, however a low percentage of the sites have so far been activated to participate in a trial. The development of those networks was largely guided by the need of dedicated development programmes. IMI recently launched a Call for proposals for a project addressing the value of diagnostics to combat antimicrobial resistance. The resulting project will implement a Standardised Care Network and run studies to demonstrate the value that diagnostics can bring to support our fight against AMR. Furthermore, a paediatric clinical trial network will be established in a project resulting from IMI2 10th Call for proposals, with an expected start date in Q1 2018. Yet each of these initiatives is driven by specific objectives and is limited in duration and scope. Existing capabilities need to be further strengthened, and validated, and gaps (e.g. in experience and capability in pivotal regulatory, specialised drug resistance and special population investigations) towards a comprehensive and sustainable European Antibacterial Clinical Trial network organisation that can address in full the challenges we face need to be addressed. The Clinical trial network should consist of four key segments that are discrete but also link expertise, resources and infrastructure where possible to establish a platform for the study of: 1) bacterial indications; 2) drug resistant infections; 3) paediatric studies; 4) validation of new diagnostics. The European Commission recently announced a call for proposals for 'Creation of a European wide sustainable clinical research network for infectious diseases' (SC1-HCO-08-2018). The resulting Coordination and Support Action is expected to develop a model for a multidisciplinary sustainable clinical research network for infectious diseases, addressing emerging epidemics, pandemics and antimicrobial resistance more broadly. It is expected that the model proposed there should serve as a basis for this action, and that this action will be integrated into the plans developed there.

13) **AMR Accelerator.** The discovery and development of new antimicrobials to address AMR is an undisputed European and global challenge that is compounded by a low return on investment (RoI). This has subsequently led to a reduction in resources applied across the pharmaceutical industry and decline in scientific discoveries. Overall this situation has compromised the delivery of new options to treat and prevent resistant infections. The AMR Accelerator is a programmatic approach, supported by a Coordination and Support Action, followed by different pillars that together should address the challenges we face and increase the overall investment in AMR research and the development of new treatment options. Pillars envisaged under the AMR Accelerator programme include: 1) A creation of a Capability Building Network (CB Network) that will accelerate scientific discoveries to enable the AMR community to deliver new ways to treat and prevent Multiple Drug Resistance (MDR) infections.

The CB Network should focus on precompetitive research in areas that are of specific interest and benefit to the AMR community as a whole. 2) Creation of multiple Portfolio Building Networks (PB Networks), that are vibrant and nimble collaborations between EFPIA companies and SMEs/academics that will advance the R&D pipeline of new and innovative agents to address AMR. 3) Progress in tuberculosis research, a pillar supporting preclinical and early clinical research activities on tuberculosis including activities aimed to shorten therapy and address AMR strains.

Expected impact of the topics:
- A pipeline of promising new agents for tackling antibiotic-resistant bacterial infections, including AMR tuberculosis.
- Improved antibiotic stewardship, decreased risk of antimicrobial resistance, and better preservation of the microbiome.
- Major impact on the improvement of public health.

Type of actions:
Research and Innovation Actions and Coordination and Support Actions

E. Translational safety

Translational safety is a key priority for the IMI2 JU programme. Translational safety activities aim at improving the safety assessment of pharmaceuticals through innovative and more predictive preclinical and clinical evaluations. The goal is to optimise the translatability to the 'real life' situation of the safety assessment paradigms and ultimately to improve the safety profile of drugs delivered to patients. In order to create synergies and avoid redundancies, activities in the translational safety area will connect with any other IMI projects relating to safety (including data management), and to other relevant European (i.e. from the European Union and the H2020 Associated Countries) and global initiatives (e.g. US Critical Path Institute, The Health and Environmental Sciences Institute/International Life Sciences Institute (HESI/ILSI), Innovative Questions (IQ) and National Institutes of Health (NIH)-driven projects).

Topics will aim at tackling safety-related attrition during drug development by better bridging preclinical and clinical areas, and as a result, should bring safer medicines to the market. Therefore, the topics planned focus on two extremes of the R&D process: on one side, on the improvement of the toolbox used during early phases of preclinical evaluation; and the other side, on clinical evaluation at late stages. The final idea is still to connect both preclinical and clinical areas through translational, integrative approaches.

Activities in 2018 will address the following topics:

14) **Translational microphysiological systems.** Over 30% of candidate drugs are stopped in clinical trials due to toxicity. Frequently, these toxicities were either undetected in preclinical models or the models underestimated clinical toxicity margins that ultimately prevented clinical progression. Therefore, improved in vitro models are needed that can prospectively help predict human toxicities using physiologically relevant human models, and retrospectively to aid in understanding preclinical to clinical translation of findings observed in in vivo animal studies, as well as understanding the relevance of mechanisms of action. Microphysiological systems (MPS) using cells derived from different species capable of predicting drug-induced toxicities earlier in drug discovery process would be of tremendous benefit. However, although many MPS have been developed, the performance of these systems, their appropriate context of use, and their translational potential have not been established particularly in organs such as kidney and the intestine. The objective of the topic is to establish a Microphysiological system (MPS) biological unit, with organ compartments (such as Gastrointestinal system, liver, exocrine pancreas, circulating white blood cells…). All these compartments should be biologically functional and connected together in a physiological manner. At least three different species should be established, rat, dog (and/or monkey and/or pig) and human, using either primary cells or preferably iPS-derived differentiated cells. Using animal MPS would allow better understanding of mechanism of toxicities in toxicology studies, their relevance to the human situation, and therefore improve the preclinical-clinical translation. The format, without being a high throughput set up, should be amenable to testing several compounds at different doses and durations. As some therapeutics may induce different toxicities or increase toxicity potential when applied to diseased tissues, animals, or higher risk patient populations (elderly, neonates) compared to healthy models that are typically used in preclinical assessments, a second phase would be the development and characterisation of diseased tissues or cells from genetically susceptible populations.

15) **Dosing in specific populations.** The term specific population has been used to describe patient attributes that may require alterations in the course of therapy when compared to typical patients; examples include renal and hepatic impaired patients, children, the elderly and pregnant women. These populations are often excluded or under-represented in pivotal trials. 50% to 80% of new molecular entities do not have explicit dosing recommendations for severe renal and hepatic impairment, respectively. Thus, dosing recommendations for some specific populations may lag for years without assurance that they will ever be studied. Modelling and simulation (M&S) approaches offer the opportunity to bridge this gap. Therefore, this topic objective is to establish a framework for developing models, criteria for establishing adequacy of predictions, and a drug development-regulatory framework for incorporation of derived dosing recommendations into product labels.

Expected Impact of the topics
- Better prediction and understanding of toxicities of drugs.
- Reduce use of animals in toxicology studies.
- Accelerate clinical development programs.
- Deliver more efficient and effective treatments in elderly populations.

Types of action: Research and Innovation Actions

F. Digital health and patient-centric evidence generation

This area of priority will address key areas that have the potential to be game changers for delivering access to innovative treatments for large patients populations. These are: 1) the challenge and opportunities of the increasing digitalisation in health research and technology, including the need for developing and implementing regulatory strategies and policies for digital health technologies; 2) the challenge to fully leverage the opportunity offered by new technologies, digitisation, telehealth, 3) the current concept of running clinical trials, how patients are recruited, how they are followed, how data are monitored and reported must be fully revisited. In this context pioneering multi-company platform trials such as I-SPY2 (breast cancer), IMI EPAD (prevention of Alzheimer's Disease), and GBM AGILE (glioblastoma multiforme) are already demonstrating the potential benefits of this approach; 3) finally, new capabilities to utilise real world data (RWD) offer powerful opportunities to complement the evidence obtained from clinical trials and this concept needs further development.

Activities in 2018 will address the following topics:

16) **Development of a platform for federated and privacy-preserving machine learning in support of drug discovery.** This topic will support activities towards the development of a federated privacy-preserving machine learning platform that is demonstrably safe and scalable enough to be deployed to a significant representation (at least half of the data) of the actual preclinical warehouses of at least 6 major pharmaceutical companies in yearly evaluation runs. The platform should be then used in an industrial setting and evaluated to establish proof-of-concept. The scope is the prediction of the activity of chemical compounds across an extensive set of biological assays. The resulting models will be evaluated on predictive performance gains in terms of accuracy and chemical and biological applicability domain, and on their impact in actual discovery projects, (e.g. how many lab experiments can be replaced by in silico predictions).

17) **Centre of excellence – remote decentralised clinical trials.** Recruitment and retention of patients are known to be one of the most challenging aspects in completion of clinical trials. The three main barriers commonly reported that discourage patients from participating in a clinical trial are: geography -distance to the clinical site, awareness and trust. Telemedicine is viewed as the central capability needed for distributing meaningful parts of clinical trial activities out to community settings. The topic aims on disaggregating the current model of running clinical trials, defining building blocks and mapping new technologies (e.g. telemedicine, mobile health, e.g. e-consent) to support the new decentralised clinical trial (DCT) approach. Activities might include among others: 1) review of experience to date to define and share challenges, obstacles, minimal requirements, solutions in DCT/home monitoring in a secured manner and assessment of data integrity and quality; 2) definition of the decentralised ecosystem and stakeholders; 3) recommendations on the creation of a Centre of Excellence on decentralised clinical trials; 4) define an intermediary model: hybrid studies mixing DCT approach with classical models, alleviating the burden for patients (e.g. rare diseases) and ensuring more real-life assessment; 5) setting up of initial pilot studies; 6) generate evidence for updating Good Clinical Practice (GCP) and International Conference on Harmonisation (ICH) guidelines.

18) **Digital Transformation of Clinical Trials Endpoints.** The program seeks to develop objective, continuous or high frequency digital measures of clinical efficacy and disability experienced by patients with respiratory, immune mediated and neurodegenerative progressive illnesses, for example Chronic Obstructive Pulmonary Disorder (COPD), Rheumatoid Arthritis (RA) and Parkinson's Disease (PD). The digital measures for each disease area will be correlated with validated clinical scales of disease severity and with the disabilities considered meaningful by patients & care-givers, to provide information acceptable to payers in assessing changes in burden and disability caused by these diseases while providing useful data for development and qualification of certain digital measures as primary and secondary endpoints of clinical efficacy.

19) **Integrated research platform for patient-centric drug development.** The platform objective is to deliver a "patient-centric" and highly efficient approach for medical research, through a collaborative public private partnership and integration of Real World Data (RWD) with clinical platform trials. Activities include the establishment of "readiness cohorts" and "longitudinal natural history studies", and the creation of a patient-centric precision medicine enabling a clinical trial platform that has the potential of allocating each patient to a treatment or combination of treatments that best fit for that patient, given the data. Synergies should be created from sharing inferences across all treatment arms, including common controls and placebo. The aim is the establishment of Integrated Research

Platforms (IRPs) in diseases of high-unmet need such as e.g. Major Depressive Disorder (MDD) and Tuberculosis (TB), and the further development of blueprints for four (4) future IRPs such as Inflammatory Bowel Disease (IBD), Non-alcoholic Steato-Hepatitis (NASH), Smoldering Multiple Myeloma (SMM) and Prostate Cancer. In addition, the objective is the creation of a hospital network to support these IRPs and multi-stakeholder alignment on Common Elements for IRPs (i.e. best practices and guidance to facilitate adoption of standards for using and re-using best practices).

Expected impact of the topics:
- Expand and democratise clinical trial participation globally and expand use of telemedicine in areas of current low uptake, potentially improving health outcomes.
- Accelerate patient access to innovative medical treatments.
- Reduce patient burden while participating in clinical trials.
- Provide benefit to society by expanding access to healthcare via telemedicine.
- Enable more efficient and cost-effective clinical trials and real world studies.
- Create business opportunities and economic growth by bringing technology companies and sensor developers into medically regulated space and drive new developments in data standards and privacy safeguards.

Type of actions:

Research and Innovation Actions

G. Oncology

IMI2 via its strategic area of oncology aims to foster a significant progress towards the extension and quality improvement of the treatment for patients living with advanced cancer.

The mission and vision is to define research initiatives that will aspire to effectively double the following parameters: 1) progression-free survival / overall survival; 2) number of patients able to access innovative personalised medicines; 3) speed of drug development; 4) treatment tolerability, and 5) cost effectiveness in cancer drug development.

In 2018 a focus will be to harness progress in next generation sequencing (NGS) to seamlessly monitor the multitude of dynamic genetic determinants of an individual cancer phenotype and integrate this data with patient profiling to advance precision oncology using a pharmacogenomics based approach. This will include a better understanding of cross talk of signal transduction pathways and of the context specificity of tumours as well as the development of better tools and methods (i.e. liquid biopsies) to monitor the molecular cancer dynamics in time and space. Another area will be to further advance, using a multipronged approach, the field of immune-oncology in order to boost the patient population that can benefit from such therapies. Finally the development of data and knowledge management solutions to enable data quality, standardisation, interoperability and full re-usability of all data generated, including also patient reported outcomes, health economic and real world evidence /data will be necessary to ensure full exploitation of results to guide future advances to better treat cancer patients. It is expected that some of the activities of this priority area might be launched as part of the large platform initiatives of the priority F: Digital health and evidence generation, when this will be considered as adding to the impact.

Activities in 2018 will address the following topic:

20) **Big data in oncology.** The topic supports activities for the creation of a centralised repository of data from patient populations affected by solid tumours (sequencing, RNA expression, protein profiling, metabolite and methylation profiling) capable of storing and processing sample information in a consistent fashion. This should be accompanied by efforts in standardisation of laboratory testing and data. This will facilitate patient access to the most advanced and appropriate treatment; speed up the enrolment of patients with rare genetic variants in clinical trials; allow the development of new clinical and molecular endpoints, and the generation of new hypotheses, methodologies and exploratory algorithms. Other elements of the solution are the establishment of an appropriate data architecture and software tools. Analytic and visualisation tools allowing deeper exploration of the data are also required, as are ways for inclusion of other sources of information, such as patient reported outcomes, health economic and real world evidence of treatment in different geographical regions.

Expected impact
- New approaches in drug development/ combination strategies for drugs in development to facilitate patient access to innovative treatments.
- Novel and better defined clinical and molecular endpoints.
- Better, more robust and higher quality screening tools and methods.
- A large positive impact in treatment outcomes, to support the adequate reimbursement of innovations in this field.
- An outcomes-focused data platform with continuous evidence generation to empower policy makers and clinicians to optimise care for patients with solid tumours in different geographical regions.

Type of actions:
Research and Innovation Actions

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

Recent advances in biomedicine are now opening the door to new treatment approaches for diseases with high unmet medical need. These approaches include advanced therapy medicinal products (ATMPs) such as products based on genetic engineering, innovative cell-based therapies and tissue-engineered products.

Activities in 2018 will address the following topics:

21) **ATMPs manufacturing.** This topic addresses the challenges of manufacturing of ATMPs. This will require developing common best practices and 'automated' production platforms, highly sensitive analytical tools/methods and scaled down/micro assays. Manufacturing knowhow and education specific for the ATMP business, regulatory sciences and Current Good Manufacturing Practice (CGMP) related to ATMP usage should also be developed.

Expected impact of the topics
▪ To enhance research and development of advanced therapies in the European Union and the H2020 Associated Countries as a fully-fledged industrial activity to make the EU more competitive and make advanced therapy products available to all patients in need.
▪ A more consistent and reproducible manufacturing of ATMPs.

Type of action:
Research and Innovation Actions

Calls for Proposals

Call number and topics	Call launch timing	IMI2 JU funding (in EUR)[2],[3]	In-kind contribution (in EUR) from EFPIA entities and Associated Partners
IMI2 Call 14 ***Immunology*** ▪ Targeted immune intervention for the management of non-response and relapse *(RIA)*[4] ▪ Non-invasive clinical molecular imaging of immune cells *(RIA)*[5] ***Digital health and patient centric evidence generation*** ▪ Development of a platform for federated and privacy-preserving machine learning in support of drug discovery *(RIA)*[6] ▪ Centre of excellence – remote decentralised clinical trials *(RIA)*[7]	15 March 2018	82.357.000	84.920.360
IMI2 Call 14 process			
Two-stage call with predefined submission deadline. Indicative Call deadline for **Short proposals**: **14 June 2018** Indicative Call deadline for **Full Proposals**: **11 December 2018** Research and Innovation Actions (RIA)			

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[2] Based on total operational commitment appropriations available in 2018. This is without prejudice to commitment appropriations to be carried over from 2017 to 2018 (to be approved during 2018).

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

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

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

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

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

Call number and indicative topics	Call launch timing	IMI2 JU funding (in EUR)[8],[9]	In-kind contribution (in EUR) from EFPIA entities and Associated Partners
IMI2 Call 15 ***Diabetes/Metabolic disorders*** ▪ The role of the gut Microbiome as modulator of type 1 Diabetes *(RIA)* ▪ Optimising future obesity treatment *(RIA)* ***Neurodegeneration and other Neuroscience Priorities*** ▪ Synaptic plasticity *(RIA)* ▪ Premotor Parkinson's disease *(RIA)* ▪ Personalised treatment for Parkinson's disease patients *(RIA)* ▪ Identification and validation of novel disease-modifying pain targets and clinically relevant biomarkers for intractable chronic pain *(RIA)* ***Immunology*** ▪ Characterization of human immunology mechanisms *(RIA)* ▪ Early disease interception of immune-dependent disease *(RIA)* ▪ Emerging technologies and tools for interrogating human immune-biology *(RIA)* ***Infection control including vaccines*** ▪ AMR Accelerator coordinator *(CSA)* ▪ AMR Accelerator *(RIA)* ▪ Sustainable European antibacterial clinical trial network *(RIA)* ***Translational safety*** ▪ Translational microphysiological systems *(RIA)* ▪ Dosing in specific populations *(RIA)* ***Digital health and patient centric evidence generation*** ▪ Digital Transformation of Clinical Trials Endpoints *(RIA)* ▪ Integrated research platform for patient-centric drug development *(RIA)* ***Oncology*** ▪ Big data in oncology *(RIA)* ***Facilitating the translation of advanced therapies to patients in Europe*** ▪ ATMPs manufacturing *(RIA)*	18 July 2018	218,775,862	182.974.457
IMI2 Call 15 process			
Two-stage call with predefined submission deadline. Indicative Call deadline for **Short proposals**: **24 October 2018** Indicative Call deadline for **Full Proposals**: **15 May 2019** Research and Innovation Actions (RIA) and Coordination and Support Actions (CSA)			

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[8] Based on estimate of total operational commitment appropriations available in 2018. This is without prejudice to commitment appropriations to be carried over from 2017 to 2018 (to be determined early 2018).
[9] The maximum possible rate of co-financing is 100 %.

Call number and indicative topics	Call launch timing	IMI2 JU funding (in EUR)[8],[9]	In-kind contribution (in EUR) from EFPIA entities and Associated Partners
Overall total		301,132,862	267,894,817

Budget

A table overview of the operational budget for 2018 is set out below.

Chapter	Heading Title 3	Budget 2018.0		Budget 2018 Amendment 2		Amended Budget 2018.2		Comments
		Commitment Appropriation (CA)	Payment Appropriation (PA)	Commitment Appropriation (CA)	Payment Appropriation (PA)	Commitment Appropriation (CA)	Payment Appropriation (PA)	
30	Implementing the research agenda of IMI2 JU	265,331,457	205,596,168			265,331,457	205,596,168	Grant agreements - Payments
C2	Appropriations carried over from previous years			209,698,405	54,683,685	209,698,405	54,683,685	
	Total operational costs Title 3	265,331,457	205,596,168	209,698,405	54,683,685	**475,029,862**	**260,279,853**	

The difference between the total budget available for Title 3 (EUR 475,029,862) and the budget available for fresh Calls in 2018 (EUR 301,132,862) is EUR 173,897,000. This amount represents the unused commitment appropriations carried over to the 2018 budget, to conclude Grant Agreements for IMI2 - Call 10 (EUR 173,890,000) and amount for IMI2 projects late payment interests (EUR 7,000).

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

Description	Commitment Appropriation (CA)	Payment Appropriation (PA)
unused operational appropriations IMI2 JU (H2020) (2017)	**7,000**	54,683,685
unused operational appropriations IMI2 JU (H2020) Call 10 EUR 173,890,000 (2017) carried over for Grant Agreements IMI2 Call 10	**173,890,000**	
unused operational appropriations carried over for new Calls to be launched in 2018	**35,808,405**	
IMI2 (H2020) Call 13 (2017)	*8,074,331*	
IMI2 (H2020) Call 9 (2017)	*722,479*	
IMI2 (H2020) Call 8 (2018)	*22,531,012*	
IMI2 (H2020) Call 11 (2018)	*1,716,007*	
IMI2 (H2020) Call 13 (2018)	*2,080,000*	
50 % unused running costs (2017) carried over for new Calls to be launched in 2018	*677,576*	
TOTAL	**209,698,405**	**54,683,685**

A table overview of the 2018 Budget is set out in Chapter 4 to this Annual Work Plan.

3.2.3 Call management (planning, evaluation, selection)

Activities related to proposals evaluation and grant preparation

Key activities in 2018 will comprise the launch of two competitive Calls for proposals implementing the 2018 scientific priorities with indicative launch dates on 15 March 2018 and 18 July 2018. In a single-stage submission evaluation procedure, from the initial publication of the Call for proposals the submission deadline will be approximately three months from the publication of the calls for proposals. IMI2 JU will utilise the H2020 Participant Portal and Horizon 2020 IT infrastructure.

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

In addition, the evaluation of short proposals and full proposals submitted to Calls launched under the AWP in 2018 will be held according to the predefined timelines established in the relevant Call for proposals.

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

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

3.2.4 Activities to support and monitor ongoing projects

58 ongoing projects will be running at different stages of their life cycle in 2018 with additional projects coming online during the year when Call 8 Ebola+ (4th and 5th cut-off), Call 10 (launched in 2016) and two calls launched in 2017 (Calls 11 and 12) complete their evaluation cycles (as indicated in the second column on the below table– "ongoing in 2018"). All 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 14 reviews for projects launched under IMI1 JU (Calls 6, 9 and 11) and IMI2 JU (Calls 1, 2, 3, 5, 6 and 7).

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[10] Article 20 of the Regulation (EU) No 1290/2013 of the European Parliament and of the Council of 11 December 2013 laying down the rules for participation and dissemination in "Horizon 2020"

The following table presents a forecast of the reporting expected for 2018.

IMI Calls	ongoing in 2018	Project periodic report due in 2018						Of which	
		1st RP	2nd RP	3rd RP	4th RP	5th to 7th RP	Total	finishing in 2018	Final report due 2018
1	0	0	0	0	0	0	0	0	0
2	0	0	0	0	0	1	1	0	1
3	3	0	0	0	0	4	4	2	3
4	3	0	0	0	0	3	3	3	2
5	1	0	0	0	0	1	1	1	1
6	1	0	0	0	0	2	2	0	1
7	1	0	0	0	0	1	1	1	1
8	3	0	0	0	4	0	4	1	2
9	2	0	0	3	1	0	4	0	2
10	1	0	0	1	0	0	1	0	0
11	8	0	1	7	0	0	8	1	1
IMI2 C1	1	0	0	1	0	0	1	0	0
IMI2 C2	4	0	1	6	0	0	7	2	5
IMI2 C3	5	0	5	0	0	0	5	0	0
IMI2 C4	0	0	1	0	0	0	1	0	1
IMI2 C5	6	1	5	0	0	0	6	0	0
IMI2 C6	4	3	1	0	0	0	4	1	1
IMI2 C7	7	7	0	0	0	0	7	0	0
IMI2 C8	3	1	1	0	0	0	2	0	0
IMI2 C9	6	6	0	0	0	0	6	0	0
IMI2 C10	8	0	0	0	0	0	0	0	0
IMI2 C11	7*	0	0	0	0	0	0	0	0
IMI2 C12	7	0	0	0	0	0	0	0	0
Total	81	18	15	18	5	12	68	12	21

* The estimated number is based on the number of key project results identified in the call text (7 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 IMI Programme Office will work with consortia on helping to communicate on project progress and dissemination of achievements.

3.2.5 Monitoring and analysis of projects' results

68 project periodic reports will be submitted in 2018 (for ongoing and finalised in 2017 IMI projects – see column 8 in the above table– "Project periodic report due in 2018 – Total"). 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. For projects resulting from IMI2 JU calls launched from December 2016 onwards, this monitoring will be done using the functionalities of the Horizon 2020 IT infrastructures.

In 2018 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.

3.2.6 Stakeholders' engagement and external collaborations

In 2018 IMI2 JU will continue to develop its relationships and engagement with key stakeholders such as patients, small and medium-sized enterprises, regulators, payers and healthcare professions to ensure that its outputs are aligned with and address the needs of society.

IMI2 JU's goal is to champion a patient centric-approach at all levels and encourage all the projects that it funds to work in partnership with patients wherever possible. IMI2 JU has listened to the needs expressed by patients and will create an IMI2 JU Patient Community which will give the patient voice a more prominent position in IMI both strategically and operationally. In addition, IMI2 JU aims to recruit a Seconded National Expert (SNE) to help drive the creation of the IMI2 JU Patient Community (IMI PC) as well as, coordinate and implement the patient engagement strategy of IMI2 JU.

Given their importance in driving employment and innovation in the European Union and the H2020 Associated Countries, the IMI2 JU will increase its engagement with SMEs and encourage their participation in IMI2 JU projects. In 2018, the IMI2 JU will continue to highlight SME opportunities in all topic texts and also embed SME participation at the earliest stages of topic development through collaboration with the Strategic Governance Groups and through exploring call designs more appealing to SMEs.

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

The regulatory environment is key to ensuring that safe and effective medicines reach the market for the benefit of patients. To date, IMI2 JU has been able to use its unique platform to create an interface between science and regulation. IMI2 JU will continue to develop this framework to engage with all relevant regulatory agencies. In particular, IMI2 JU will support optimising the scientific engagement of the European Medicines Agency (EMA) in IMI2 JU, expected to operate at three levels: strategic science-based recommendation, topics of interest definition within a specific research area, and engagement with research projects. IMI2 JU will also continue to foster engagement with competent national authorities as well as relevant HTA bodies in order to progress the goal of end-to-end integration in medicine development.

One important strategic objective for IMI2 JU is the involvement of other than the pharmaceutical sectors. For example, IMI2 JU has successfully brought together the major European diagnostics companies in 2017, an effort that will continue to be strengthened and supported throughout 2018. Likewise, important steps to engage the major players in the food and nutrition sector in discussions around a potential programme dedicated to the microbiome, started in 2017, and will be further facilitated in 2018.

IMI2 JU and ECSEL JU (www.ecsel.eu) initiated in 2017 the first discussions to explore possibilities for cooperation between both JU's in the domain of smart health along three thematic areas: sensors and diagnostics, imaging, and patient monitoring platforms. For 2018, dedicated workshops between sensor and diagnostics projects of the respective JU's are planned to explore synergies and potential collaborations, as well as follow-up discussions to identify gaps and a roadmap of common strategic priorities.

As the healthcare challenges faced by society are global, IMI2 JU will explore interactions and seek synergies with non-EU organisations when appropriate, for example in the area of antimicrobial resistance and biopreparedness. In an effort to align strategies and ensure complementarities, IMI2 JU and the Coalition for Epidemic Preparedness Innovations (CEPI) have agreed in 2017 to refer to each other's activities on their websites. In 2018, IMI2 JU will continue to exchange with CEPI and explore potential collaboration.

IMI2 JU and the Critical Path Institute (C-Path) are aligned in many of their scientific priorities, formalised by a Memorandum of Understanding (MoU) signed in 2011. IMI2 JU will continue to interact with C-PATH in 2018 and adapt the relationship as needed. IMI2 JU will also continue to sit on the Scientific Advisory Committee of C-FAST, an initiative formed in June 2012 by CDISC (Clinical Data Interchange Standards Consortium) and C-Path to accelerate clinical research and medical product development by creating and maintaining data standards, tools and methods for conducting research in therapeutic areas that are important to public health.

In order to share best practice 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. For example, for Q4 2018, a cross project meeting in the area of Mental Health involving IMI2-JU- funded projects as well as projects currently funded under H2020 and collaborating/synergistic initiatives funded by NIMH/NIH (examples are https://www.nimh.nih.gov/about/organization/dtr/index.shtml; https://www.nimh.nih.gov/research-priorities/research-initiatives/fast-fast-fail-trials.shtml; https://www.nimh.nih.gov/research-priorities/rdoc/index.shtml) and SFARI (https://www.sfari.org/) is envisaged. The meeting will allow cross-fertilisation between the projects with a focus on the aspects of digital technology applications in this research area.

3.2.7 Dissemination and information about projects results

Although the first and foremost responsibility of maximising the impact of their own research and innovation lies with the project consortium, promoting the successes of IMI2 JU projects is a core element of both the IMI2 JU Communications and Dissemination Strategies.

The IMI 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. In addition, IMI will continue to explore how to make better use of EU specific dissemination channels for the promotion of projects and their results. In addition, following on from a pilot study performed in 2016 on the impact of IMI2 JU projects on the 3Rs (i.e. the replacement, reduction and refinement of animal use in research), IMI2 JU will undertake a more detailed analysis in 2018 on the contribution of project results to this specific area.

In 2018, the IMI2 JU expects to receive 21 final project reports. These reports will come from projects finishing in 2017 but reporting in 2018 (11 projects) and those finishing and reporting in 2018 (10 projects). In addition, 2 projects reaching their end date in 2018 will report in 2019. Capturing the outcomes and impacts of these projects presents IMI with a continuing challenge of ensuring that project results are disseminated widely and taken up by researchers in the field.

It is expected that at least 20 close-out meetings will be organised around the time of the final report submission. The close out meeting provides an opportunity for the consortium to present to the IMI2 JU how the project has reached its objectives, to highlight tangible results and to put the achievements of the project into context and to discuss the potential impact and legacy management. Members of EFPIA, the EC, IMI2 JU Scientific Committee and relevant SGG will be invited to attend the close out meetings to share not only in the results but also in the learnings and experiences of the project consortia. 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.

3.2.8 Socio-economic impact study

The second phase of the socio-economic impact study begun in 2017 will continue in 2018. The study utilises the previously developed methodology and applies it to the next wave of IMI1 projects that have completed or are drawing to a close. As with the original study this new evaluation looks at short-term outcomes (2-3 years) such as improved scientific quality, enhanced knowledge production, network-based R&D capacity building, and human resources development. It also considers mid-term impacts (4-5 years) and longer term outcomes, known as 'wealth and health' benefits. Mid-term impacts indicators include concrete results on biomarker validation/toxicology test, big data and shared IT infrastructures, improved knowledge transfer and communication. This study is necessary in order to enhance our performance evaluation framework which is currently under review.

The final report will be ready for publication by the end of 2018 and will be disseminated to all stakeholders, including policy makers at the European level. It is expected that this study will cost approximatively 20.000 EUR.

3.3   Call management rules

All proposals must conform to the conditions set out in the H2020 Rules for Participation (http://ec.europa.eu/research/participants/data/ref/h2020/legal_basis/rules_participation/h2020-rules-participation_en.pdf and the Commission Delegated Regulation with regard to IMI2 JU http://eur-lex.europa.eu/legal-content/EN/TXT/PDF/?uri=CELEX:32014R0622&from=EN.

The following general conditions shall apply to the IMI2 JU Calls for Proposals. They are based on the General Annexes to the Horizon 2020 Work Programme 2018-2020[11].

LIST OF COUNTRIES AND APPLICABLE RULES FOR FUNDING

By way of derogation[12] 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 IMI 2 JU provided their participation is deemed essential for carrying out the action by the IMI 2 JU or when such funding is provided for under a bilateral scientific and technological agreement or any other arrangement between the Union and the country in which the legal entity is established[13].

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 and for CSA short proposals is 20 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 and for CSA full proposals is 50 pages.

STANDARD ELIGIBILITY CONDITIONS

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

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

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

[12] 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

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

The participants from EFPIA constituent entities and affiliated entities and other 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 other Associated Partners.[14]

TYPES OF ACTION: SPECIFIC PROVISIONS AND FUNDING RATES

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

TECHNOLOGY READINESS LEVELS (TRL)

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

EVALUATION RULES

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

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

Award criteria and scores:

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

Type of action	Excellence	Impact	Quality and efficiency of the implementation
RIA and IA 1st stage evaluation	The following aspects will be taken into account, to the extent that the proposed work corresponds to the topic description in the call for proposals and referred to in the IMI2 annual work plan: Clarity and pertinence of the proposal to meet all key objectives of the topic; Credibility of the proposed approach; Soundness of the concept, including trans-disciplinary considerations, where relevant; Extent that proposed work is ambitious, has	The following aspects will be taken into account, to the extent to which the outputs of the project should contribute at the European and/or International level: The expected impacts of the proposed approach as mentioned in the call for proposals Added value from the public private partnership approach on R&D, regulatory, clinical and healthcare practice as relevant; Strengthening the competitiveness and industrial leadership and/or addressing specific societal challenges; Improving European citizens' health and wellbeing and	The following aspects will be taken into account: Coherence and effectiveness of the outline of the project work plan, including appropriateness of the roles and allocation of tasks, resources, timelines and approximate budget; Complementarity of the participants within the consortium (where relevant) and strategy to create a successful partnership with the industry consortium as mentioned in the topic description in the Call for proposal;

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[14] 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	Impact	Quality and efficiency of the implementation
	innovation potential, and is beyond the state of the art; Mobilisation of the necessary expertise to achieve the objectives of the topic, ensure engagement of all relevant key stakeholders	contribute to the IMI2 objectives[15].	Appropriateness of the proposed management structures and procedures, including manageability of the consortium.
RIA and IA Single stage, and 2nd stage evaluation	The following aspects will be taken into account, to the extent that the proposed work corresponds to the topic description in the call for proposals and referred to in the IMI2 annual work plan and is consistent with the stage 1 proposal: Clarity and pertinence of the proposal to meet all key objectives of the topic; Credibility of the proposed approach; Soundness of the concept, including trans-disciplinary considerations, where relevant; Extent that proposed work is ambitious, has innovation potential, and is beyond the state of the art; Mobilisation of the necessary expertise to achieve the objectives of the topic, ensure engagement of all relevant key stakeholders.	The following aspects will be taken into account, to the extent to which the outputs of the project should contribute at the European and/or International level: The expected impacts of the proposed approach as mentioned in the call for proposals; Added value from the public private partnership approach on R&D, regulatory, clinical and healthcare practice as relevant; Enhancing innovation capacity and integration of new knowledge; Strengthening the competitiveness and industrial leadership and/or addressing specific societal challenges; Improving European citizens' health and wellbeing and contribute to the IMI2 objectives;[15] Any other environmental and socially important impacts; Effectiveness of the proposed measures to exploit and disseminate the project results (including management of IPR), to communicate the project, and to manage research data where relevant.	The following aspects will be taken into account: Coherence and effectiveness of the project work plan, including appropriateness of the roles and allocation of tasks, resources, timelines and budget; Complementarity of the participants within the consortium (where relevant); Clearly defined contribution to the project plan of the industrial partners (where relevant); Appropriateness of the management structures and procedures, including manageability of the consortium, risk and innovation management and sustainability plan.

Type of action	Excellence	Impact	Quality and efficiency of the implementation
CSA **1st stage** **evaluation**	The following aspects will be taken into account, to the extent that the proposed work corresponds to the topic description in the Call for proposal and referred to in the IMI2 annual work plan: Clarity and pertinence of the proposal to meet all key objectives of the topic Credibility of the proposed approach; Soundness of the concept, including trans-disciplinary considerations, where relevant; Quality of the proposed coordination and/or support measures. Mobilisation of the necessary expertise to achieve the objectives of the topic, ensure engagement of all relevant key stakeholders.	The following aspects will be taken into account, to the extent to which the outputs of the project should contribute at the European and/or International level: The expected impacts of the proposed approach as mentioned in the Call for proposal; Added value from the public private partnership approach on R&D, regulatory, clinical and healthcare practice as relevant. Strengthening the competitiveness and industrial leadership and/or addressing specific societal challenges; Improving European citizens' health and wellbeing and contribute to the IMI2 objectives[16].	The following aspects will be taken into account: Coherence and effectiveness of the outline of the project work plan, including appropriateness of the roles and allocation of tasks, resources, timelines and approximate budget; Complementarity of the participants within the consortium (where relevant) and strategy to create a successful partnership with the industry consortium as mentioned in the topic description in the Call for proposal. Appropriateness of the proposed management structures and procedures, including manageability of the consortium.
CSA **Single stage and 2nd stage** **evaluation**	The following aspects will be taken into account, to the extent that the proposed work corresponds to the topic description in the Call for proposal and referred to in the IMI2 annual work plan and is consistent with the stage 1 proposal: Clarity and pertinence of the proposal to meet all key objectives of the topic;	The following aspects will be taken into account, to the extent to which the outputs of the project should contribute at the European and/or International level: The expected impacts of the proposed approach as mentioned in the Call for proposal; Added value from the public private partnership approach on R&D, regulatory, clinical and health care practice as relevant	The following aspects will be taken into account: Coherence and effectiveness of the project work plan, including appropriateness of the roles and allocation of tasks, resources, timelines and budget; Complementarity of the participants within the consortium (where relevant);

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

Type of action	Excellence	Impact	Quality and efficiency of the implementation
	Credibility of the proposed approach; Soundness of the concept, including trans-disciplinary considerations, where relevant; Quality of the proposed coordination and/or support measures. Mobilisation of the necessary expertise to achieve the objectives of the topic and to ensure engagement of all relevant key stakeholders.	Strengthening the competitiveness and industrial leadership and/or addressing specific societal challenges; Improving European citizens' health and wellbeing and contribute to the IMI2 objectives[17]. Effectiveness of the proposed measures to exploit and disseminate the project results (including management of IPR), to communicate the project, and to manage research data where relevant.	Clearly defined contribution to the project plan of the industrial partners (where relevant); Appropriateness of the management structures and procedures, including manageability of the consortium, risk and innovation management and sustainability plan.

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

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

The full evaluation procedure is described in the IMI2 JU Manual for submission, evaluation and grant award in line with the H2020 Rules for Participation.[18]

Where appropriate and duly justified, IMI 2 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.

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

[18] http://www.imi.europa.eu/sites/default/files/uploads/documents/apply-for-funding/call-documents/imi2/IMI2_ManualForSubmission_v1.6_October2017.pdf

Under the two-stage evaluation procedure, and on the basis of the outcome of the first stage evaluation, the applicant consortium of the highest ranked short proposal (first stage) for each topic[19] will be invited to discuss with the relevant industry consortium the feasibility of jointly developing a full proposal (second stage). The applicant consortia of the second and third-ranked short proposals (first stage) for each topic may be invited for preliminary discussions with the industry consortium if the preliminary discussions with the first ranked proposal and the industry consortium fail. In such a case, the first applicant consortium and the industry consortium shall be responsible for jointly notifying the IMI2 JU if the preparation of a joint full proposal is not feasible. This notification must be accompanied by a joint report clearly stating the reasons why a joint full proposal is considered not feasible. Upon acknowledgement and after consideration of the specific circumstances, the IMI2 JU may decide to invite the next-ranked applicant consortium in priority order, i.e. the second ranked proposal is contacted only after failure of preliminary discussions with the first ranked, and the third ranked after the second ranked.

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

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

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

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.

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

CONDITIONS RELATED TO OPEN ACCESS TO RESEARCH DATA

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

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

SUBMISSION TOOL

Proposals in response to a topic of the IMI2 JU Call for proposals must be submitted on-line, before the call deadline, by the coordinator via the Electronic Submission Service of the Participant Portal: http://ec.europa.eu/research/participants/portal/desktop/en/home.html

No other means of submission will be accepted.

OTHERS

For proposals including clinical trials/studies/investigations, a specific template to help applicants to provide essential information on clinical studies in a standardised format is available under: http://www.imi.europa.eu/apply-funding/call-documents/imi2-call-documents#imi2-call-documents-collapsible-1.

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

Ethical issues should be duly addressed in each submitted proposal to ensure that the proposed activities comply with ethical principles and relevant national, Union and international legislation. Any proposal that contravenes ethical principles or which does not fulfil the conditions set out in the H2020 Rules for Participation, or in the IMI2 JU Call for proposals shall not be selected. [20]

In order to ensure excellence in data and knowledge management consortia will be requested to Disseminate scientific publications on the basis of open access[21] (see "Guidelines on Open Access to Scientific Publications and Research Data in Horizon 2020").

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

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

Applicants intending to submit a proposal in response to the IMI2 JU Calls should also read the topic text, the IMI2 JU Manual for submission, evaluation and grant award, and other relevant documents[22] (e.g. IMI2 JU model Grant Agreement).

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

[21] Article 43.2 of Regulation (EU) No 1290/2013 of the European Parliament and of the Council laying down the rules for participation and dissemination in "Horizon 2020 - the Framework Programme for Research and Innovation (2014-2020)" and repealing Regulation (EC) No 1906/2006

[22] http://www.imi.europa.eu/apply-funding/call-documents/imi2-call-documents

3.4   Support to Operations

3.4.1   Communication and events

Communication objectives

The overarching objectives of IMI2 JU's communications efforts are:
- to raise awareness and perception of IMI2 JU among all target groups;
- to encourage experts from all relevant groups to apply for funding under IMI2 JU Calls for proposals (with a particular focus on groups such as patients and SMEs).

The year 2018 marks the 10th anniversary of the very first IMI Call for proposals and this will represent an excellent opportunity to both showcase what IMI has achieved and discuss its future direction. In addition, IMI2 JU is now gathering growing numbers of success stories from both ongoing and closed projects, and this will help to support the message that IMI is a successful initiative, delivering scientifically excellent results and offering value for money to taxpayers.

IMI's 10th anniversary

In 2018, IMI will celebrate its 10th anniversary, and this is an excellent hook for communications. IMI2 JU will therefore plan a year-long programme of events and activities across its communications channels to promote IMI's successes and encourage discussion on its future plans. Highlights of the year will include:
- a scientific symposium featuring IMI2 JU-funded research;
- a book of IMI projects;
- a series of short video interviews.

Development of the IMI2 JU website

The IMI2 JU website is undergoing a redesign that will be completed in late 2017. In 2018, IMI2 JU will focus on refining the content, and on building on the dedicated sections for core stakeholder groups, namely universities, patients, SMEs, regulatory bodies, HTA, payers, and industry.

Further develop success stories

IMI2 JU now holds meetings with the representatives of projects that have finished, learning about what the projects have achieved and their legacy. With a large number of projects scheduled to finish in 2017 and 2018, these meetings will provide IMI2 JU with a wealth of success stories that can be adapted for different audiences and channels and back up IMI2 JU's key messages. IMI2 JU will also continue to maintain close contacts with ongoing projects to gather and promote their latest news and results.

Media outreach

The coverage of IMI2 JU in both the general and specialist press tends to be either neutral or positive in tone. In 2018, IMI2 JU will work to ensure that this trend continues by building and maintaining links with journalists, issuing regular press releases, organising press interviews, and inviting journalists to IMI2 JU events.

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

Communication channels

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

Key events in 2018

Event	Timeline
Promote IMI2 JU projects	Ongoing
IMI2 JU presence in the European Parliament	Ongoing
IMI2 JU presence at relevant external events, e.g. BIO, BIO-Europe, ESOF, BioFIT	Throughout year
Event with and for patients	Q2
Promote IMI2 JU Calls for proposals (webinars, info days, website, etc.)	Q2, Q4
IMI2 JU scientific symposium (10 years)	Q4
IMI2 JU Stakeholder Forum 2018	Q4

3.4.2   Procurement and contracts

In order to reach its objectives and adequately support its operations and infrastructures, IMI2 JU will allocate funds to procure the necessary services and supplies. To make tender and contract management as effective and cost-efficient as possible, IMI2 JU makes as much use as possible of multi-annual framework contracts, several of which are inter-institutional in nature.

In 2018, IMI2 JU intends to implement one such framework contract by concluding a specific contract for the provision of external audit services for its 2018 and 2019 accounts. Most essential framework contracts are already in place or and will be running beyond 2018. The framework contract for the provision of IT services (for all Joint Undertakings occupying the White Atrium building) will come to an end in 2018. An open procedure will have to be launched in Q1 2018 to ensure seamless service continuity. The estimated budget for this tender is approximately 4,500,000 EUR, covering the needs of all contracting Joint Undertakings over a four-year period.

Furthermore, the IMI2 JU will launch an open call for tender for the conclusion of a communication services contract, for which the estimated value is 250,000 EUR, designed to cover the tenth anniversary events and activities mentioned in Section 2.4.1.

Finally, the framework contract for the provision of Ex-Post Audits for the Framework Programme 7 (for all EC services, DG RTD being the lead contractor) came to an end in 2017. An open call for tender will be launched in Q1 2018 for a cascade type framework contract with other Joint Undertakings (FCH JU and Clean Sky JU), with IMI2 JU as lead contractor, to ensure seamless service continuity. The estimated budget is 1,600,000 EUR, covering the needs of all contracting Joint Undertakings over a four-year period.

3.4.3   IT and logistics

IMI2 JU information and communications technologies (ICT) 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 IMI. Operations and administration information systems and infrastructure aim at making all IMI processes simpler and more efficient.

In order to achieve the afore-mentioned goal IMI2 JU IT will focus its 2018 activities on three areas:

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

2.4.3.1 Business operations information systems

In 2017, IMI2 JU's business operations started utilising the full suite of H2020 IT tools for the management of IMI2 calls, applications, evaluations and grants.

With the full transition expected to be completed by the end of 2017, IT will monitor satisfactory functioning for all end-users, in close liaison with EC services.

IMI1 projects remain in IMI's in-house developed application SOFIA.

The reporting needs of various IMI's stakeholders are supported by Qlikview, which is a reporting tool with a variety of tailor-made dashboards, enabling the analysis of scientific and financial data regarding IMI calls and projects.

Since IMI1 projects continue running until at least 2020 the following developments are foreseen for SOFIA application:

- Maintenance (continuous) of the application with helpdesk support, bug fixes and implementation of service requests (Q1 – Q4 2018)

Moreover, the following developments are foreseen for Qlikview:

- Addition of reports based on the needs of external, for example EFPIA Office, SRG, and internal stakeholders, and improvement of currently available dashboards (Q1 – Q4 2018)

2.4.3.2 Collaboration, communication and administration management information systems

IMI 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.

Furthermore, a number of web-based applications, related to human resources management, time management, mission management, document management, incident management and internal communications are available to IMI2 JU staff.

Last but not least, a new website was implemented in 2017, replacing the look and feel but also the back-end web content management system.

The following developments are foreseen in 2018 in order to safeguard the continuous improvement and increase of scope of the afore-mentioned systems:

- Enhancement of the applications regarding performance, usability and user interface in order to improve the end-user experience and facilitate IMI2 JU staff work (Q1 – Q4 2018)
- Maintenance (continuous) of the applications with helpdesk support, bug fixes and implementation of service requests (Q1 – Q4 2018)
- Implementation of the paperless office concepts based on the assessment of the practicality of current document repository application to support the automation of IMI2 JU's administrative processes compared to commercial off-the-shelf products with applied workflows, which is taking place in 2017 (Q2-Q4 2018).

Furthermore, in 2017 IMI2 JU considered the possibility of using the EC application SYSPER II for personnel time management. In 2018, IMI2 JU should move to SYSPER II, therefore all the necessary IT changes will have to take place in order to support this transition (Q3-Q4 2018).

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 2018, which are expected to provide with efficiency gains in the operation of the organisation:

- Maintenance (continuous) of the common infrastructure and networks and end-user office-automation support covering incidents, service requests and improvements (Q1 – Q4 2018)

- A new call for tenders for the provision of IT services (office support, IT infrastructure maintenance, etc.) that will lead to the signature of a new framework contract. (Q3- Q4 2018)

Moreover, IMI2 JU utilises an online infrastructure in order to host its business operations information systems, and the collaboration, communication and administration information systems mentioned above. The following activities are anticipated to take place in 2018 in the context of the dedicated infrastructure:

- Maintenance (continuous) of the online infrastructure (Q1 – Q4 2018).

3.4.4   Human Resources

The 2018 objective for HR shall be: recruit, train, assess, motivate and retain highly qualified staff with a view to ensure effective and efficient operation of the JU as well as ensuring equal opportunities. This objective will be implemented through the following four main themes:

Staffing

The staffing needs of IMI2 JU will be the same as in 2017. The total number of staff remains to 54 temporary and contract agents as well as 2 additional seconded national experts.
In accordance with the Staff Regulations, technical adaptations have been made to the Staff Establishment Plan in order to create margin for reclassification (promotions) of staff. Those adaptations do not affect the total number of staff, 54 (39 temporary agents and 15 contract agents).

The Human Resources team will implement the selection and recruitment actions.

Organisation development

Human resources will advise management on means and actions to enhance operational efficiency and effectiveness. The main action shall be the oversight of duties and responsibilities that has been assigned to best achieve fulfilment of objectives and tasks.

HR management

Human Resources will deal with core functions such as day-to-day management of administrative workflows and process, performance management and assessment, safety and wellbeing at work, salary, compensation and benefits, employee motivation, communication, and training.
In addition, during the second semester of 2018, IMI2 JU is expected to move to SYSPER II, which will help in the personnel administration.

Inter-JU cooperation

The efficiency and cost effective management of IMI2 JU resources is also based on a close collaboration with other Joint Undertakings through arrangements and mechanisms of pooling expertise for specific time-bound tasks. In 2018, the JUs will continue to share human resources IT tools where necessary, common calls for tender as well as a common approach to implementing rules of the EU Staff regulation.

3.4.5 Administrative budget and finance

Budget 2018

A table overview of the administrative budget for the financial year 2018 is set out below.

Chapter	Heading Title 1	Budget 2018.0		Budget 2018 Amendment 2		Amended Budget 2018.2	
		Commitment Appropriation (CA)	Payment Appropriation (PA)	Commitment Appropriation (CA)	Payment Appropriation (PA)	Commitment Appropriation (CA)	Payment Appropriation (PA)
11	Staff in active employment	5,425,000	5,425,000			5,425,000	5,425,000
12	Staff recruitments - miscellaneous expenditure	20,000	20,000		13,975	20,000	33,975
13	Missions and duty travels	190,000	190,000		36,906	190,000	226,906
14	Socio-medical structure	360,000	360,000		22,517	360,000	382,517
17	Representation	20,000	20,000		431	20,000	20,431
	Title 1 - Total	**6,015,000**	**6,015,000**	**0**	**73,830**	**6,015,000**	**6,088,830**

Chapter	Heading Title 2	Budget 2018.0		Budget 2018 Amendment 2		Amended Budget 2018.2	
		Commitment Appropriation (CA)	Payment Appropriation (PA)	Commitment Appropriation (CA)	Payment Appropriation (PA)	Commitment Appropriation (CA)	Payment Appropriation (PA)
20	Office building and associated costs	729,000	729,000		168,355	729,000	897,355
21	Information technology purchases	712,000	712,000		603,585	712,000	1,315,585
22	Office equipment (movable property and associated costs)	153,000	153,000			153,000	153,000
23	Current administrative expenditure	123,000	123,000		7,744	123,000	130,744
24	Telecommunication and postal expenses	68,000	68,000		42,956	68,000	110,956
25	Expenditure on formal meetings	158,000	158,000		28,401	158,000	186,401
26	Running costs in connection with operational activities	300,000	300,000		74,138	300,000	374,138

	Heading Title 2	Budget 2018.0		Budget 2018 Amendment 2		Amended Budget 2018.2	
27	External communication, information and publicity	625,000	625,000		100,617	625,000	725,617
28	Service contracts	730,000	730,000		308,686	730,000	1,038,686
29	Expert contracts and cost of evaluations	700,000	700,000		41,216	700,000	741,216
	Title 2 - Total	4,298,000	4,298,000		1,375,697	4,298,000	5,673,697
	Total running costs Title 1 + Title 2	10,313,000	10,313,000		1,449,527	10,313,000	11,762,527

The payment appropriations carried over to the 2018 budget are related to the commitments carried forward from 2017 to 2018.

The operational budget is covered under section 3.2.2. Calls for proposals.

A table overview of the 2018 budget is set out in Chapter 4 of this Annual Work Plan.

Financial Management

During 2018, 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 availability of a Manual of Financial Procedures that is under regular revision. 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.

3.4.6   Data protection

Objectives	To implement the Data Protection reform following the adoption of the General Data Protection Regulation [Regulation (EU) 2016/679 of 27 April 2016] which enters into application on 25 May 2018 after a two-year transition period. To continue to promote a culture of data protection at IMI2 JU. To support processes and projects in establishing common minimum requirements for protecting and sharing personal data.
Planned Activities	To implement the data protection reform following the adoption of the General Data Protection Regulation and in particular: ▪ increased accountability: advise and support controller and data processors on their responsibility and liability for further processing; ▪ higher data handling standards: reinforce the Data Protection Officer role (e.g. performance of data protection impact assessments, further recording of processing activities and collection of evidence for obtaining consent); ▪ data security: establish internal procedures in relation to the use of technologies; ▪ transparency: implement changes in consent and take into account the shifting of the burden of proof for compliance. To continue to promote a culture of data protection at IMI2 JU: ▪ training and advising; ▪ implement the revised procedure for handling notifications; ▪ participate in the EU network for Data Protection Officers and implement best practices; ▪ follow-up progress on implementation and potential impact of the new EU framework for data protection. To support processes and projects in establishing common minimum requirements for protecting and sharing data: ▪ advising; ▪ follow-up on recommendations addressed to IMI2 JU by the European Data Protection Supervisor.
Expected results	To ensure that personal data is protected, that the General Data Protection Regulation is complied with and that the implementation of the related legal requirements for EU agencies and bodies is handled smoothly. Actions: ▪ train newcomers; ▪ inform IMI2 JU staff on data protection matters during internal meetings; ▪ provide advice upon request; ▪ support the preparation of internal notifications; ▪ prepare prior-checking notifications and/or their updates; ▪ attend EDPS and Data Protection Officers meetings; ▪ prepare standard operating procedures.

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 output closer to the public. In this context, the programme office will further develop a transparency policy on activities of its governance bodies in accordance with the Council Regulation setting up IMI2 JU.

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

▪ Improving public awareness of IMI2 JU activities and processes;
▪ Stimulating the interaction on key issues.

3.5   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, Scientific Committee, States Representatives Group and management.
- Align planning activities (strategy, annual work plans and related budget) and the following monitoring and reporting activities.
- Improve responsibilities and accountability.
- Enhance communication and transparency.

IMI2 JU will continue to provide support to the Governing Board, the Scientific Committee, the States Representatives Group, and the Stakeholders' 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** will continue in its advisory role to the Governing Board of the IMI2 JU and will notably be consulted on the scientific priorities to be addressed in Annual Work Plans and on the scientific achievements to be described in the Annual Activity Report.

At least two meetings of the Scientific Committee are planned for 2018.

The term of the current Scientific Committee members will come to end in 2018, and a new Committee will be appointed in 2nd half of 2018.

The Chair will participate in Governing Board meetings as observer. Information can be found at: http://www.imi.europa.eu/about-imi/governance/scientific-committee

The **States Representatives Group** will be consulted on the Annual Work Plans and will receive information on Calls outcomes and evaluation process. At least two meetings of the States Representatives Group are planned for 2018. With the end of the current mandate of the SRG Chair and Vice-Chair, an election process will be held. The Chair will participate in Governing Board meetings as observer. Information can be found at: http://www.imi.europa.eu/about-imi/governance/states-representatives-group

In addition, a joint meeting between the IMI2 Scientific Committee and the States Representatives Group is planned in order 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 develop the IMI2 JU objectives, IMI2 JU will pursue its action to attract a wide range of legal entities, notably promoting the possibility to become **Associated Partners** at programme or topic level. 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 IMI Programme Office and the IMI2 JU Scientific Committee. Currently, the seven established SGGs focus on the following areas: immunology; diabetes / metabolic disorders; neurodegeneration; translational safety; digital health and patient-centric evidence generation; infections control, and oncology. In early 2018, the Digital Health and Patient-Centric Evidence Generation SGG evolved from the former SGG "Data and Knowledge Management" (DKM), and received a new mandate focused on digital health and evidence generation, building on the achievements and the initial mandate of the SGG DKM.

In 2018 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 IMI activities and developments.

An objective in 2018 will also be to facilitate better cross SGG coordination and interactions by putting in place an updated IT platform and organising dedicated cross-SGG meetings. These improved efficiency mechanisms will facilitate the increased flow of information not only within a given SGG, but also with IMI2 governance bodies (GB, SC, SRG). Therefore, the SGG meeting agendas, publishable minutes and attendance lists will be more readily available. In addition, they will be called upon to advise on how best to exploit IMI2 JU projects' outputs, enhance cross-projects' collaboration as well as explore synergies with similar or complementary activities at national and global level.

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

Expected results

- Streamlined governance activities

Actions:

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

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

3.6   Internal Control framework

Internal control

The IMI2 JU is aligning its Internal Control Framework (ICF) to the revised control framework adopted by the European Commission on 19 April 2017[24]. The new ICF moves away from a compliance-based to a principle-based system and provides the necessary flexibility to adapt to specific characteristics and circumstances while ensuring a robust internal control with a consistent assessment throughout the IMI2 JU. This approach aims at helping the organisation to achieve its objectives and sustain operational and financial performance[25]. In that context, the activities foreseen for 2018 will essentially aim at maintaining throughout the JU Office the achieved level of effectiveness and efficiency of the internal control framework while in parallel setting up the tools, functions and methodologies needed for the implementation of the new approach.

Financial procedures

Financial procedures guide IMI2 JU operations and lay out how the JU uses and manages its funds and resources.

In 2018 focus will be put on the following:

- periodic revision of the operating financial procedures and in particular of the Manual of Procedure for financial Operations (MoP);
- follow up and implementation of the results of the validation performed during 2017 by DG BUDG on the accounting management system of the IMI2 JU.

Ex-ante and ex-post controls

Ex-ante controls

In accordance with Article 18 of IMI 2 JU Financial Rules "each operation shall be subject at least to an ex ante control based on a desk review of documents and on the available results of controls already carried out relating to the operational and financial aspects of the operation". In that view, ex-ante controls are essential to prevent errors and avoid the need for ex-post corrective actions. Those controls are performed by the IMI2 JU in the form of a desk and mid-term review and definitely assure the implementation of the principle of sound financial management throughout the IMI2 JU operations.

In 2018 the IMI2 JU will continue to assess and update the procedures defining the controls to be performed by project and finance officers for every cost claim, invoice, commitment and payment taking into account risk based and cost-effectiveness considerations. Specific attention will be placed on the:

- continued implementation of the joint guidance on H2020 ex-ante controls for interim and final payments adopted by the Commission Common Support Centre;
- financial checks during the Grant Agreement Preparation (GAP) phase;
- information and communication campaigns for IMI2 JU beneficiaries on H2020 rules and how to avoid errors in cost reporting.

Ex-post controls

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

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[24] Communication on the revision of the Internal Control Framework (ICF) – C(2017)2373.

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

Representative and, if necessary, risk-based audits of beneficiaries will be launched during the year to cover new cost claims received and validated by IMI since the last audited period. In parallel, risk-based audits of accepted declarations of in-kind contributions by EFPIA companies will also be continued and followed-up.

As regards the IMI2 JU programme, IMI's ex-ante and ex-post controls of grants are both aligned with the harmonised strategies adopted for the entire H2020 Programme. The IMI programme office will carry out the ex-ante checks as prescribed in the H2020 Control strategy. As for ex-post controls, the Commission Common Audit Service (CAS) will carry out the H2020 audits in accordance with the common H2020 audit strategy. IMI2 JU contributes to the implementation of the audit strategy in close cooperation with the CAS. The harmonised legal framework will enable IMI2 JU to draw an additional element of assurance from extension of audit results on shared beneficiaries across the H2020 programme.

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

Internal and external audits

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

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

The IAS will continue performing the internal audit function. IAS will perform an in-depth risk assessment in IMI2 JU in the course of 2018, which will result in a new Strategic Internal Audit Plan for the period 2019-2021.

In 2018, the Audit manager will contribute to the overall corporate objective of receiving an unqualified ('clean') ECA audit opinion and positive statement of assurance.

ECA will audit and issue opinions on the legality and regularity of the underlying transactions. In accordance with the IMI2 Financial rules, IMI2 JU's 2017 annual accounts will be audited by an external audit company while the Court will draw an opinion on the basis of their work.

The Audit Manager will continue to examine and evaluate risk management, control and governance processes of the IMI2 JU to provide independent assessment and consulting aimed at adding value and improving IMI2 JU's operations.

Anti-fraud strategy

Anti-fraud measures are an essential part of sound financial management required under the EU Financial Regulation, safeguards to financial interests of the Joint Undertaking and contribute to its reputation.
In 2018 IMI2 JU will make an assessment of the first three years of implementation of its anti-fraud Action Plan.
Additional actions will focus on:

- awareness about fraud risk across the JU as well as among partners and beneficiaries;
- fraud risk analysis and reviews especially in areas considered vulnerable;
- training of staff disseminating relevant reports within the JU as appropriate and maintaining operational contacts with the European Anti-fraud Office (OLAF).

4 Budget 2018

An overview of the 2018 budget per chapters is set out below.

	STATEMENT OF REVENUE							
	Heading Revenue	**Budget 2018.0**		**Budget 2018 Amendment 2**		**Amended Budget 2018.2**		**Comments**
Chapter		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)	270,487,957	208,398,668			270,487,957	208,398,668	Commitment appropriations include EUR 5,156,500 for running costs and EUR 265,331,457 for operational costs. Payment appropriations include running costs of EUR 5,156,500 and operational costs of EUR 203,242,168.
C2	Appropriations carried over			209,698,405	56,133,212	209,698,405	56,133,212	The amount carried over from previous years. Administrative expenditure - payment appropriation. Operational expenditure - commitment and payment appropriation.
	Title 1 - Total	**270,487,957**	**208,398,668**	**209,698,405**	**56,133,212**	**480,186,362**	**264,531,880**	
20	EFPIA contribution	5,156,500	5,156,500			5,156,500	5,156,500	EFPIA contribution to IMI JU running costs.
21	EFPIA constituent entities or their affiliated entities contributions	-	1,000,000			0	1,000,000	EFPIA companies contributions to operational payment appropriations
	Title 2 - Total	**5,156,500**	**6,156,500**	**0**	**0**	**5,156,500**	**6,156,500**	
30	Associated Partners contributions	-	1,354,000			0	1,354,000	Bill and Melinda Gates Foundation contribution to operational payment appropriations
	Title 3 - Total		**1,354,000**	**0**	**0**	**0**	**1,354,000**	
	Total contributions	**275,644,457**	**215,909,168**	**209,698,405**	**56,133,212**	**485,342,862**	**272,042,380**	

STATEMENT OF EXPENDITURE

Chapter	Heading Title 1	Budget 2018.0		Budget 2018 Amendment 2		Amended Budget 2018.2		Comments
		Commitment Appropriation (CA)	Payment Appropriation (PA)	Commitment Appropriation (CA)	47	Commitment Appropriation (CA)	Payment Appropriation (PA)	
11	Staff in active employment	5,425,000	5,425,000			5,425,000	5,425,000	Salaries
12	Staff recruitments - miscellaneous expenditure	20,000	20,000		13,975	20,000	33,975	Miscellaneous expenditure on staff recruitment: travel expenses, etc.
13	Missions and duty travels	190,000	190,000		36,906	190,000	226,906	Mission expenses
14	Socio-medical structure	360,000	360,000		22,517	360,000	382,517	Other staff costs: training, language classes, medical service, interim staff
17	Representation	20,000	20,000		431	20,000	20,431	Representation, receptions and internal meetings
	Title 1 - Total	**6,015,000**	**6,015,000**	**0**	**73,830**	**6,015,000**	**6,088,830**	

Chapter	Heading Title 2	Budget 2018.0		Budget 2018 Amendment 2		Amended Budget 2018.2		Comments
		Commitment Appropriation (CA)	Payment Appropriation (PA)	Commitment Appropriation (CA)	Payment Appropriation (PA)	Commitment Appropriation (CA)	Payment Appropriation (PA)	
20	Office building and associated costs	729,000	729,000		168,355	729,000	897,355	Rent, works, common/IMI charges and parking. Additional costs: indexation, insurance, water/gas, electricity, heating, maintenance + repairs, security and surveillance.
21	Information technology purchases	712,000	712,000		603,585	712,000	1,315,585	IT purchases, software licences, software development, IMI website.
22	Office equipment (movable property and associated costs)	153,000	153,000			153,000	153,000	Purchases and rental of office equipment, maintenance and repair.
23	Current administrative expenditure	123,000	123,000		7,744	123,000	130,744	Office supply. Literature, subscriptions, translation services, bank charges and miscellaneous office expenditure.
24	Telecommunication and postal expenses	68,000	68,000		42,956	68,000	110,956	Data communication such as telephone, video conferences and postal services.
25	Expenditure on formal meetings	158,000	158,000		28,401	158,000	186,401	Official meetings such as SRG, Scientific committee, Governing Board and working groups created by GB.
26	Running costs in connection with operational activities	300,000	300,000		74,138	300,000	374,138	Expenditure in connection with research activities and objectives of IMI (workshops, meetings and events targeting IMI projects).
27	External communication, information and publicity	625,000	625,000		100,617	625,000	725,617	External communication and events such as Info Days, stakeholder forums.
28	Service contracts	730,000	730,000		308,686	730,000	1,038,686	Studies, audits.
29	Expert contracts and cost of evaluations	700,000	700,000		41,216	700,000	741,216	Costs linked to evaluations, expert contracts.
	Title 2 - Total	**4,298,000**	**4,298,000**	**-**	**1,375,697**	**4,298,000**	**5,673,697**	
	Total administrative costs Title 1 + Title 2	*10,313,000*	*10,313,000*	*-*	*1,449,527*	*10,313,000*	*11,762,527*	

Chapter	Heading Title 3	Budget 2018.0		Budget 2018 Amendment 2		Amended Budget 2018.2		Comments
		Commitment Appropriation (CA)	Payment Appropriation (PA)	Commitment Appropriation (CA)	Payment Appropriation (PA)	Commitment Appropriation (CA)	Payment Appropriation (PA)	
30	Implementing the research agenda of IMI JU	265,331,457	205,596,168			265,331,457	205,596,168	Grant agreements - Payments
C2	Appropriations carried over from previous years			209,698,405	54,683,685	209,698,405	54,683,685	
	Total operational costs Title 3	*265,331,457*	*205,596,168*	209,698,405	54,683,685	*475,029,862*	*260,279,853*	
	Total contributions	**275,644,457**	**215,909,168**	209,698,405	**56,133,212**	**485,342,862**	**272,042,380**	

An overview of the 2018 budget and structure per budget lines is set out in the table below:

Expense budget line	Description	Commitment appropriations (CA)	Payment appropriations (PA)	C2 - Payment Appropriation (PA)
A01100	Staff in active employment and costs linked to employment	3,644,000	3,644,000	
A01101	Family Allowances	374,000	374,000	
A01102	Transfer and expatriation allowance	405,000	405,000	
A01110	Contract Agents	636,000	636,000	
A01111	Seconded National Experts	0	0	
A01130	Insurance against sickness	98,000	98,000	
A01131	Insurance against accidents and occupational diseases	15,000	15,000	
A01132	Unemployment insurance for temporary staff	39,000	39,000	
A01133	Pension	0	0	
A01140	Birth and death allowance	10,000	10,000	
A01141	Annual travel costs from the place of employment to place of origins	59,000	59,000	
A01144	Fixed local travel allowances	3,000	3,000	
A01149	Other allowances	0	0	
A01172	Cost of organizing traineeships within IMI	32,000	32,000	
A01175	Translation and typing services and work to be contracted	0	0	
A01177	Other services rendered	5,000	5,000	
A01178	PMO fees	45,000	45,000	
A01180	Sundry recruitment expenses	0	0	
A01181	Travelling expenses (taking up duty)	5,000	5,000	
A01182	Installation allowance	43,000	43,000	
A01183	Moving expenses	0	0	
A01184	Temporary daily allowance	10,000	10,000	
A01190	Weightings (correction coefficient)	2,000	2,000	
A01191	Salaries adaptation	0	0	
11	**Staff in active employment**	**5,425,000**	**5,425,000**	**-**
A01200	Miscellaneous expenditure on staff recruitment	20,000	20,000	13,975
12	**Staff recruitments - miscellaneous expenditure**	**20,000**	**20,000**	**13,975**
A01300	Mission expenses	190,000	190,000	36,906

Expense budget line	Description	Commitment appropriations (CA)	Payment appropriations (PA)	C2 - Payment Appropriation (PA)
13	**Missions and duty travels**	**190,000**	**190,000**	**36,906**
A01401	Socio-medical structure, EU school	80,000	80,000	
A01410	Other trainings	110,000	110,000	122
A01430	Medical service	5,000	5,000	
A01440	Trainings covered by the SLA	6,000	6,000	12,675
A01490	Other interventions	159,000	159,000	9,720
14	**Socio-medical structure**	**360,000**	**360,000**	**22,517**
A01700	Representation expenses	20,000	20,000	431
17	**Representation**	**20,000**	**20,000**	**431**
	Title 1 - Total	**6,015,000**	**6,015,000**	**73,830**
A02000	Rentals	569,000	569,000	105,869
A02001	Guarantees	0	0	
A02002	Contributions	0	0	
A02010	Insurance	0	0	
A02020	Water gas electricity and charges	131,000	131,000	912
A02030	Cleaning and maintenance	0	0	
A02040	Furnishing of premises (works)	10,000	10,000	61,574
A02050	Security and surveillance	19,000	19,000	
A02090	Other expenditure on buildings	0	0	
20	**Office building and associated costs**	**729,000**	**729,000**	**168,355**
A02101	Hardware, infrastructure and related services	218,000	218,000	275,917
A02102	Software development, licenses and related services	494,000	494,000	327,667
A02103	Other expenses maintenance and repair	0	0	
21	**Information technology purchases**	**712,000**	**712,000**	**603,585**
A02200	Purchase	123,000	123,000	
A02201	Rentals	10,000	10,000	
A02202	Maintenance utilisation and repair	20,000	20,000	
A02203	Other office equipment	0	0	
22	**Office equipment (movable property and associated costs)**	**153,000**	**153,000**	**-**
A02300	Stationery and office supply	40,000	40,000	1,872
A02320	Bank charges	0	0	
A02321	Exchange rate losses	0	0	
A02329	Other financial charges	0	0	

Expense budget line	Description	Commitment appropriations (CA)	Payment appropriations (PA)	C2 - Payment Appropriation (PA)
A02330	Legal expenses	0	0	
A02350	Other operating expenditure	13,000	13,000	5,872
A02351	Petty expenses	0	0	
A02360	Library stocks purchase of books and subscriptions	44,000	44,000	
A02370	Translation interpretation	26,000	26,000	
23	**Current administrative expenditure**	**123,000**	**123,000**	**7,744**
A02400	Correspondence and communication expenses	68,000	68,000	42,956
24	**Telecommunication and postal expenses**	**68,000**	**68,000**	**42,956**
A02500	Formal meetings	158,000	158,000	28,401
25	**Expenditure on formal meetings**	**158,000**	**158,000**	**28,401**
A02600	Running costs in connection with operational activities	24,000	24,000	13,276
A02601	Events	0	0	
A02602	Workshops	270,000	270,000	56,862
A02603	Knowledge Management	6,000	6,000	4,000
26	**Running costs in connection with operational activities**	**300,000**	**300,000**	**74,138**
A02700	External communication	225,000	225,000	74,958
A02701	Events	300,000	300,000	19,519
A02702	Material	100,000	100,000	6,140
27	**External communication, information and publicity**	**625,000**	**625,000**	**100,617**
A02800	Ex-post Audits	536,000	536,000	277,153
A02801	Studies, consultancy, services	114,000	114,000	
A02802	Audit services	80,000	80,000	31,533
28	**Service contracts**	**730,000**	**730,000**	**308,686**
A02900	Evaluation Experts meetings	600,000	600,000	40,309
A02901	Evaluation Facilities	100,000	100,000	907
A02902	Evaluations ENSO	0	0	
29	**Expert contracts and cost of evaluations**	**700,000**	**700,000**	**41,216**
	Title 2 - Total	**4,298,000**	**4,298,000**	**1,375,697**
B03000	Implementing the research agenda of IMI1 JU	0		
B03001	Call 1	0	57,000	
B03002	Call 2	0	700,000	
B03003	Call 3	0	6,086,573	
B03004	Call 4	0	2,630,148	

Expense budget line	Description	Commitment appropriations (CA)	Payment appropriations (PA)	C2 - Payment Appropriation (PA)
B03005	Call 5	0	0	
B03006	Call 6	0	7,500,000	
B03007	Call 7	0	54,426	
B03008	Call 8	0	9,206,582	
B03009	Call 9	0	6,927,000	
B03010	Call 10	0	1,200,000	
B03011	Call 11	0	21,523,399	
B03012	ENSO 2012	0	0	
B03013	ENSO 2013	0	0	
B03020	Implementing the research agenda of IMI2 JU	0		
B03021	IMI2 Call 1	0	2,900,000	
B03022	IMI2 Call 2	0	16,784,857	
B03023	IMI2 Call 3	0	7,679,759	
B03024	IMI2 Call 4	0	113,000	
B03025	IMI2 Call 5	0	7,001,500	
B03026	IMI2 Call 6	0	8,060,000	
B03027	IMI2 Call 7	0	4,147,984	
B03028	IMI2 Call 8	0	19,592,850	
B03029	IMI2 Call 9	0	1,000,000	
B03030	IMI2 Call 10	0	58,008,218	
B03031	IMI2 Call 11	0	2,627,194	
B03032	IMI2 Call 12	0	21,795,678	
B03033	IMI2 Call 13	0	0	
B03034	IMI2 Call 14	82,357,000	0	
B03035	IMI2 Call 15	182,974,457	0	
B03036	IMI2 Call 16	0	0	
B03037	IMI2 Call 17	0	0	
30 – C1	Implementing the research agenda of IMI JU	265,331,457	205,596,168	
B03020 - C2	Implementing the research agenda of IMI2 JU	7,000		54,683,685
B03030 - C2	IMI2 Call 10	173,890,000		
B03035 - C2	IMI2 Call 15	35,801,405		
30 - C2	Implementing the research agenda of IMI JU	209,698,405	-	54,683,685
	Title 3 - Total	475,029,862	205,596,168	54,683,685
	Total expenditures	485,342,862	215,909,168	56,133,212

4.1 Staff Establishment Plan 2018

Grade	Establishment Plan 2017			Year 2018											
				Posts evolution						Organisational evolution			Establishment Plan 2018		
				Promotion / Career advancement			Turn-over (departures/arrivals)			New posts (per grade)			Requested (Budget)		
	PERM	TEMP	TOTAL	Officials	TA - LT	TA - ST	Officials	TA - LT	TA - ST	Perm	TA - LT	TA - ST	PERM	TA	TOTAL
AD16															
AD15															
AD14		1	1											1	1
AD13															
AD12		2	2											2	2
AD11		2	2											2	2
AD10															
AD9		3	3		+ 2									5	5
AD8		7	7		- 2 +2									7	7
AD7		6	6		- 2									4	4
AD6					+2									2	2
AD5		12	12		- 2									10	10
Total AD	**33**	**33**												**33**	**33**
AST11															
AST10															
AST9															
AST8		1	1											1	1
AST7															
AST6															
AST5															
AST4					+ 2									2	2
AST3		4	4		- 2									2	2
AST2															
AST1		1	1											1	1
Total AST	**6**	**6**												**6**	**6**
SC6															
SC5															
SC4															
SC3															
SC2															
SC1															
Total SC	**0**	**0**												**0**	**0**
Overall Total	**39**	**39**												**39**	**39**

Contract Agents Grade	2017	2018
FG IV	2	2
FG III	12	12
FG II	1	1
FG I	0	0
Total CA	15	15

Seconded National Experts	2017	2018
	2	2

Annex I - IMI2 Call 14 topics text

Introduction

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

The Innovative Medicines Initiative 2 Joint Undertaking (IMI2 JU) has been created[26] following the principles below:

- Research related to the future of medicine should be undertaken in areas where societal, public health and biomedical industry competitiveness goals are aligned and require the pooling of resources and greater collaboration between the public and private sectors, with the involvement of Small- and Medium-sized Enterprises (SMEs).
- The scope of the initiative should be expanded to all areas of life science research and innovation.
- The areas should be of public health interest, as identified by the World Health Organisation (WHO) report on priority medicines for Europe and the World[27].

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

The initiative should therefore seek to involve a broader range of partners, including mid-sized companies[28], 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)[29] is the main reference for the implementation of research priorities for IMI2 JU. The scientific priorities for 2018 for IMI2 JU have been prepared based on the SRA.

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

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

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

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[26] Council Regulation (EU) No 557/2014 of 6 May 2014 establishing the Innovative Medicines Initiative 2 Joint Undertaking (IMI2 JU).
[27] http://www.who.int/medicines/areas/priority_medicines/en/
[28] 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.

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

Applicant consortia shall ensure that where relevant their proposals are in compliance with the General Data Protection Regulation (EU) 2016/679[30] and Clinical Trial Regulation (EU) 536/2014[31] (and/or Directive 2001/20/EC[32)]) and any relevant legislation[33].

Before submitting a proposal, applicant consortia should familiarise themselves with all Call documents such as the IMI2 JU Manual for evaluation, submission and grant award[34], 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).

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[30] 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.

[31] 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.

[32] 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.

[33] 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: http://eur-lex.europa.eu/legal-content/EN/TXT/?uri=celex:31995L0046

[34] http://www.imi.europa.eu/sites/default/files/uploads/documents/apply-for-funding/call-documents/imi2/IMI2_ManualForSubmission_v1.6_October2017.pdf

Topic 1: Targeted immune intervention for the management of non-response and relapse

Topic details

Topic code	IMI2-2018-14-01
Action type	Research and Innovation Action (RIA)
Submission and evaluation process	2 stages

Specific challenges to be addressed

A large number of patients suffering from immune-mediated diseases fail to respond well or at all to current standard-of-care treatments or quickly relapse while on, or following, treatment. Currently, one of the most challenging questions in human immunology is to understand whether it is possible to accurately predict which patients will fail to respond to treatment, which patients will sustain a longer term treatment response, or which patients will suddenly flare up during periods of disease control. At present, there is a lack of a mechanistic understanding of non-response combined with an absence of biomarkers to predict clinical responses. Detailed analysis of clinical samples before and during treatment would enable breakthrough discoveries on the mechanisms, the clinical management of non-response, and the identification of patients prone to relapse. The topic focuses on the application of state-of–the-art molecular and immune technologies and sophisticated informatics approaches to highly annotated pre- and post-therapy bio-samples obtained from patients with systemic lupus erythematosus (SLE), rheumatoid arthritis (RA), multiple sclerosis (MS), ulcerative colitis (UC), Crohn's disease (CD), asthma, and chronic obstructive pulmonary disease (COPD), in order to identify novel biomarkers that are predictive of clinical disease behaviour and response. In addition, this topic provides an opportunity for the discovery of cross-disease biomarkers with relevance to a group of immune-mediated inflammatory diseases. Biomarkers of treatment or therapeutic response to a given therapy across multiple diseases may provide key insights.

We have a poor understanding of the immune factors driving chronic progressive diseases, triggers of immune-mediated exacerbations and relapses and their underlying molecular signals. These episodes are highly clinically relevant, yet are often poorly controlled. The topic, through the study of patients who respond or do not respond to treatment, as well as placebo patients, aims to identify molecular mechanisms that can be targeted to control immune-mediated exacerbation and relapse. The topic represents a great opportunity for the use of patient-centric monitoring/sampling devices in order to obtain correlated data from patient reported outcomes/symptoms and associated bio-samples (e.g. tissue biopsies from skin, kidney, mucosal and lung, sputum, stool, blood and urine). Patient bio-resources should be ideally matched with high dimensional profiling of patients' signs and symptoms including patient reported outcomes, and the use of digital tools to capture patient outcomes and environment.

The topic addresses the challenge of translating insights from treatment non-response and disease exacerbation into new treatment paradigms at the individual patient level.

Subtopics and the Call process

To ensure that the topic attracts high-level clinical and scientific expertise for the indications selected, and to provide in-depth technical knowledge for the profiling and informatics of bio-samples, the topic is divided into the following four subtopics:
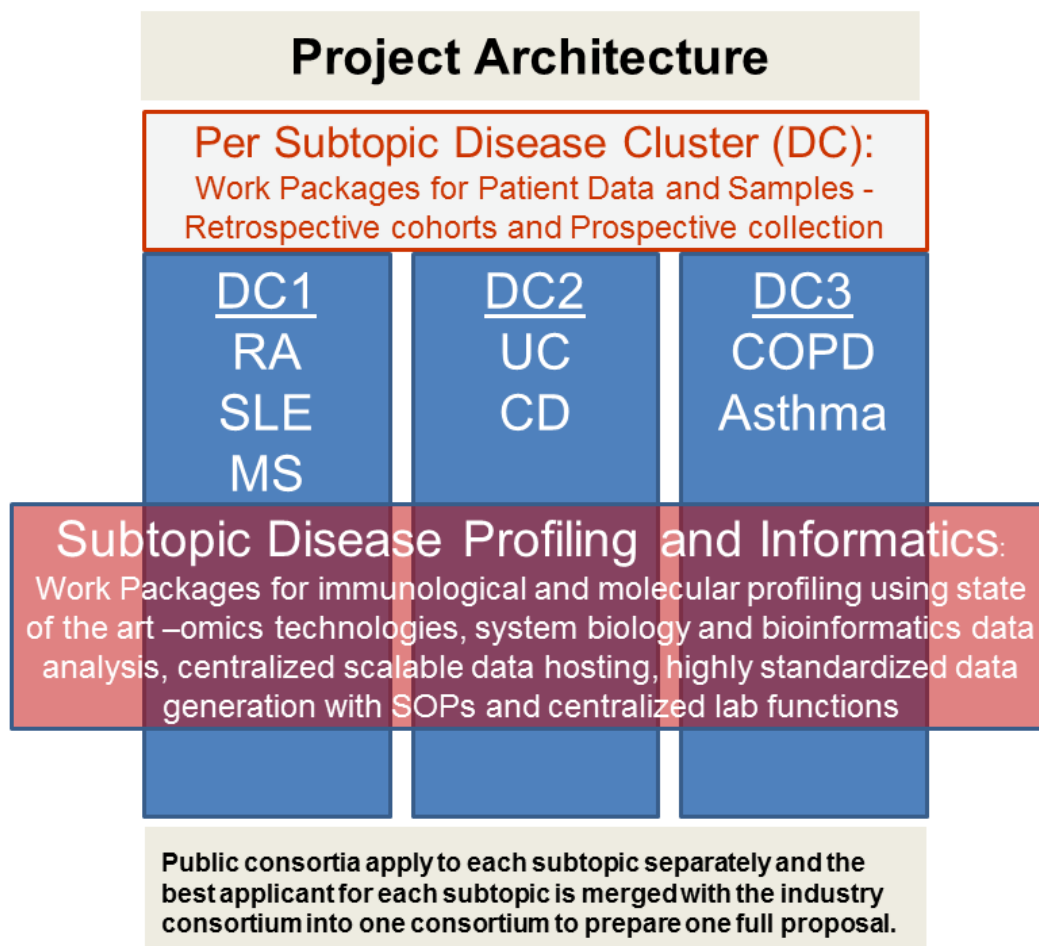
Subtopic 1: Disease profiling and informatics: state-of-the-art molecular and immune technologies in combination with cutting edge systems biology approaches to identify biomarkers predictive of treatment non-response, relapse and flare-up;

Subtopic 2: Disease cluster 1 (DC1): SLE, RA, and MS;

Subtopic 3: Disease cluster 2 (DC2): UC and CD;

Subtopic 4: Disease cluster 3 (DC3): Asthma and COPD.

Subtopics 2-4 focus on specific disease clusters. Applicant consortia will comprise disease-specific experts in clinical, scientific, biostatistics and regulatory affairs who have access to retrospective and prospective patient cohorts, bio-samples and data. These disease cluster teams will collaborate with each other and with the 'Disease profiling and informatics" subtopic 1 team in order to establish novel biomarkers and algorithms predictive of clinical disease behaviour and response.

Project Architecture

Per Subtopic Disease Cluster (DC): Work Packages for Patient Data and Samples - Retrospective cohorts and Prospective collection

DC1	DC2	DC3
RA	UC	COPD
SLE	CD	Asthma
MS		

Subtopic Disease Profiling and Informatics: Work Packages for immunological and molecular profiling using state of the art –omics technologies, system biology and bioinformatics data analysis, centralized scalable data hosting, highly standardized data generation with SOPs and centralized lab functions

Public consortia apply to each subtopic separately and the best applicant for each subtopic is merged with the industry consortium into one consortium to prepare one full proposal.

Two-stage Call process: at stage 1, sub-consortia will be formed for each subtopic 1-4. At stage 2, the selected sub-consortia will be combined with the industry consortium into a single consortium.

At Stage 1, applicant consortia should submit short proposals to only one of the four subtopics 1-4.

Applicants can submit short proposals to any of the subtopics and to more than one, provided a separate short proposal is submitted for each subtopic.

A key objective of this topic is to create a research and technology platform for all the disease clusters to discover and validate novel biomarkers predictive of treatment response or non-response. To maximise cross-learning and to enable data sharing, it is envisioned 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.

Thus, at stage 2 the full proposal will be submitted by the consortium composed of the winning applicant sub-consortia of all four subtopics and the industry consortium.

An overall coordinator (selected from the winning consortium of the subtopic 1 Disease profiling and informatics) 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 of no short proposal being over the threshold for one or two disease cluster subtopics, the second stage of the Call will still be initiated by the merger of the remaining consortia and the industry consortium, but the net IMI2 funding and the EFPIA in-kind contributions will be adapted accordingly.

Considering the essential role of subtopic 1 for the preparation of the full proposal and implementation of the funded action, potential applicants must be aware that the whole topic may be discontinued and the stage 2 evaluation may not take place if no short proposal is selected under this subtopic.

Need and opportunity for public-private collaborative research

In a field of medicine where the diseases and underlying science are so complex, no critical mass exists to make significant progress. In order to develop a better understanding of human immune-mediated diseases, only a large international scientific collaborative project that includes excellence in academia, the pharmaceutical industry, SMEs and regulatory authorities, coupled with a critical amount of high quality data, can be successful. Hence, translating basic science into the clinic cannot be achieved by a single entity but requires the definition of common strategies, setting new standards and the necessary critical mass created by all key stakeholders both from the private and public sectors. The proposed work will focus on seven prominent immune-mediated diseases where a public-private partnership will advance our understanding and help accelerate the development of personalised drug treatments for patients.

In addition, to achieve significant impact and drive a timely change in the field for the benefit of patients, it is necessary to kick-start the process by building on all available assets and learnings, and, via a combination of key resources globally, mobilising stakeholders in EU Member States and H2020 Associated Countries and potentially beyond.

Scope

The action generated by this topic aims to provide better control of immune-mediated diseases.

In particular, the topic aims to identify new approaches to:

- characterise human immune-mediated diseases;
- profile and analyse immune cells obtained from non-blood tissues;
- discover individual disease and cross-disease biomarkers predictive of treatment response, non-response, relapse and flare-up;
- perform early phase clinical trials (e.g. enriched study populations for certain molecular pathways; adaptive and basket trial designs etc.) and identify potential novel patient-centric treatment approaches. The focus will be on patients from well-characterised immune-mediated diseases (SLE, RA, MS, UC, CD, Asthma and COPD).

The ultimate goal is to develop a translational research platform that will improve patient management and personalised treatment by identification/validation of predictive biomarkers for non-response, rapid progression and remission. This would lead to an increased likelihood of treatment success with decreased costs for:

- patients and society, due to fewer side effects and a reduction in the treatment of patients who are unlikely to respond;

- pharmaceutical companies, due to decreased development costs as a function of being able to demonstrate efficacy and safety in smaller, more targeted patient populations that are likely to show greater or earlier response rates.

Expected key deliverables

Subtopic: Disease profiling and informatics

- Molecular profiling of non-responders that will lead to a better understanding of the pathways regulating the response to treatment in seven different diseases (RA, SLE, MS, UC, CD, COPD and asthma), and reveal drug targets for therapeutic intervention.

- Discovery of biomarkers predictive of clinical responses (e.g. non-response, depth of remission, duration of response, rebound effects, frequency and severity of flares).

- Establishment of technology platforms, including transcriptomics (e.g. single cell-, BCR-, TCR-, RNA-Seq), genomics (e.g. SNP, Immunochip, exome sequencing), microbiomics, metabolomics, epigenetics (e.g. DNA methylation, ATAC-Seq, ChIP-Seq), immunophenotyping (flow cytometry/CyTOF), proteomics and exosome profiling.

- Utilise a core set (scRNA-Seq, genetics, microbiomics (stool)) of state-of-the-art and emerging molecular and immune technologies and cutting-edge systems biology approaches to profile and analyse non-blood affected disease tissue samples to identify biomarkers predictive of treatment non-response, relapse and flare-up.

- Single cell RNA-Seq of non-blood tissue samples to determine the role of different cell types and identify distinct cell sub-populations that contribute to clinical response and disease progression and correlate with peripheral markers/signatures.

- Analysis of -omics datasets leading to the generation of novel methods and models to predictively identify and stratify responder, non-responder and relapse-prone patients aligned with specific therapies.

- Generation and hosting of an integrated large-scale data storage and computing platform to collect, store, analyse and integrate data to allow data mining for new targets and pathways.

- Establishment of a sustainable repository of well-annotated bio-samples to allow for the identification, tracking, storage and retrieval for subsequent profiling and analysis.

For each of the subtopics DC1, DC2 and DC3

- Analysis of retrospective and prospective clinical and biomarker cohorts with access to patient data and bio-samples.

- Patient bio-resources that should be ideally matched with high dimensional profiling of patients' signs and symptoms including patient reported outcomes and the use of digital tools to capture patient outcomes and environment.

- Establishment of an interface with the Disease profiling and informatics subtopic 1 to efficiently receive, send, track and store data and bio-samples, and establish necessary processes for high dimensional data analysis.

- Functional and clinical validation of biomarkers using human-based disease models (e.g. organoids / organ on a chip).

- Development of best practice for emerging biomarker validation and clinical application in immune-mediated diseases with early engagement of the European Medicines Agency (EMA) / Food and Drug Administration (FDA) (e.g. scientific advice, see http://www.imi.europa.eu/sites/default/files/uploads/documents/apply-for-funding/call-documents/imi2/RegulatoryRequirementsGuide.pdf)

Expected impact

Currently patients are treated as a 'statistical mean' due to our limited molecular insight into individual patients' disease biology and treatment response. This approach fails to appreciate the underlying heterogeneity in disease mechanisms that leads to indistinguishable clinical phenotypes. Better understanding of the link between the molecular characteristics of disease and non-response to targeted drug treatments will increase the likelihood of treatment success and thus decrease costs to patients (side effects) and society.

Similarly, the establishment of early markers of response will allow the identification of disease endotypes that may be responsive to different therapies.

The proposed precision-immunology approach is expected to achieve a reduction in failure rates in early clinical trials and to provide access for novel therapeutics to the most appropriate patient populations. Insights gained from this study will inform the design of platform trials for single indications with multiple mechanisms, further supporting precision medicine approaches. In addition, a more accurate definition of subcategories of auto-immune disorders and their responses to particular therapies on an individual patient level will fuel novel target discovery, decrease phase 2 proof of concept (POC) attrition, and decrease the costs of development to achieve regulatory approval and appropriate reimbursement.

To this end, the action generated by this topic would be a powerful and unique instrument, with the capability to significantly move forward the development of a consensus on the best treatment options for defined subgroups of patients with high unmet medical needs, such as patients suffering from immune-mediated diseases. Such an instrument currently does not exist within Europe or elsewhere. Furthermore, beyond advancing our understanding of the disease, informing personalised approaches to patient care, and delivering potential novel treatments, the topic has the potential to establish Europe in a leadership position in this field of biology and medicine.

Small and medium-sized enterprises (SMEs) can be of great benefit to IMI2 JU projects. Their involvement in the action might offer a complementary perspective to industry and academia, and help deliver the long-term impact of the project. Therefore applicants should indicate how their proposals will impact and strengthen the competitiveness and industrial leadership of Europe by, for example, engaging suitable SMEs.

Potential synergies with existing consortia

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

In particular, the action generated from this topic should, among others, consider:

- IMI projects:

  BTCURE (http://btcure.eu/)
  RTCURE (http://cordis.europa.eu/project/rcn/211964_en.html)
  PRECISESADS (http://www.precisesads.eu/)
  U-Biopred (http://www.europeanlung.org/projects-and-research/projects/u-biopred/home)
  INNODIA (https://innodia.eu/)
  European Lead Factory (https://www.europeanleadfactory.eu/)

- Human Immunology Project Consortium (**HIPC**) (https://www.immuneprofiling.org/hipc/page/show)

- CD and UC: Inflammatory Bowel Disease Biomarkers Programme (**IBD-BIOM**) (http://www.ibdbiom.eu/), Inflammatory Bowel Disease Characterization by a multimodal integrated biomarker study **(IBD-CHARACTER)** (http://www.ibdcharacter.eu/), A System Medicine Approach to Chronic Inflammatory Disease (**SYSCID**) (http://syscid.eu/), Biological Therapy Cycles Towards Tailored, Needs-driven, Safer and Cost-effective Management of Crohn's Disease (**BIOCYCLE**) (https://biocycle-project.eu/), the next generation epigenetic medicine for inflammation (**EPIMAC**) (http://cordis.europa.eu/project/rcn/193846_en.html), Harnessing Targeted Nanotheranostics to Reprogram Activated Leukocytes in Inflammatory Bowel Disease (**LeukoTheranostics**) (http://cordis.europa.eu/project/rcn/198445_en.html), Identifying microbiotal triggers of inflammatory

bowel disease through the lens of the immune system (**IMMUNOBIOME**)
(http://cordis.europa.eu/project/rcn/197878_en.html)

- MS: **MultipleMS** (http://www.multiplems.eu/) and **EUReMS** (http://www.emsp.org/projects/eurems/)

- RA and SLE: Accelerating Medicines Partnership (**AMP**) (https://www.nih.gov/research-training/accelerating-medicines-partnership-amp), Mechanisms to Attack Steering Effectors of Rheumatoid Syndromes with Innovated Therapy Choices (**Masterswitch**) (http://cordis.europa.eu/project/rcn/89367_en.html), Towards Early diagnosis and biomarker validation in Arthritis Management (**Euro**-**TEAM**) (http://cordis.europa.eu/project/rcn/105516_en.html), Monitoring innate immunity in arthritis and mucosal inflammation (**MIAMI**) (http://miamiproject.eu/), Relapses prevention in chronic autoimmune disease: common mechanisms and co-morbidities (**RELENT**) (https://www.relent.eu/), **SYSCID** (http://syscid.eu/)

- SLE: **SYSCID** (http://syscid.eu/) and **Lupus Europe** (http://www.lupus-europe.org/)

- Asthma and COPD: **Ga2Len** (http://www.ga2len.net/), **synergy-COPD** (http://www.synergy-copd.eu/) and **EvA** (http://cordis.europa.eu/project/rcn/87739_en.html)

- MS, RA, SLE: Immune Tolerance Network (**ITN**) (https://www.immunetolerance.org/)

Industry consortium

The industry consortium is composed of the following EFPIA companies:

- Sanofi (overall lead; disease profiling and informatics subtopic lead; DC1 subtopic lead)

- Roche (overall co-lead)

- Takeda (DC2 subtopic lead)

- AstraZeneca (DC3 subtopic lead)

- GlaxoSmithKline

- Janssen

- Novartis

- Pfizer

The industry consortium will provide bio-samples (e.g. blood, stool, sputum, urine, tissue biopsies, DNA, RNA) and patient characterised datasets (deep-clinical phenotyping) from various prospective clinical trials (baseline, active comparator and/or placebo) for SLE, RA, MS, UC, CD, asthma, and COPD. Note that there will be a difference in design of these clinical trials, and the specificities of the available bio-samples will be confirmed during the full proposal preparation. In addition, the availability and disease type of the bio-samples obtained from future prospective clinical trials performed by the industry consortium carries some attrition risk due to discontinuation of development activities, incompatibility of informed consent for certain profiling and analyses and/or legal considerations.

The industry consortium will contribute with technology platforms for bio-sample analysis to complement technologies provided by the public participants.

The industry consortium will include informatics and systems biology experts and clinical statisticians. Immunology expertise to contribute to functional validation of pathways and targets will be made available, as well as biomarker expertise to support validation activities and assay development.

Indicative duration of the action

The indicative duration of the action is 84 months.

Future project expansion

Potential applicants must be aware that the Innovative Medicines Initiative 2 Joint Undertaking (IMI2 JU) may, if exceptionally needed, publish at a later stage another Call for proposals restricted to the consortium already

selected under this topic, in order to enhance their results and achievements by extending their duration and funding. The consortium will be entitled to open to other beneficiaries as they see fit.

A consensus is emerging that common immune-mediated diseases share common pathways, with molecular support provided by analysis of transcriptomics, HLA haplotypes and GWAS studies. One of the goals of this topic is to identify single and multi-parameter biomarker sets in individual diseases and across multiple diseases to assist in determining responder versus non-responder patients. However, this profile will be derived from a limited number of patients, so it cannot be assumed that the profile defining these categories is exclusive in determining response. For example, there may be some patients with a non-responder profile who actually may benefit from the treatment. Thus, the candidate responder versus non-responder profile uncovered by this topic will be exploratory and not definitive, and will need to be followed up by future validation studies that include large numbers of patients and novel endpoints. Also, it is critical to maintain long-term follow up of the patients in these studies to validate which candidate biomarkers can accurately predict the depth of remission.

Future follow up studies will also be necessary as some patients may be non-responsive to therapy by virtue of being placed on an initial inappropriate treatment or having generated anti-drug antibody responses with initial or subsequent loss of efficacy. Thus, anti-drug responses may need to be assessed in patients on clinical trials of therapeutic proteins for incidence, titer, neutralising activity, and duration, as well as to generation of hypersensitivity responses. The generation of such anti-drug antibody responses and clinical responses may identify a distinct population of patients and provide a profile of those most prone to generate anti-drug antibody responses. This may lead to the development of tolerance induction protocols for such patients.

Indicative budget

The indicative EFPIA in-kind contribution is EUR 40 320 000.

The EFPIA in-kind contribution for each subtopic is:

Subtopic 1 (Profiling & informatics): EUR 16 128 000

Subtopic 2 (DC1 – SLE, RA, and MS): EUR 12 096 000

Subtopic 3 (DC2 – UC and CD): EUR 8 064 000

Subtopic 4 (DC3 – Asthma and COPD): EUR 4 032 000.

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

The financial contribution from IMI2 JU for each subtopic is:

Subtopic 1 (Profiling & informatics): a maximum of EUR 16 128 000

Subtopic 2 (DC1 – SLE, RA, and MS): a maximum of EUR 12 096 000

Subtopic 3 (DC2 – UC and CD): a maximum of EUR 8 064 000

Subtopic 4 (DC3 – Asthma and COPD): a maximum of EUR 4 032 000.

For all subtopics: in light of the fact that a single full proposal will be created at stage 2, where a common governance, management and other transversal activities will have to be agreed and developed, applicants have to be aware there might be a need for some slight modifications in the budgets from the stage 1 submissions.

Applicant consortium

One applicant consortium per subtopic will be selected on the basis of the short proposals submitted.

The first-ranked applicant consortium for each subtopic is expected to address all the research objectives of a particular subtopic and to make key contributions to the defined deliverables in synergy with the proposed industry consortium contributions (stage 1).

Applicants should summarise their know-how and expertise to demonstrate their ability to make critical contributions to the expected key deliverables within the duration of the action.

All first ranked applicant consortia of each subtopic are expected to work collaboratively with the industry consortium to develop a full proposal combining the key objectives of each individual subtopic (stage 2).

This may require mobilising, as appropriate, the following expertise and resources.

Expertise and resources required for subtopic on disease profiling and informatics

The expertise and resources required are as follows:

- experience in the establishment of a bio-sample repository to allow for the identification, tracking, and storage for subsequent profiling and analysis;

- expertise in standardised isolation, storage, processing and –omics analysis;

- centralised lab functions for state–of-the-art and emerging technologies for –omics analysis (e.g. single cell transcriptome analysis, spatial transcriptomics, genomics, epigenetics, microbiome, metabolomics, flow cytometry/CyTOF, proteomics, and exosome profiling) in clinical sample types (e.g. tissue biopsies, sputum, stool, blood, plasma, urine) across the selected diseases;

- expertise in the generation and hosting of an integrated, large-scale data platform and informatics pipeline to collect, store and analyse these data;

- expertise in data integration and/or harmonisation techniques and cutting-edge systems biology approaches to model multiple –omics datasets from multiple diseases to identify biomarkers that predict treatment non-responders or relapse-prone patient populations;

- expertise in informatics analysis and modelling to support patient stratification, future clinical trial design and precision medicine approaches;

- experience in collaborative functional validation of novel pathways, drug targets and biomarker candidates; proven expertise in efficiently managing and maintaining timelines for large, multi-institutional scientific projects, and proven expertise in project management including resources for project administration, management and communication;

- expertise in regulatory science and inclusion of regulatory experts.

Expertise and resources required for Subtopics DC1, DC2 and DC3

The expertise and resources required are as follows:

- access to pre-existing bio-samples (non-blood tissues required and matching blood samples desired) and patient data from retrospective biomarker and clinical trials suitable (e.g. tissue frozen, not fixed) for profiling using state–of-the-art and/or emerging technologies;

- ability to design and conduct interventional prospective clinically relevant and actionable biomarker trials to obtain high quality clinical data and well-annotated bio-samples;

- expertise in the development of human-based disease models based on novel insights from the –omics studies (e.g. organoids) - note mouse models are not applicable;

- the inclusion of patients and patient organisations in the consortia applying to the disease cluster subtopics (DC1, DC2, DC3) is actively encouraged;

- ability to anticipate the early integration of health economic evaluation and health technology assessment (HTA) where applicable;

- ability to contribute insights on patient reported outcomes and quality of life (QoL) elements for the definition of clinical response.

Partners providing medical record-based information (e.g. data from registries, bio-samples) as project background must be mindful that they, as background contributor, should have sufficient title to said background to authorise its use within the project pursuant to the IMI2 JU intellectual property (IP) and legal framework. Consideration should also be given to any additional information that may be introduced after the start of the project but is not listed as project background at the start date. The applicants need also to take into consideration that the sharing of data and samples within the consortium should be allowed and be in conformity with the applicable data privacy laws and laws regarding ethical matters.

In addition to academic groups, relevant small and medium-sized enterprises (SMEs) with relevant proven expertise are encouraged to participate in the applicant consortium. SMEs can be of great benefit to IMI projects and, among other things, strengthen the competitiveness and industrial leadership of Europe. Their involvement might offer a complementary perspective to industry and the academia, and strengthen the long-term impact of the project. For these reasons, applicants should consider engaging SMEs throughout the proposal. Under this topic, the contribution of SMEs would be considered especially beneficial for the establishment of a bio-sample repository, the generation and hosting of an integrated large scale data platform, and the specialty profiling of bio-samples, using state-of-the-art and/or emerging technologies. In addition, SMEs would be considered beneficial for the project management and administration capabilities required of the applicant consortium, which is expected to include resources for project administration, management and communication.

The size of the applicant consortia should reflect the expertise needed to achieve the proposed objectives of the subtopic and to be in line with the proposed budget, while ensuring the manageability of the final consortium to allow efficient and effective team work. Therefore, the size of the applicant consortium needs to be justified in the proposal.

Suggested architecture of the full proposal

Each applicant consortium should include suggestions for creating the full proposal architecture in their short proposal, taking into consideration the industry contribution, existing technology platforms, and the clinical and scientific expertise needed for the immune-mediated diseases being studied.

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.

Governance of the overall project will be assured by the project coordinator and the scientific project lead.

The coordinator will be agreed upon by the full consortium created by the merger of the winning subtopic consortia at the start of the preparation of the full proposal and it will be nominated from the winning disease profiling and informatics subtopic 1.

This may require slight adjustment of the disease profiling and informatics subtopic work package 1 to accommodate any new structure changes. This topic consists of four subtopics, each with several distinct and common work packages, which in combination will deliver the objectives of the project. In the full proposal, the subtopic-specific governance structures will be maintained and guaranteed for each sub-topic by a partnership among the leading members of the respective applicant consortium together with one leading member designated by the industry consortium (see above, industry consortium section).

Particular attention will be given to implementing the scientific exchange of the specialist experts within and across the four subtopics, ensuring the integration of learnings, synergies and cross-fertilisation, and thereby maximising the outcome of this action.

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

Sustainability

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

The architecture outlined below for the full proposal and for the short proposals submitted to each subtopic is a suggestion; different innovative project designs are welcome, if properly justified.

All subtopics

Common work package: Project management, communication, dissemination and sustainability

This work package should be described by each submitting applicant consortium, and should include the elements necessary to ensure the proper functioning of each subtopic, bearing in mind that some modifications will be necessary at the stage 2 full proposal to adapt for an overall governance and integration, and that several activities will be shared among all participants of the full consortium to insure integration and avoid redundancy.

The goals of this work package will be as follows:

- overall coordination of the scientific work packages;
- budget administration;
- dissemination of scientific results and research data;
- development of a sustainability plan to facilitate continuation of the project beyond its anticipated duration;
- communication within the consortium and with external collaborators.

Expected applicant consortium contribution: coordination of work packages, budget administration, dissemination of scientific results, and development of a sustainability plan.

EFPIA consortium contribution: communication, dissemination of results, and development of sustainability plan.

Subtopic disease profiling and informatics

Work package 1 – Profiling

The goals of this work package will be as follows:

- coordinate the receipt, curation, storage and retrieval of bio-samples;
- reduce technical variability introduced during sample processing;
- minimise batch effects via centralised profiling on the same platforms\instruments.

Expected applicant consortium contribution:

- molecular profiling of non-blood tissue samples from DC1, DC2 and DC3 patients using RNA-Seq, single cell RNA-Seq, genetics (all three required), and flow cytometry/CyTOF (desired);

- profiling of DC1, DC2 and DC3 patient stool samples using microbiome and metabolome (required for DC2 and desired for DC1 and DC3);

- epigenetic, metabolomics, microbiomic (lung, skin), proteomic and exosome profiling on patient bio-samples from DC1, DC2 and DC3 (desired);

- to limit batch effects and to ensure comparable results across these diverse sets of bio-samples the profiling of DC1, DC2 and DC3 bio-samples should be performed at the fewest sites possible, on the same instruments, and utilise a common core set of standard operating procedures for sample isolation, preparation and labelling. In addition, development of a quality control plan that includes control steps, control samples, blinding operators and randomisation of samples is desired;

- develop a bio-repository platform for the receipt, curation, tracking, storage and retrieval of bio-samples received from DC1, DC2 and DC3;

- transfer of profiling datasets to a centralised scalable data hosting and computing platform.

EFPIA consortium contribution:

- EFPIA partners may, if relevant, provide molecular profiling of bio-samples from DC1, DC2 and DC3 patients using RNA-Seq, single cell RNA-Seq, genetics (all required), and flow cytometry/CyTOF (desired);

- profiling of DC1, DC2 and DC3 patient stool samples using microbiomics and metabolome (required for DC2 and desired for DC1 and DC3);

- epigenetic, metabolomic, microbiomic (lung, skin), proteomic and exosome profiling of non-stool bio-samples obtained from DC1, DC2 and DC3 patients (desired);

- transfer of profiling datasets to a centralized scalable data hosting and computing platform generated and maintained by the disease profiling and informatics subtopic;

- provide informatics support to the disease profiling and informatics subtopic.

Work package 2 – Informatics

The goals of this work package will be as follows:

- characterise variations in –omics datasets generated at high resolution;

- establish a centralised, scalable data hosting and computing platform;

- identify novel biomarkers predictive of clinical disease behaviour and response;

- develop disease and clinical response-specific data that can be used to identify biological targets for drug development and biomarkers for patient stratification.

Expected applicant consortium contribution:

- analysis of –omics datasets of treatment non-responders to discover novel biomarkers predictive of clinical responses;

- use sophisticated data integration and harmonisation techniques and apply cutting-edge systems biology approaches to model multiple –omics datasets from multiple diseases to identify biomarkers or clusters of biomarkers that predict non-response. Inclusion in the project plan of data sets from other consortia (such as those mentioned in the Synergies section) via proposed collaborations could be considered;

- molecular profiling of non-responders that will lead to a better understanding of the pathways regulating the response to treatment in the seven different immune-mediated diseases and reveal drug targets for therapeutic intervention;

- analysis of –omics and clinical datasets to provide a better understanding of human immune-mediated diseases;

- integration of historic and prospective data for the identification of biomarkers and generation of models that predict treatment non-responders and/or relapse-prone patient populations in the seven indicated diseases. Determine whether commonalities exist (e.g. biomarkers) across the seven

different diseases for identifying treatment non-responder and relapse-prone patients. Opportunities to integrate biomarker data of disease non-response from other disease could be considered if relevant;

- provide analysis and models to support patient stratification, future clinical trial design and precision medicine approaches;

- establishment of a centralised scalable data hosting and computing platform to enable data storing, sharing and data mining.

EFPIA consortium contribution:

- EFPIA partners will, where applicable, transfer prospective –omics and clinical datasets to the disease profiling and informatics subtopic for data hosting, mining and analysis;

- provision of scientific, clinical, profiling and informatics expertise for patient data and -omics datasets;

- provision of informatics expertise for discovery and confirmation of potential biomarkers predictive of clinical responses.

Subtopic DC1 – SLE, RA, and MS

Work package 1 – DC1 diseases, patients, cohorts, validation

The goals of this work package will be as follows:

- provide longitudinal bio-samples, including non-blood tissue samples from DC1 patients suitable for profiling by multiple –omics and emerging technologies;

- interface with the disease profiling and informatics teams to integrate the required clinical and scientific DC1 expertise and ensure appropriate design and interpretation of the data analysis;

- develop confirmation and validation assays using human models and primary cells.

Expected applicant consortium contribution:

- access to pre-existing DC1 patient cohorts, clinical data and a minimum of three longitudinal bio-samples for each patient, obtained pre-treatment, early post-treatment (2-4 weeks), and at the time of peak clinical response for the specific treatment and disease being studied from retrospective studies. For at least one of these time points, a non-blood affected disease tissue sample, such as RA synovium, lupus skin and/or kidney, or MS cerebrospinal fluid is required; and other matching tissue samples, such as joint fluid, blood, plasma, stool and urine samples are desired. Additional bio-samples are highly desired including follow-up samples taken during the remission and/or relapse phase or after treatment is withdrawn;

- interventional (approved standard-of-care therapies only) prospective biomarker trials to obtain clinical data and at least three longitudinal bio-samples for each patient, obtained pre-treatment, early post-treatment (2-4 weeks), and at the time of peak clinical response for the specific treatment and disease being studied. For at least one of these time points, a non-blood affected disease tissue sample, such as RA synovium, lupus skin and/or kidney, or MS cerebrospinal fluid is required; and other matching tissue samples, such as joint fluid, blood, plasma, stool and urine samples are desired. Additional bio-samples are highly desired including follow-up samples taken during the remission and/or relapse phase or after treatment is withdrawn;

- retrospective and prospective DC1 patient cohort immune interventions should ideally be an EMA/FDA approved targeted immune-therapy (biologic or small molecule therapeutic) which includes anti-TNFs: infliximab, adalimumab, certolizumab, golimumab, etanercept and biosimilars; BAFF inhibitor, benlysta (belimumab); hydroxychloroquine. Broad immunosuppresants such as azathioprine and non-immune therapy such as antibiotics are to be excluded from the study. Non-approved and off-label used drugs are not recommended;

- provide non-blood tissue samples suitable (e.g. frozen, not fixed) for single cell RNA-Seq and genetics (required) and other –omics, such as epigenetics, metabolomics, flow cytometry/CyTOF, proteomics and exosome profiling (desired). Note, for samples in which single cell RNA-Seq is performed it is desired that bulk RNA-Seq also be performed in parallel or duplicate sample aliquots be stored for future sequencing; however, bulk RNA-Seq should not be performed in lieu of single cell RNA-Seq;

- longitudinal stool samples from DC1 patient cohorts suitable for microbiome and metabolome are desired;

- breath analysis for volatile organic compounds (VOCs) on DC1 patients is desired;

- provide bio-samples, clinical data and any relevant datasets to the disease profiling and informatics subtopic for profiling and data analysis;

- interface with the disease profiling and informatics subtopic to ensure that clinical and scientific expertise in DC1 diseases is fully integrated into the design and interpretation of the data analysis being performed by the informatics teams;

- develop confirmation and validation assays using human models such as organoids and 'skin and/or kidney on a chip' type assays that focus on primary cells or induced pluripotent stem (IPS) cell derivatives are desired. Note mouse models are not applicable.

EFPIA consortium contribution:

- provide highly annotated clinical data and three or more longitudinal bio-samples for each patient with SLE, RA, or MS obtained pre-treatment, early post-treatment (2-4 weeks) and at the time of peak clinical response from the standard of care/active comparator arm of prospective clinical trials;

- provide samples and/or profiled –omics datasets to the Disease Profiling and Informatics subtopic for profiling, storage, data hosting and data analysis;

- provide scientific, clinical and developmental expertise to the DC1 and Disease Profiling and Informatics teams;

- interface with the Disease Profiling and Informatics subtopic to ensure that clinical and scientific expertise in DC1 diseases is fully integrated into the design and interpretation of the data analysis being performed by the informatics teams;

- provide scientific expertise necessary to develop human based models for confirmation and validation studies.

Subtopic DC2 − UC and CD

Work package 1 – DC2 diseases, patients, cohorts, validation

The goals of this work package will be as follows:

- provide longitudinal bio-samples, including non-blood tissue samples from DC2 patients suitable for profiling by multiple –omics and emerging technologies;

- interface with the Disease Profiling and Informatics teams to integrate the required clinical and scientific DC2 expertise and ensure appropriate design and interpretation of the data analysis;

- develop confirmation and validation assays using human models and primary cells.

Expected applicant consortium contribution:

- access to Crohn's disease (CD) cohorts including inflammatory disease, fibrostenosis and fistulising sub-groups, with and without active peri-anal disease. Other considerations would be early onset disease vs. late onset disease, post-operative Crohn's disease, and patients with extra intestinal manifestations. Overlap with autoimmune disease would be of special interest;

- access to ulcerative colitis (UC) cohorts based on disease distribution, extent of ulcerative colitis (E1-E3); it would be of special interest to study hospitalised acute, severe UC responsive vs. non-responsive to anti-TNF. UC with extra-intestinal manifestations, risk of deep venous thrombosis and overlap with psoriasis would be special populations of interest. Early onset disease vs. late onset disease analysis is desired;

- access to pre-existing DC2 patient cohorts, clinical data and a minimum of three longitudinal bio-samples for each patient, obtained pre-treatment, early post-treatment (2-4 weeks), and at the time of peak clinical response for the specific treatment and disease being studied from retrospective studies. For at least one of these time points, an affected disease mucosal tissue sample is required and other matching tissue samples, such as blood, plasma and urine samples are desired. Additional bio-

samples are highly desired, including follow-up samples taken during the remission and/or relapse phase or after treatment is withdrawn;

- interventional (approved standard-of-care therapies only) prospective biomarker trials to obtain clinical data and at least three longitudinal bio-samples for each patient, obtained pre-treatment, early post-treatment (2-4 weeks), and at the time of peak clinical response for the specific treatment and disease being studied. For at least one of these time points, an affected disease mucosal tissue sample is required and other matching tissue samples, such as blood, plasma and urine samples are desired. Additional bio-samples are highly desired including follow-up samples taken during the remission and/or relapse phase or after treatment is withdrawn;

- provide a minimum of three longitudinal stool samples per patient suitable for microbiome and metabolome (both required). Samples where 16S data is available are desired. Metabolomic platforms that assay microbial and host bio-actives and IgA sequencing are desired;

- retrospective and prospective DC2 patient cohort immune interventions should ideally be an EMA/FDA approved targeted immune-therapy (biologic or small molecule therapeutic) which includes anti-TNFs: Infliximab, adalimumab, certolizumab, golimumab, and biosimilars; anti-integrin: vedolizumab and natalizumab, and anti-p40: ustekinumab. Broad immunosuppressants such as azathioprine and non-immune therapy such as antibiotics are to be excluded from the study. Non-approved and off-label use is not recommended; however, faecal microbiota transplantation (FMT) intervention(s) may be considered;

- for DC2 immune intervention endpoints, the clinical phenotype of primary non-response should be distinguished from secondary loss of response. In the latter subgroup, inclusion of secondary loss of response in patients without anti-drug antibody is desired. Responders should have a clear 6-12 month response to the drug. Other notable sub-groups include long-term treatment responders (>5 years ideally on mono-therapy). While it is understood that clinical studies in patients with IBD use a variety of endpoints to define response and remission (including PRO and endoscopy/histology as per draft guidance from EMA and FDA), the present IMI2 collaboration uses for consistency the classical clinical endpoints;

- Crohn's Disease Activity Index (CDAI): response defined as Δbaseline $\geq$100, remission absolute CDAI < 150;

- Mayo Clinic Score (MCS): response defined as Δbaseline $\geq$ 3, remission absolute MCS < 2 with bleeding subscore 0 or 1; partial MCS, i.e., without endoscopy, is also acceptable;

- provide non-blood tissue samples (required) and matching blood samples (desired) suitable (e.g. frozen not fixed) for single cell RNA-Seq and genetics (required) and other –omics, such as epigenetics, metabolomics, flow cytometry/CyTOF, proteomics and exosome profiling (desired). Note that for samples in which single cell RNA-Seq is performed, it is desired that bulk RNA-Seq also be performed in parallel or duplicate sample aliquots be stored for future sequencing; however, bulk RNA-Seq should not be performed in lieu of single cell RNA-Seq;

- breath analysis for volatile organic compounds (VOCs) on DC2 patients is desired;

- provide bio-samples, clinical data and any relevant datasets to the disease profiling and informatics subtopic for profiling and data analysis;

- interface with the disease profiling and informatics subtopic to ensure that clinical and scientific expertise in DC2 diseases is fully integrated into the design and interpretation of the data analysis being performed by the informatics teams;

- develop validation assays using host epithelial cell – immune cell, host immune cell and microbe, host epithelial cell and microbe as examples of host microbial interactions. Organoid and 'gut on a chip' type assays that focus on primary cells or IPS cell derivatives are desired. Note that mouse models are not applicable.

EFPIA consortium contribution:

- provide highly annotated clinical data and three or more longitudinal bio-samples for each patient with UC or CD obtained pre-treatment, early post-treatment (2-4 weeks) and at the time of peak clinical response from the standard of care/active comparator arm of prospective clinical trials;

- provide samples and/or profiled –omics datasets to the disease profiling and informatics subtopic for profiling, storage, data hosting and data analysis;

- provide scientific, clinical and developmental expertise to the DC2 and disease profiling and informatics teams;

- interface with the disease profiling and informatics subtopic to ensure that clinical and scientific expertise in DC2 diseases is fully integrated into the design and interpretation of the data analysis being performed by the informatics teams;

- provide scientific expertise necessary to develop human based models for confirmation and validation studies.

Subtopic DC3 – Asthma and COPD

Work package 1 – DC3 diseases, patients, cohorts, validation

The goals of this work package will be as follows:

- provide longitudinal bio-samples, including non-blood tissue samples from DC3 patients suitable for profiling by multiple –omics and emerging technologies;

- interface with the disease profiling and informatics teams to integrate the required clinical and scientific DC3 expertise and ensure appropriate design and interpretation of the data analysis;

- develop confirmation and validation assays using human models and primary cells.

Expected applicant consortium contribution:

- retrospective and prospective DC3 patient cohort immune interventions should ideally be approved drugs such as Omalizumab, Mepolizumab, bronchodilators (LABA, SABA, LAMA), anti-inflammatory agents (ICS, oral steroid, Roflumilast), antibiotics and placebo arm (with or without standard of care treatment);

- DC3 patient immune intervention trial endpoints should include FEV1, EXACT for respiratory symptoms and St George's respiratory questionnaire for quality of life assessment for COPD patients, asthma control questionnaire, asthma symptom score, rate of exacerbations, time to next exacerbations;

- access to pre-existing DC3 patient cohorts, clinical data and a minimum of three longitudinal bio-samples obtained pre-treatment, early post-treatment (2-4 weeks), and at the time of peak clinical response for the specific treatment and disease being studied from retrospective studies. For at least one of these time points a non-blood affected disease tissue, such as sputum, lung biopsy, or bronchoalveolar lavage (BAL) fluid is required; and other matching tissue samples, such as blood, plasma, stool and urine are desired. Additional bio-samples are highly desired including follow-up samples taken during the remission and/or relapse phase (exacerbation) or after treatment is withdrawn;

- interventional (approved standard-of-care therapies only) prospective biomarker trials on DC3 patient cohorts to obtain clinical data and at least three longitudinal bio-samples obtained pre-treatment, early post-treatment (2-4 weeks), and at the time of peak clinical response for the specific treatment and disease being studied. For at least one of these time points a non-blood affected disease tissue, such as sputum, lung biopsy, or bronchoalveolar lavage (BAL) fluid is required; and other matching tissue samples, such as blood, plasma, stool and urine are desired. Additional bio-samples are highly desired including follow-up samples taken during the remission and/or relapse phase (exacerbation) or after treatment is withdrawn;

- provide non-blood tissue samples suitable (e.g. frozen not fixed) for single cell RNA-Seq and genetics (required) and other –omics, such as epigenetics, metabolomics, flow cytometry/CyTOF, proteomics and exosome profiling (desired). Note, for samples in which single cell RNA-Seq is performed it is desired that bulk RNA-Seq also be performed in parallel or duplicate sample aliquots be stored for future sequencing; however, bulk RNA-Seq should not be performed in lieu of single cell RNA-Seq;

- provide sputum or BAL fluid suitable for lung microbiome (required) and stool samples suitable for microbiome and metabolomics (desired);

- analysis of exhaled breath volatile organic compounds (VOC) for patient stratification and as an endpoint is desired for retrospective studies and required for prospective studies;

- transfer bio-samples, clinical data and any relevant datasets, to the disease profiling and informatics subtopic teams for profiling and data analysis;

- interface with the disease profiling and informatics subtopic to ensure that clinical, developmental and scientific expertise in DC3 diseases is fully integrated into the design and interpretation of the data analysis being performed by the informatics teams;

- develop validation assays using host epithelial cell – immune cell, host immune cell and microbe. Organoid and 'lung on a chip' type assays that focus on primary cells or IPS cell derivatives and originating from stratified patients are desired. Note that mouse models are not applicable.

EFPIA consortium contribution:

- provide highly annotated clinical data and three or more longitudinal bio-samples for each patient with asthma or COPD obtained pre-treatment, early post-treatment (2-4 weeks) and at the time of peak clinical response from the standard of care/active comparator arm of prospective clinical trials;

- provide samples and/or profiled –omics datasets to the disease profiling and informatics subtopic for profiling, storage, data hosting and data analysis;

- provide scientific, clinical and developmental expertise to the DC3 and disease profiling and informatics teams;

- provide informatics, scientific, clinical, and developmental expertise to identify respiratory phenotypes that steer away from asthma and COPD and are more aligned to 'treatable traits' and their response to standard of care;

- interface with the disease profiling and informatics subtopic to ensure that clinical and scientific expertise in DC3 diseases is fully integrated into the design and interpretation of the data analysis being performed by the informatics teams;

- provide scientific expertise necessary to develop human based models for confirmation and validation studies.

Topic 2: Non-invasive clinical molecular imaging of immune cells

Topic details

Topic code	IMI2-2018-14-02
Action type	Research and Innovation Action (RIA)
Submission and evaluation process	2 stages

Specific challenges to be addressed

Current pharmacodynamic (PD) assessments of immune cells are based on peripheral blood biomarkers, or from biopsy samples which are acquired by invasive procedures. Some existing medical imaging modalities provide a quantifiable, non-invasive, repeatable and localised measure of biological processes in the living body. However, current methodology and technology provides limited information on time-dependent and disease-specific relevant immune cell subpopulations and compartments types, or measures of direct engagement of immune targets.

Imaging tracers designed to bind specific immune cells ('immunotracers') or targets within immune-mediated pathways would enable the clinical imaging of the target immune cell subtypes and immune markers of disease in a clinical setting, which in turn would provide *in vivo* insights into effects of immunomodulatory therapies at disease sites (organs/tissues) and improve knowledge about the pathophysiology of various immune-mediated diseases. The ultimate ambition of clinical imaging with immunotracers is to enable tailored immunotherapy by allowing for:

- patient stratification based on immune status (personalised medicine);
- prediction of response or long-term outcome of therapeutic interventions;
- dose selection including personalised dosing;
- target engagement within the tissue of interest both regionally and focally.

Molecular imaging agents, (hybrid) imaging modalities, and image processing algorithms to image immune cells *in vivo* are advancing within the imaging field and can provide an immediate, non-invasive read-out of target expression over time. However, further novel imaging agents and technologies will need to be developed in order to extend the applicability of immune cell imaging to additional disease areas, additional tissue sites, and/or immune cell subpopulations especially by increasing the specificity of imaging agents. Therefore there remains a need to better understand the currently available markers and validate them extensively for clinical use. Thus, a strategic consortium that can connect innovative immunology research, imaging technology, and translational development to implement transformational immunotracers in the clinic is a requirement for the successful execution of this topic.

Need and opportunity for public-private collaborative research

This topic focuses on a set of immune cells of key importance in various disease areas involving widely differing organ/tissue systems, with the ultimate goal to develop a transformational set of clinical imaging agents and non-invasive methods that are capable of monitoring immune cell phenotype and function. A large number of potential therapies acting upon these immune cells exist or are being developed, and successful methods established within this topic will be broadly applicable in many indications across many different organisations and research groups. Even though, the field of (semi-)quantitative clinical imaging of defined immune cell subsets is advancing and moving from qualitative to quantitative measures, it would still require a very broad spectrum of diverse technical and biological expertise to move forward efficiently. This combination is unlikely to be within the scope of investment and capabilities for any one company or organisation, but collaborative efforts in a public-private partnership are most likely to harness all the skills and expertise required.

The topic provides a unique platform for leading experts from industry, academia and regulators. This platform is needed not only to define and create new and target-specific probes, but also for the testing/validation of imaging technologies and novel imaging algorithms, the generation of reagent packages, and ultimately for the clinical validation of the immunotracers and imaging technology in clinical trials. Generation and validation of a clinical immune-cell imaging platform that provides a non-invasive early indicator to detect immune cells of different phenotypes, correlations with efficacy, and benefit of a therapeutic intervention for various disorders will require collaboration between a diverse set of stakeholders with expertise in immunology, imaging technologies, data management, analytics and regulatory sciences.

Scope

This topic aims to establish a consortium that can develop and validate a quantitative, non-invasive, immune cell imaging platform, which includes novel and target-specific molecular imaging agents, (hybrid) imaging modalities, and image processing algorithms. The topic aligns with the IMI2 Strategic Research Agenda, as it aims to validate immune cell targets based on human biology and to facilitate precision medicine by identification and stratification of patients and prediction of therapeutic outcomes. In addition, it is expected that these agents will facilitate early diagnosis of the disease and/or classification of disease based on the immune phenotype.

The following objectives are within the scope of the proposal:

- clinical validation of existing imaging agents (e.g. agents targeting CD8$^+$ T-cells and immune pathways);

- development and characterisation of novel molecular imaging agents to be used for imaging CD4$^+$ T-cells, CD8+ T-cells, regulatory T-cells, B-cells, macrophages, and NK-cells, reflecting the presence of these cells in tissues/organs/tumours, or denoting markers of the activation status of these immune cells. The new imaging agents should be highly specific for these targets in order to improve their detection;

- establishing molecular imaging platforms in disease areas for which biopsies for validation of the imaging platform can be obtained (e.g. cancer, chronic obstructive pulmonary disease (COPD)/asthma, atopic dermatitis, vasculitis, psoriasis, Sjögren's syndrome, inflammatory bowel disease (IBD), rheumatoid arthritis (RA), and transplant). The platform is initially to be validated in a small number of diseases (identified as common denominator of all participating companies), and could subsequently be used for other disease areas e.g. should brain penetrant tracers be identified/developed neurodegenerative diseases and multiple sclerosis could also be considered;

- optimisation of the quality of immunotracers to ensure appropriate specificity of binding as well as pharmacokinetic and bio-distribution profiles;

- implementing non-invasive imaging modalities that can deliver quantitative data. Whole-body imaging technologies with the capability to image deep-seated tissue/tumours are preferred (e.g. PET, SPECT, MRI, hybrid modalities, PET/SPECT-CT), but depending on the disease area other non-ionizing methods or pre-targeting approaches can be evaluated (e.g. optical imaging and/or photoacoustic imaging of skin lesions, salivary glands, endoscopic/bronchoscopic examinations for IBD, COPD);

- pre-clinical studies to evaluate and validate the novel molecular imaging agents/immunotracers and the immune cell imaging platform as required as a proof of concept to enable to enable translation into the clinic.

Expected key deliverables

Expected primary key deliverables of the topic include:

- identification and evaluation of promising molecular imaging agents and non-invasive imaging modalities (single platform or hybrid) suitable for use with the proposed immunotracers;

- generation of immunotracers for at least two of the following key cell types of interest: CD4+, CD8+, regulatory T-cells, B-cells, NK-cells, macrophages;

- immunotracer optimisation in the context of the planned use (e.g. with respect to pharmacokinetic and bio-distribution profile, suitability for repeated use in longitudinal studies);

- appropriate resolution and sensitivity (at least semi-quantitative) of the immunotracer and imaging modality combination(s) to allow delineation of organs of interest and determination of relative changes in tissue immune cell involvement and/or activation status;

- clinical proof of concept utilising at least one immunotracer / imaging modality combination(s) for cells and tissues of interest;

- imaging modalities and processing tools suitable for accurate co-registration of multi-modality images e.g PET/CT to co-register anatomy and functionality.

Expected impact

Molecular imaging of immune cells could provide an early indicator of whether patients are likely to benefit from a given (immuno-) therapeutic intervention (surrogate of response). The technology to be delivered is expected to have the potential to also provide information for tissue/organ sites which are not biopsy-accessible, thus representing a significant advance in the assessment of the immune marker status for the relevant indications. Patients can be stratified by marker expression, with the potential to offer the most appropriate treatment and thereby reduce the implementation of treatment regimens that are unlikely to be efficacious and would therefore have a negative benefit-risk profile for the individual patient (personalised health care, PHC). For example, in the treatment of certain cancers, identification of particular immune cells subsets could be determined for individual patients (e.g. CD8/CD4-imaging) to determine and predict the response and which patient population would most likely to benefit from co-stimulatory treatments.

By visualising and quantifying the impact of therapy on specific target sites and related immune-mediated pathways, the planned technology is also expected to reduce ambiguity in the evaluation of efficacy during clinical trials (e.g. provide early indications of patient responses, assessment of variability between and within individuals, facilitate proof of mechanism (POM) and proof of concept (POC) studies of new mechanisms). Spatio-temporal complexity can be studied due to longitudinal imaging capabilities.

This topic is a unique instrument to strongly support and enable research and development activities addressing diseases with a strong immunological component, for which currently no or only very limited treatment options are available. Furthermore, it will have significant impact on personalised approaches to detect and better monitor these diseases already in the early and better treatable stages. It will support and guide physicians and patients in determining the most appropriate care, leading to improved efficiency in the health care system and patient benefits. It is envisioned that the topic will ultimately result in the regulatory acceptance of standardised protocols with validated immune-imaging approaches. Consequently, those approaches will significantly reduce the time and cost of clinical trials.

Small and medium-sized enterprises (SMEs) can be of great benefit to IMI2 JU projects. Their involvement in the action might offer a complementary perspective to industry and academia, and help deliver the long-term impact of the project. Therefore applicants should indicate how their proposals will impact and strengthen the competitiveness and industrial leadership of Europe by, for example, engaging suitable SMEs.

Potential synergies with existing consortia

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

In particular, the action generated by this topic should, among others consider initiatives such as the FNIH Partnership for Accelerating Cancer Therapies (PACT) https://fnih.org/what-we-do/current-research-programs/partnership-for-accelerating-cancer-therapies or the IMI projects **BTCURE** (http://btcure.eu/), **RTCURE** (http://cordis.europa.eu/project/rcn/211964_en.html), **PRECISESADS** (http://www.precisesads.eu/) and **TRISTAN** (http://www.imi.europa.eu/projects-results/project-factsheets/tristan).

Industry consortium

The industry consortium is composed of the following EFPIA companies:

- Roche (lead)
- AstraZeneca
- Bayer
- Janssen
- Novartis
- Pfizer
- Sanofi

The industry consortium will include expertise in clinical operations, protein engineering, validation of immune cell targeting, and will contribute mainly in the form of:

- provision and detailed investigation of antibodies, antibody fragments, and/or small molecule probes;
- prospective clinical trials for selected diseases (immunotracers to be applied in these prospective on-going clinical trials with dedicated imaging activities);
- samples from prospective clinical trials;
- immuno-histochemical and other appropriate analyses of biopsy material to validate the imaging results;
- historical samples for validation;
- omics data analysis.

Indicative duration of the action

The indicative duration of the action is 60 months.

Future project extension

Potential applicants must be aware that the Innovative Medicines Initiative 2 Joint Undertaking (IMI2 JU) may, if exceptionally needed, publish at a later stage another Call for proposals restricted to the consortium already selected under this topic, in order to enhance their results and achievements by extending their duration and funding. The consortium will be entitled to open to other beneficiaries as they see fit; should appropriate imaging modalities and/or technologies are developed within the context of the consortium and require additional investigation outside the scope of the proposed sustainability plan.

Direct visualisation of immunophenotypes in target organs would advance the field by providing a mechanistic insight into the pathogenesis of disease which in turn could, with additional studies, lead to the improvement of treatment decisions for physicians and help guide therapeutics development by allowing the visualisation of response to therapy. The proposed focus is to validate existing agents that target immune cells and molecular pathways using biopsies from multiple diseases and target sites as a starting point.

Thus, the knowledge gained from the clinical validation of existing imaging reagents should help augment the development of new tracers, and the pre-clinical studies from them will speed up patient access to innovation. However, addressing all these points is outside the scope of the current initiative as the insights uncovered by this topic will be exploratory and not definitive, and will need to be followed up by future validation studies in patients.

Indicative budget

The indicative EFPIA in-kind contribution is EUR 15 000 000.

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.

The financial contribution from IMI2 JU is a maximum of EUR 15 000 000.

Applicant consortium

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

- basic and clinical immunology, in particular as this relates to the proposed cell types and indications;

- strong expertise in chemistry and molecular biology to improve the target specificity of imaging agents;

- biological validation of specific immunotracers in well-characterised animal models for the particular diseases to be investigated

- expertise with appropriate non-invasive imaging technologies and optimisation of quantitative data generation and analysis;

- expertise in immunotracer development, for example in identification of (novel) selective and specific immune cell markers, generation and optimisation of targeting moiety/tracer conjugates;

- proven expertise in project administration, management and communication;

- extensive expertise in interaction and communication with global regulators, patients, practitioners and payers, who may be members of an advisory board which would be established by the action. These responsibilities will be executed in collaboration with the industry consortium;

- strong data management expertise;

- proven experience in managing and coordinating a multi-centre multi-node clinical-research data-generation activity of comparable scope;

- essential experience in dealing with the legal and ethical challenges associated with integrating multi-centre patient-derived data, as well as physical data-processing and data management practices (privacy, security);

- proven capability to deliver analytical platforms to facilitate the above-mentioned advanced analytical approaches for a range of scientific/medical and analytical communities.

In addition to academic groups, relevant SMEs with relevant proven expertise are encouraged to participate in the applicant consortium. SMEs can be of great benefit to IMI projects and, inter-alia strengthen the competitiveness and industrial leadership of Europe. Their involvement might offer a complementary perspective to industry and academia, and strengthen the long-term impact of the project. For these reasons, applicants should consider engaging SMEs throughout the proposal. Under this topic, the contribution of SMEs would be considered especially beneficial in imaging agents and technologies, advanced analytical approaches and data management practices.

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

Suggested architecture of the full proposal

The applicant consortium should submit a short proposal which includes their suggestions for creating a full proposal architecture, taking into consideration the industry participation including their contributions and expertise.
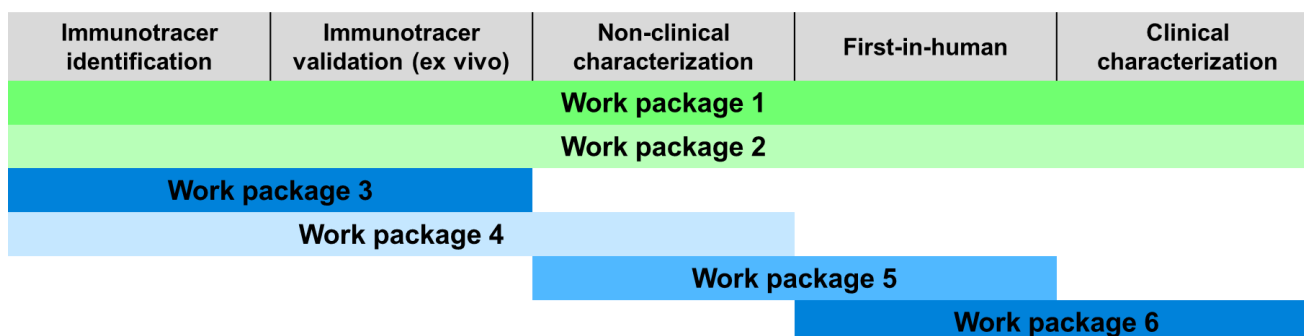
In the spirit of the partnership, and to reflect how IMI2 JU Call topics are built on identified scientific priorities agreed together with EFPIA beneficiaries/large industrial beneficiaries; these beneficiaries intend to significantly contribute to the programme and project leadership as well as project financial management.

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

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

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

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

Immunotracer identification	Immunotracer validation (ex vivo)	Non-clinical characterization	First-in-human	Clinical characterization
Work package 1				
Work package 2				
Work package 3				
Work package 4				
		Work package 5		
			Work package 6	

Work package 1 – Management, coordination, dissemination and sustainability

The goals of this work package will be as follows:
- overall coordination of the scientific and clinical work packages;
- budget administration;
- dissemination of scientific results and research data;
- development of a sustainability plan to facilitate continuation of the project beyond its anticipated duration;
- communication within the consortium and with external collaborators.

Expected applicant consortium contribution: coordination of work packages, budget administration, dissemination of scientific results and development of a sustainability plan.

EFPIA consortium contribution: communication, dissemination of results and development of sustainability plan.

Work package 2 – Data storage and analysis

The goals of this work package will be as follows:
- managing/coordinating multi-centre (clinical) research data including legal and ethical considerations;
- data sharing, data integration infrastructure, and bio-banking;
- analysis of retrospective clinical trials and design and execution of prospective clinical trials.

Expected applicant consortium contribution: coordinating a multi-centre multi-node clinical-research data-management.

EFPIA consortium contribution: prospective clinical trials for selected diseases (immunotracers to be applied in these prospective on-going clinical trials with dedicated imaging activities); provide samples from prospective clinical trials.

Work package 3 – Generation of imaging reagents to uniquely identify specific cell types

The goals of this work package will be as follows:
- specification of cell types and appropriate surface tags;
- generation of detection reagents;
- characterisation by histology and/or flow cytometry or other laboratory techniques;
- qualification of immunotracers for use in confirmatory assay types and ensuring suitability in different assay types.

Expected applicant consortium contribution: identification and evaluation of promising molecular imaging agents; generation of immunotracers for at least two of the following key cell types of interest: CD4+, CD8+, and/or regulatory T-cells, B-cells, NK-cells, and macrophages; immunotracer optimisation in the context of the planned use (e.g. with respect to pharmacokinetic and bio-distribution profile, suitability for repeated use in longitudinal studies).

EFPIA consortium contribution: immuno-histochemical and other appropriate analyses of biopsy material to validate the imaging results, historical samples for validation, omics data analysis.

Work package 4 – Imaging technique development and optimisation

The goals of this work package will be as follows:
- specification of optimal imaging modality;
- development of imaging protocol for specific immunotracers (e.g. definition of dose, imaging time point etc.) in preclinical models and with support from data from work package 5, where applicable.

Expected applicant consortium contribution: biological validation of specific immunotracers in well-characterised experimental animal models; proof of principle preclinical imaging studies using known immuno-modulators.

EFPIA consortium contribution: biological validation of specific immunotracers in well-characterised experimental animal models; proof of principle preclinical imaging studies using known immuno-modulators.

The allocation and distribution of resources will be agreed during the elaboration of the full project proposal, as this is dependent on the distribution of expertise between EFPIA and successful (academic/SME) applicant consortium partners.

Work package 5 – Validation of immunotracers in animal models (non-clinical *in vivo* characterisation)

The goals of this work package will be as follows:

- validation of novel immunotracers in rodent and/or monkey models of human disease;
- *in vivo* pre-clinical animal models will be used to measure the utility of the immunotracers;
- characterisation of non-clinical safety.

The allocation and distribution of resources will be agreed during the elaboration of the full project proposal, as this is dependent on the distribution of expertise between EFPIA and successful (academic/SME) applicant consortium partners.

Work package 6 – Human clinical trials

The goal of this work package is to confirm the safety of new immunotracers and reagents and to demonstrate clinical utility in human trials.

Expected applicant consortium contribution: contribute to the preparation of regulatory documentation (Investigator Brochure, clinical protocol, Clinical Trial Application dossier etc.).

EFPIA consortium contribution: prospective clinical trials for selected diseases (immunotracers to be applied in these prospective on-going clinical trials with dedicated imaging activities); provide samples from prospective clinical trials.

Topic 3: Development of a platform for federated and privacy-preserving machine learning in support of drug discovery

Topic details

Topic code	IMI2-2018-14-03
Action type	Research and Innovation Action (RIA)
Submission and evaluation process	2 stages

Specific challenges to be addressed

Enabled by an ever-expanding arsenal of model systems, analysis methods, libraries of chemical compounds and other agents (like biologics), the amount of data generated during drug discovery programmes has never been greater, yet the biological complexity of many diseases still defies pharmaceutical treatment. Hand in hand with rising regulatory expectations, this growing complexity has inflated the research intensity and associated cost of the average discovery project. It is, therefore, imperative that the learnings from these data investments are maximised to enable efficient future research. This could be empowered by the big data analysis and machine learning approaches that are currently driving the digital transformation across all industries. These approaches not only rely on data generated specifically within a given project to learn from (as more established machine learning approaches tend to do), they also evaluate all other available data from different data sources and types for relevance to the question at hand. This extended approach will extract the maximum information present within the data, which in turns enables a gradual virtualisation of drug discovery processes and increases efficiency in bringing more and safer drug candidates towards clinical trials.

The success of the digital transformation in the pharmaceutical industry will thus highly depend on unlocking the maximal amount of data for the learning tasks at hand, and make these data amenable to the latest approaches in machine learning. To accomplish this, the following specific challenges need to be addressed.

- Unlocking of proprietary and confidential data that is currently distributed across multiple data owners within the pharmaceutical sector without disclosure of the actual data and related assets themselves. In order to convince data owners to share their highly confidential and proprietary databases, which have been established over many years at considerable cost, the following conditions need to be fulfilled.

  - **Privacy preservation** denotes the strict protection of the confidential and intellectual property (IP)-sensitive data and assets. In drug discovery, examples of IP-sensitive data and assets include the activity data of compounds in assays, the assay annotations, and predictive models derived from these data. In the strictest sense, privacy preservation implies that these data and assets never leave the control of the respective data owners.

  - **Federated machine learning** denotes here the distribution of the learning effort over physically separated partners. This goes beyond the currently more established concept of federated databases where the data are distributed, but not the data functionalisation (i.e. the learning from the data). It is key to enable owner control over data and other assets during learning.

- Unlocking of data volumes from data sources or types that have hitherto remained untapped. In drug discovery, examples include image or transcriptional profiles or primary data points acquired in high throughput screens, all of which provide rich but hard-to-interpret biological annotation of chemical compounds.

- Adapt recent advances in machine learning such as multi-task learning and deep learning for the above data expansion strategies.

Need and opportunity for public-private collaborative research

The digital transformation that is driven by ever more exhaustive data collection and exploitation, is disrupting the entire industrial landscape. Sectors and geographies that fail to embrace this transformation will find themselves challenged in their remit by newcomers with a strong footing in data sciences.

In this context, a collaboration among pharmaceutical partners, academia and knowledge partners from small and medium-sized enterprises (SMEs) and other commercial organisations offers the perspective of doubling economies of scale in bringing better and safer drugs to patients. Firstly, it enables cost sharing and thereby bolsters the position of the European pharmaceutical industry in the global competition for data science and ICT resources. Secondly, it encourages data and method standardisation, thus expanding the volume of collective data that can fuel the big data revolution. Notably, these collective data should not be misinterpreted as a freely accessible and hence a fully precompetitive resource. Privacy-preserving approaches enable the reconciliation of collaborative investment with healthy within-sector competition.

The concepts of federated and privacy-preserving machine learning apply beyond the discovery remit, for instance in development and other clinical settings (like real-world evidence settings). They even apply beyond the health setting. Indeed, by providing data owners the confidence that their data and the corresponding predictive models will remain private, the methodologies developed will encourage the formation of data and model consortia in various commercial (including non-pharmaceutical) and non-commercial contexts where data and knowledge ownership is at play. This creates opportunities for SMEs or other commercial partners that offer front-end or back-end services in the areas of software-as-a-service products in big-data analytics, clouded high-performance computing and privacy-preserving solutions. The public-private partnership proposed enables such partners to get exposed to, on the one hand, a strong application field with relevant use cases and clear ICT and security requirements, and on the other hand, academia and other knowledge partners with deep expertise in rapidly evolving science and technology fields.

Scope

The topic aims for:

The delivery of a federated and privacy-preserving machine learning platform, initially validated on publicly accessible data, that is demonstrably safe enough (privacy-preserving in the face of legitimate and illegitimate (attempted) access and use) and scalable enough to be deployed to a significant representation of private data in the actual preclinical data warehouses of the participating major pharmaceutical companies in yearly evaluation runs. This effort will be mainly driven by the applicant consortium and enabled by the EFPIA partners.

The industry partners will subsequently drive the evaluation of the security, scalability and operational and predictive performance of the above platform on real industrial data (which is much more extensive than that in the public domain). As an indication of scale, the anticipated collective private compound and activity data sets from the industrial partners that will be used during the evaluations and that are to be accommodated comprehensively in each of the at least yearly runs, will include:

- at least 5 million chemical compounds annotated with dose-response quality activity data;
- at least 10 million chemical compounds annotated with some activity;
- at least 1 billion assay activity data points collected at single dose (low-complexity i.e. 1 to a few numerical values per compound, e.g. as from high-throughput screening);
- at least 100 million activity data points collected in dose response (over a range of doses, e.g. as from follow-up/secondary screening);
- several high-complexity activities collected at high-throughput (at least 100 thousand compounds in a standardised setting, e.g. high-resolution microscopy images or transcriptional profiles with 1000 readouts per well).

The above data are generated as part of the industry partners' normal drug discovery activities and, as such, are not generated in the scope of the project. Other than anonymised assay identifiers, the industry partner data will not include assay meta-information, such as specification of which drug target is tested. As a part of the effort, the industry partners will agree on protocols to standardise, format and normalise their private data for optimal interoperability and will openly release the software they develop to do so, to promote its broadest adoption, within or outside of the context of the proposed machine learning platform. The applicant consortium is encouraged to closely cooperate with this aim.

The economic value of the platform lies in its ability to learn to predict the activity of chemical compounds in documented assays from descriptors of their chemical structure in the absence of meta-information such as the drug target of these assays. For training the predictive models, the platform will leverage the activity data points for all assays (which remain under the control of their respective owner) and as much of the further available side information for compounds (images and transcriptional profiles) as possible. Methods within the scope of this topic should be compatible with the full scale and richness and with the limitations of the above data. For example, given the absence of assay meta-information, no predictive performance gains can be realised by constructing models across data columns with similar or shared annotations.

Predictive performance improvements from federated learning are expected to stem from the multi-task effect across partners. In the rich data sets described above, most assays are poised to show some linear or non-linear correlation with (a combination of) other assays. In a multi-task setting, this allows the model predictivity to be boosted for chemistry that was not documented in the training set for a given assay, but that was documented in some correlated assay(s). In a federated learning setting, such information transfer will occur across partners, through common representation of tasks/assays in federated (as in shared among the data participants) model components. Privacy preservation on the other hand implies that each pharma owner/contributor of assay data builds up (on IT infrastructures under his own control) complementing model components that are specific for his own assays. Federated and privacy-preserving learning combines federated model components (enabling transfer learning across partners) and private model components (to preserve the confidential nature of the modelled assays) to yield better informed, yet overall private models for the respective data owners/contributors. This combination of better learning with preserving the privacy of the underlying data and assets is the core value of the proposed platform.

In terms of predictive performance, the concrete outcome of the evaluation of the platform will be relevant metrics of the predictive performance of the platform as a function of design and setup choices, aggregated by the platform across all the assays from all the partners. Platform-mediated aggregation ensures that contributions of the individual participants to the overall performance are anonymised, in order that here too, privacy is preserved. The aggregated performance metrics will be shared with the consortium partners to guide and improve design choices, and ultimately document the predictive performance of the final versions of the platform, a key objective of the proposal, without however disclosing the underlying confidential data and/or any predictive models derived therefrom.

For future exploitation, platform versions must be designed that can also produce the individual predictive models for the assays of respective data contributors, in a form that persists after completion of the run. It should be noted, however, that the generation of such persistent individual predictive models, which are inseparably linked to the private compound and activity data from the EFPIA partners, is not essential for the computation of the aggregated performance metrics during the cross-pharma evaluation rounds. Indeed, these aggregated performance metrics can also be computed using alternative platform versions that do not produce persistent individual predictive models, but this would burden the consortium with the development and audit of an alternative version for each platform iteration. It is crucial to understand that the preservation of privacy and confidentiality of the data to be learned from and the individual models derived therefrom is a key component in the successful implementation of the topic, not only in the current context of discovery and preclinical research but also for any potential future extensions using clinical data. It is also a condition for the involvement of the extensive private datasets of the EFPIA partners.

Technically, privacy preservation is interpreted to exclude any persistent or non-persistent consolidation of assay data or annotations, or the corresponding predictive models, which were described above as the private model components (even encrypted) outside of IT architectures under direct and sole control of their respective owners. It also implies the confidential treatment of all related data and protection from access to them by third parties.

The proposed project aims for federated machine learning which is not the same thing as machine learning on federated data. The difference is as follows: in the former case, the machine learning effort itself is distributed over the parties involved; in the latter case, the machine learning is executed centrally over federated data, which is incompatible with the proposed interpretation of privacy preservation. Upon completion of a modelling exercise, no data (derived or otherwise) should persist outside of those architectures. The pharma IT departments will consolidate their IT security requirements, including those covering compatible cloud services proposed as part of the platform IT architecture, based on current industry standards that aim to protect against illegitimate access to or use of the data or predictive models.

The expected time and cost efficiency gains in a development context (using clinical data) will most likely far outweigh those in the current discovery setting, given the obvious privacy considerations concerning clinical data. It is, therefore, important that the platform is designed with future use in a clinical setting in mind. However, this project focuses on the core objective of developing the federated, privacy-preserving machine learning method in a preclinical setting. Tackling the complexities of clinical data handling in terms of adequately addressing ownership and privacy legislation implications would take place in a future initiative.

To further bolster the confidence in the proposed methods of the pharmaceutical partners (and of potential other future adopters), an intrinsic part of the proposal should focus on analysing the privacy preservation of the proposed methods in the case of legitimate use (targeting questions like 'can a model owner reconstruct parts of the chemical or bioactivity data of individual other parties based on model components they can legitimately access'). Public data (prepared and processed by the pharma partners using the same protocols as for their own data) can be leveraged to this end. ChEMBL and PubChem represent the main public information sources, but other open data opportunities of relevant scale can be considered.

In summary, the power of the proposed federated and privacy-preserving machine learning platform resides in the fact that it operates in such a way that it can extract a maximum of learnings without the need to directly access the underlying private data. This makes the methodology generic and widely applicable in a great diversity of settings, with a high potential in settings where learnings are envisaged from highly confidential data, such as patient-related data in a clinical setting.

Expected key deliverables

- An early software prototype for federated learning compatible with privacy preservation (not enterprise ready) is delivered by month 2 to allow the algorithm to be documented and to enable an analysis of privacy preservation by the use of legitimate modelling results. This prototype should be based on software already existing at project start.

- A coherent, federated, privacy-preserving machine learning platform that conforms with the following requirements should be delivered by month 12 and updated at least annually.

    - For each iteration, an early software prototype is made available 10-12 months ahead of the enterprise-ready release, to allow algorithm documentation and to enable an analysis of privacy preservation.

    - For each iteration, a report on the privacy preservation performance of the platform using public data, listing algorithmic or parameter options to navigate performance/privacy trade-offs, is prepared. This includes evaluating vulnerabilities to e.g. differential attacks. These reports will enable conceptual sign-off for use on the massive proprietary and confidential pharma datasets.

    - For each iteration, based on the signed-off conclusions of the privacy preservation report, enterprise-ready code is delivered, i.e. ready for independent code audit against joint pharma security requirements (that should preclude to reasonable standards illegitimate access to or use of data or models, and that covers compatible IT architecture options including cloud services). A favourable audit report is a prerequisite for exposure of the massive pharma datasets.

    - Ability to be run on a requirements-compatible IT architecture in a standalone and federated learning setting.

    - From the 2nd year onwards, the solutions should enable participants to mutually benefit from the inclusion of high throughput image or transcriptional datasets annotating sets of more than 100k compounds.

- Establishment of proof-of-concept of this platform, by deploying and evaluating it in an industrial setting.

    - EFPIA partners to propose common protocols to standardise, format and normalise their private data for optimal interoperability and openly release the software they develop to do so.
    - EFPIA partners to consolidate their necessary and sufficient IT security requirements including those covering compatible cloud services proposed by the applicant consortium as part of the platform IT architecture. Part of the infrastructure will need to be under the control of the respective data and asset owners.
    - To evaluate the predictive performance of the platform when deployed on industrial scale datasets as a function of design and setup choices, by performance metrics aggregated by the

platform across all assays and partners. Relevant performance metrics to include established metrics that can be used with annotated compound sets, like the AUC of the ROC curve and logarithmic loss metrics or root mean squared prediction error for all assays, aggregated as distributions across all assays and partners. In addition, performance metrics are to be collected, in an aggregated modality, that measure the information gain (i.e. certainty, credibility or precision gain) over the platform of predictions for unannotated compounds.

- Standalone and cross partner runs yielding these performance metrics (aggregated by the platform across all assays and partners) to be executed on a requirements-compatible ICT infrastructure and comparison of the resulting aggregated metrics. The algorithmic, software and ICT infrastructure choices proposed should cost-efficiently enable a full cross-partner run to complete in maximally four weeks. This may or may not imply provision of hardware acceleration options, and – to ensure availability of such options for all participants – cloud services.
- At least in one exercise, the aggregated predictive performance of inclusion vs. exclusion of image-derived or transcriptional features in a federated modelling run are compared head-to-head.
- At least in one exercise, the aggregated predictive performance of the developed methodology is compared head-to-head to that of a credible established non-federated single-task method (minimally support vector machine (SVM), random forest or a comparably performant method).

- Sustainability plans that detail how the applicant consortium intends to make the developed methodologies accessible to the pharmaceutical industry and to other future adopters after the project ends.

- Publication and dissemination of guidelines, advice, detailed processes (workflows and specific technical details), ICT and security standards, and of the predictive performance (at an aggregated level) to promote the uptake of the developed methodologies in the pharma and other) sectors.

- Identification and publication of any barriers to the uptake of the proposed methodology and publication of solutions to reduce those barriers.

Expected impact

The *in silico* predictions from the platform developed within the project will increasingly replace the costly and time-consuming *in vitro* testing, resulting in cost and time savings on compound synthesis and measurement in assays and preclinical studies, and therefore increase the efficiency of pharmaceutical discovery research. Although out of the direct scope of the present topic, the application of similar concepts to clinical data to enable faster recruitment of more targeted patients holds the longer-term promise of reducing costs of development.

The concepts developed within the project will be generic and will apply not only to the pharmaceutical discovery and clinical development setting, but also to other clinical applications, including real-world evidence analysis. Beyond the health area, they will prove relevant to multiple alternative industrial and other commercial or non-commercial settings where parties are interested in different predictive models that benefit from indirect access to the same volumes of private data. By providing data owners with the confidence that their data and the corresponding predictive models will remain private, this project will facilitate access to much larger data sets and therefore improve performance over that of conventional machine learning approaches.

For knowledge and ICT partners, federated learning presents a line of research and product development beyond that of data federation.

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

Potential synergies with existing consortia

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

For example, several IMI projects have already faced the challenge of facilitating research on private data, see http://www.sciencedirect.com/science/article/pii/S1359644615004249 and http://www.mdpi.com/1422-0067/15/11/21136/html

Another IMI project aims at the systematic FAIRification of data (the capture and management of data to make them Findable, Accessible, Interoperable and Reusable). The project consortium is encouraged to seek synergies with projects for the FAIRification of data (e.g. consider applying learnings and technologies from such projects), but should avoid replication of such efforts.

Industry consortium

The industry consortium is composed of the following EFPIA companies:

- Janssen Pharmaceutica NV (lead)
- Astellas Pharma Europe BV
- AstraZeneca AB
- Bayer AG
- Boehringer Ingelheim Pharma GmbH & Co. KG
- GlaxoSmitKline R&D Ltd
- Institut de Recherches Internationales Servier
- Merck KGaA
- Novartis Pharma AG

Key contributions from EFPIA partners:

- agreed protocols and solutions for processing data with the necessary and sufficient level of standardisation to enable the machine learning exercises. To encourage broader adoption, the partners will opt for open solutions where possible. Insights on data standards and technologies from ongoing EU-funded projects (e.g. those in the context of the FAIRification IMI topic) will be considered;
- the anticipated collective industry datasets outlined under Scope, above;
- data management;
- formulation of joint security requirements in line with industry standards;
- set up independent audit of all enterprise-readied code against those requirements;
- evaluation of the analysis of privacy preservation based on legitimately accessed models;
- expertise in cheminformatics and machine learning at scale in the context of this topic;
- upon enablement by the consortium (access to secure software solutions), execute provided solutions on own data (standalone);
- evaluate the aggregated predictive performance in terms of accuracy and related metrics (for annotated compounds) and information gain and precision (for unannotated compounds);
- extensive experience in drug discovery and development, including knowledge, of all *in vitro* and preclinical assays modelled;
- expertise in image and omics analysis, to facilitate the accommodation of image or transcriptional information in the developed methods;
- project management coordination across pharma;
- project management support by a subcontracted project management office;
- dissemination activities within the sector.

Indicative duration of the action

The indicative duration of the action is 36 months.

Future Project Expansion

Potential applicants must be aware that the Innovative Medicines Initiative 2 (IMI2) Joint Undertaking, may publish at a later stage another call for proposals restricted to those projects already selected under this call in order to enhance and progress their results and achievements by extending their duration and funding. Consortia will be entitled to open to other beneficiaries as they see fit. If proof-of-concept in terms of privacy and predictive performance is established in the discovery setting, there is the possibility of a restricted call that would adapt the platform developed under the present call for use on clinical datasets, i.e. deliver and evaluate an extended version of the platform that would:

1. map relevant clinical concepts to specific platform components; and
2. meet all additional legal requirements associated with the handling of patient data (e.g. those related to the protection of patient privacy).

Indicative budget

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

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 contribution.

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

Applicant consortium

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

The applicant consortium is expected to address all the research objectives and make key contributions to the defined deliverables in synergy with the industry consortium which will join the selected applicant consortium in preparation of the full proposal for stage 2. Therefore, the applicant consortium should be able to demonstrate the full scope of experience and expertise needed to effectively address all the objectives outlined in this topic. The size 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 team work. 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 project.

To meet the ambitions of the topic and ensure a first version can be deployed by the end of year one, the applicant consortium should describe the workhorse algorithms they intend to use in their short proposal, in sufficient detail to convincingly demonstrate their compatibility with the type of data made available for this topic and with the proposed federated and privacy-preserving machine learning concepts, preferably with (not necessarily secure or enterprise ready yet) software prototypes. If there are dependencies on other than open source software, the consortium members preferably collectively hold all necessary background rights, so that licensing costs are kept minimal within project and the service can ultimately be offered at an attractive cost. This also ensures that an independent auditor can get access to all parts of the code to attest that it only comprises the intended functionalities.

Given the runs will involve the handling of private preclinical data sets at an unprecedented scale, the applicant consortium is expected to mobilise across academia, SMEs and other commercial organisations as appropriate, the following:

- demonstrated extensive hands-on expertise in solutions for big data handling at industrial scale;
- demonstrated extensive hands-on expertise in ICT security and information leakage aspects;

- demonstrated extensive hands-on expertise with deployment on high performance computing infrastructures;

- demonstrated extensive hands-on expertise in software engineering;

- demonstrated extensive hands-on expertise in machine learning technologies, including in the context of federated learning;

- demonstrated hands-on expertise of deploying computational approaches in the context of drug design, drug discovery and development;

- demonstrated hands-on expertise in 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 in communication tools and systems for project management purposes), in the context of EU-funded projects.

The short proposal should include a description as to how the applicant consortium intends to make the developed methodologies accessible to the pharmaceutical and other industries after the project ends. To this end, it is suggested to allocate responsibility for ensuring sustainability (including software, licensing, infrastructure options, potential broker services) to a specific consortium partner. While a broker role is acceptable, and could for example be filled by an SME, this role must be compatible with the outlined interpretation of federated and privacy-preserving machine learning (for instance the broker function will not have access to assay data, annotation or the corresponding models).

Suggested architecture of the full proposal

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

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

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

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

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

Work package 1 − Pre-processing of data up to a level of necessary and sufficient standardisation

The goals of this work package will be as follows:

- select methodology for standardised pre-processing of data and implement in scripts, including feature extraction, dimensionality reduction, weighted data integration;

- enable participants to deploy scripts in standardised ways compatible with the architectures proposed for the exercise;

- execute pre-processing of data and make it available (including public data for work package 3).

Industry consortium contribution

Methodology selection, implementation and execution.

Expected applicant consortium contribution

Enable architecture-compatible deployment, scientific advice.

Work package 2 – Industrial IT technical scoping and deployment

The goals of this work package will be as follows:
- joint pharma user requirements;
- independent software audit (in-kind pharma contribution) of the resulting software (from work package 5);
- enable/execute runs on ICT infrastructure under pharma control (these may be cloud services).

Industry consortium contribution

Formulation of user requirements, set-up of audit, enable runs.

Expected applicant consortium contribution

Liaison between pharma-driven work package 2 and consortium driven WP5 (software implementation), to ensure solutions match requirements and can be run on pharma controlled infrastructures.

Work package 3 – Federated machine learning algorithms

The goal of this work package will be as follows:
- development and scientific and software prototyping of the algorithm;
- initial predictive performance estimation (on public data);
- machine-learning security analysis of algorithms (on public data), to enable security evaluation.

Industry consortium contribution

Experts in machine learning applied to the domain of the topic.

Expected applicant consortium contribution

Expertise to carry out the activities listed above.

Work package 4 – Evaluation of privacy and performance balance and of predictive performance of the versions up to implementation in discovery projects

The goals of this work package will be as follows:
- evaluation of balance between performance and privacy preservation (on prototypes);
- evaluation in terms of the aggregated predictive performance metrics (enterprise-ready product) .

Industry consortium contribution

Expertise to carry out the activities listed above.

Expected applicant consortium contribution

Scientific support for activities listed above.

Work package 5 – Software Implementation

The goals of this work package will be as follows:

- balance in WP4 (scientific) and WP2 (data privacy), to be readied to the point that it can be securely deployed on the massive pharma datasets;
- this includes aspects of software engineering, ICT security, knowledge of ICT infrastructure to run on, with respect to software implications (high performance computation enablement, hardware acceleration, …).

Industry consortium contribution

Industrial experts in ICT, security, machine learners and modelling.

Expected applicant consortium contribution

Expertise to carry out the activities listed above.

Work package 6 – Secure standalone and federated infrastructure

The goal of this work package will be as follows:

- provision of infrastructure that will operate under control of the respective EFPIA data and asset owners during standalone and federated runs (may be cloud services);
- provision of central ICT infrastructure that can connect to the infrastructures under control of the respective EFPIA data and asset owners involved, ensuring security and performance requirements;
- operation support.

Industry consortium contribution

Industrial experts in ICT.

Expected applicant consortium contribution

Selecting, setting up and providing the secure infrastructure for standalone and federated modelling runs to be procured under the action.

Work package 7 – Operations and deployment

The goals of this work package will be as follows:

- establish a detailed software and operating model with pharma organisations;
- monitoring execution of runs upon initiation by pharma.

Industry consortium contribution

Industrial experts in ICT and modelling.

Expected applicant consortium contribution

Main drivers, may include partners involved in sustainability plans.

Work package 8 – Overall project governance, project management, dissemination and sustainability

The goals of this work package will be as follows:
- grant administration;

- strategic, operational, IP and financial management;

- communication (within the consortium and with relevant external collaborators);

- dissemination of scientific results and research data to the scientific community and within the pharma sector;

- detailed sustainability plan to make results accessible beyond the duration of the action.

Industry consortium contribution

Programme leadership with respect to application and valorisation aspects, project and financial management, contribution to communication and dissemination.

Expected applicant consortium contribution

Scientific and technical programme coordination, reporting to the IMI2 JU (supported by the industry-provided project management expertise and support).

Topic 4: Centre of excellence – remote decentralised clinical trials

Topic details

Topic code	IMI2-2018-14-04
Action type	Research and Innovation Action (RIA)
Submission and evaluation process	2 stages

Specific challenges to be addressed

Developing new medicines/health solutions and improving patient health rely on the successful conduct of clinical trials to generate relevant safety and efficacy data. Recruitment and retention of patients are some of the most challenging aspects in clinical trial protocol adherence. The 2017-global CISCRP survey reported the main barriers to patients' participation as 'lack of patients' awareness of clinical trials' (~61%); and the 'geography and the distance to the clinical site' (60%)[35]. This geographical burden on patients, including the duration and number of clinical visits, also drives their decision to participate in a trial. In addition, within patients who consent, an alarming 30% dropout across all clinical trials is observed.[36] Therefore, by the same token, improving the patients' experience through protocol optimisation to ease the patient burden, whether perceived or real, should improve data quality and increase the probability of success.

TransCelerate[37] and IMI initiatives have already led to significant achievements in this area. For example, the first European Electronic Health Records data platform[38], which connects more than 20 European hospitals, has already resulted in reduced recruitment times. More recently, the emergence of digital technology has increased the feasibility of decentralised clinical trials (DCTs), a disruptive approach consisting in setting the trial around the patient rather than a centralised trial site. DCTs conducted to date have allowed the patient to participate in either all or many (depending on the model) study visits remotely, either in their home or through the use of more local medical facilities. Positive results of an acne phase 2 trial that enrolled adolescents with a reduced enrolment time of 50 percent, have recently been communicated.[39] Additionally, several other trials have been conducted or are starting, such as the VERKKO trial in Europe, which will help to inform the best practices.[40]

Combining the adoption of digital endpoints and telemedicine as applied to trials, the DCT model could improve patient access to trials, increase the participation of more diverse populations, and enhance data collection. In addition, the DCT model can help to fill the gap between clinical development and the real world setting, providing useful real life experience while the patient is followed from home or community care. The improved clinical trial efficiency may accelerate patient access to medical breakthroughs. Digital endpoints and tools will need to be evaluated with the goal to include some of these key enablers of the model while balancing the goal to minimize additional complexities.

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[35] Center for Information & Study on Research Participation (CISCRP). Perceptions & Insights Study. 2017
[36] Levitan, B et al. Assessing the Financial Value of Patient Engagement: A Quantitative Approach from CTTI's Patient Groups and Clinical Trial Project. Therapeutic Innovation & Regulatory Science; 2017
[37] http://www.transceleratebiopharmainc.com/
[38] www.ehr4cr.eu
[39] https://www.science37.com/science-37-aobiome-complete-industry-first-virtual-clinical-trial-metasite-decentralized-operating-model and https://www.centerwatch.com/news-online/2016/06/22/eclinicalhealth-announces-successful-results-entirely-remote-online-clinical-trial
[40] VERKKO trials and eClinicalHealth, e.g. Langel, K. Case Study: Remote Blood Glucose Profiling in Diabetes – Streamlining The Clinical Trial Process For Diabetes Trials. Industrial Pharmacy, Volume 50, Number 1, June 2016, pp. 11-13(3)

Need and opportunity for public-private collaborative research

This action offers a common forum to engage key stakeholders (e.g. patients, healthcare providers (HCPs), regulators, small and medium-sized enterprises (SMEs), pharmaceutical industries) to define the European remote DCT implementation considering its environment (e.g. regulatory and ethics, International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (ICH),[41] Good Clinical Practices (GCP)[42], and EU clinical trials regulations[43]).

Since DCTs could represent a dramatic shift both in the way clinical trials are conducted in the EU, as well as in the EU environment for clinical trials, a multidisciplinary collaborative approach among all stakeholders involved in clinical research and development is essential. While improving clinical trial access is a key goal, this needs to be balanced with the top priority to maintain the safety and welfare of the patient. The role of the investigator will need to be explored to resolve how they can support the decentralized model while still maintaining the necessary oversight for the patient's medical care. Federating multiple academics, clinical centres, patients' associations, regulatory bodies, SMEs, pharmaceutical and medical technology industries will ensure the concrete positioning of remote DCTs within the clinical 'journey' including best practices, recommendations for the fully remote DCT approach and the hybrid model. This approach should seek to build trust between all stakeholders involved in clinical trials and support efficiently the process for updating ICH guidelines.

To efficiently implement the concept regarding e.g. quality process, data relevance, confidentiality, integrity, and risk assessment, a broad number of stakeholders from both the public and private sectors are needed.

- The pharmaceutical industry brings experience on running remote DCTs in the US and in the EU. The project will build upon this experience to set the scene for coordinating a pan-EU remote DCT pilot.

- Clinical centres and health care providers are necessary to provide feedback on existing and future DCT initiatives and to contribute to the definition of the best practices on running full or partly remote DCTs in the EU environment. Leading clinical centres are also needed to coordinate the pan-EU remote DCT pilot and engage other centres across the EU in a different setting than the traditional one (where each site is a principal investigator).

- Regulators and stakeholders involved in the revision of GCP and clinical guidelines are pivotal in the approach both at national and EU level to ensure the appropriate positioning of remote DCTs as well as an efficient alignment with the ICH guideline update. Obtaining regulators feedback and position on the acceptance of DCT-generated data is also a key goal.

- SMEs are necessary to contribute at different levels, such as the evaluation of the DCT process, training tools for healthcare professionals and other relevant stakeholders, and telemedicine expertise.

- Patients and patient associations are also highly important in the definition and deployment of a patient-centric approach.

- Other organisation profiles, including (but not limited to) those with telemedicine expertise and medical technology expertise, are required to implement efficiently the remote decentralised process across the EU.

- Technology enablers and sites/site networks are critical stakeholders in defining how to reduce the burden on patients and thus increase patients' access to clinical trials.

To this end, the IMI2 JU is the most efficient programme in the EU to federate all stakeholders on a well-balanced approach, building trust and defining recommendations for conducting fully remote DCTs across the EU.

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[41] http://www.ich.org/home.html
[42] https://www.ich.org/fileadmin/Public_Web_Site/ICH_Products/Guidelines/Efficacy/E6/E6_R1_Guideline.pdf
[43] Regulation (EU) No 536/2014 of the European Parliament and of the Council of 16 April 2014 on clinical trials on medicinal products for human use, and repealing Directive 2001/20/EC, OJ L 158, 27.5.2014, p. 1-76.

Scope

The action will focus on disaggregating the current model of running clinical trials, defining building blocks and mapping new technologies (e.g. telemedicine, mobile health…) to support the new DCT model. The objective is to demonstrate the feasibility of running remote DCTs in Europe. This will increase access of patients to clinical research, enriching clinical trial data from a more diverse and representative patient population and improve patient experience during the trials, with a higher speed of recruitment and better retention.

This funded action will rely on learning from historical and ongoing case studies, conducted by the members of the winning consortium, to build on clear recommendations and define guidance for conducting remote DCTs in Europe. It will assess various options including hybrid models (combining DCTs with the traditional approach), as well as specific needs according to the disease / therapeutic area (e.g. rare diseases, HIV[44]). The recommendations will consider the relevance of the model and supportive technologies for gaining approval from ethics committees, and authorities responsible for approving CTs and for securing data quality, data integrity and ultimately data acceptability by regulatory agencies.

The impact of remote DCTs on the relationship between patients and their treating physicians, according to the model (fully remote vs. hybrid) will also be investigated. The funded action will also revisit the investigating site definition, and principal investigator responsibilities according to ICH/GCP. Compliance with and respect of the General Data Protection Regulation (EU) 2016/679[45] and Clinical Trial Regulation (EU) 536/2014[46] (and/or Directive 2001/20/EC[47] and its national implementation laws) and any updates, and the enforcement of data security will also be addressed.

The proposed work is based on a 3-step approach and a transversal objective for ensuring the most reliable organisation at pan-EU level for conducting fully remote DCTs.

- Step 1: Define the best practices for the conduct of remote DCTs using individual partner case studies (US and EU) and identify the positioning of such trials among clinical development.

- Step 2: Analyse the EU clinical trial environment and upgrade accordingly the best practices for remote DCTs at EU level using the outcomes of the individual partner case studies analysed in step 1. This should result in preliminary guidance to be used for the setting-up of the pan-EU pilot.

- Step 3: Design and run a pan-EU pilot remote DCT and define the positioning of fully remote or hybrid model regarding clinical development. Although the project consortium will need to decide on a specific study and disease, the pilot will focus on the technology and clinical organisation. The particular indication(s) and investigational medicinal product(s) for piloting the remote DCT will be selected as part of the project activities. Any pilot will need to be fully transparent with all processes and data, including challenges, openly shared.

- Transversal objective: Contribute to the update of ICH guidelines on remote DCTs and provide recommendations with supporting tools for implementing fully remote DCTs in the EU.

Expected key deliverables

- Definition of best practices using case studies (historical and ongoing) from industries and academics (indicatively by month 12):
  - define and leverage set of criteria to analyse case studies;
  - define the operational feasibility;

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[44] Stephenson, R., Freeland, R., Sullivan, S. P., Riley, E., Johnson, B. A., Mitchell, J., McFarland, D. and Sullivan, P. S. (2017). Home-Based HIV Testing and Counseling for Male Couples (Project Nexus): A Protocol for a Randomized Controlled Trial. *JMIR Research Protocols*, *6*(5), e101. http://doi.org/10.2196/resprot.7341

[45] 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

[46] 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.

[47] 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.

- assess data relevance, integrity and acceptability by regulators;
- analyse and report on either the hybrid or fully decentralised model to facilitate the remote DCT approach in EU.

- Technology scan for remote DCTs in an end-to-end journey assessing e.g. quality and data integrity, security, connectivity, communication interface, stakeholders' feedbacks such as patients, principal investigators, regulators, sponsors (indicatively by month 24). The scan on 'remote DCT technologies' will include an assessment of a broad technology range (available or with a validated proof-of-concept) in order to enable seamless communication, data monitoring and collection from distant locations. The 'technology package' is composed of:
  - a connected central platform enabling the management of all information collected and generated in a remote DCT, e.g. central management of information and data, communication with the enrolled patients and their ecosystem (including webpages or generating personalised text message reminders/alerts). It should enable local connectivity with various sets of connected devices or wearables and collection of data on the fly;
  - a 'mobile technology/app with/without wearables' designed for patient enrolment and to ensure communication between patients and their ecosystem: physicians, nurses, medical laboratory staff and investigators. This mobile technology will be connected to the central platform (defined above). All data generated should be eligible for collection by this platform and open to real time data integration with more traditional existing safety and efficacy calculation systems;
  - related services: recruitment/retention strategy, recruitment networks/patient group, recruitment advertising, project management, investigator management, records retention.

All the technologies stated above should comply with GCP (Good Clinical Practices), GDPR and CTR, e-Signature process and security standards on health data.

- External review of the technology scan for remote DCT and approval of the final 'technology package' to be tailored and used for running the pan-EU pilot remote DCT.
- Review and analysis of the EU clinical trial ecosystem, and anticipated changes for the pan-EU 'remote decentralised clinical trial centre' (indicatively by mid-term):
  - preliminary guidance for the launch of the pan-EU DCT including hybrid model and to support ICH guidelines;
  - changes/adaptations to the EU environment for clinical trials;
  - definition of metrics to measure success including approved technology specificities.
- Pan-EU pilot study designed and launched from a 'central' access (by a referenced public centre) using a remote DCT approach.
- Final recommendations on the fully remote DCT and the hybrid model.
- Final set of tools (training materials, contract templates, technology requirements…) to be used for remote DCTs in Europe.

Expected impact

Combined with the adoption of digital endpoints, the funded action should have the following **main expected impacts**:

- increase flexibility of patient follow-up during clinical trials, reducing the burden both on patients and hospitals;
- increase the frequency and quality of data collection;
- improve patient recruitment and retention in trials;
- accelerate clinical research and the access by the patients to more breakthrough innovative therapies;
- support directly the update of the ICH guidelines all along the process by generating evidence;
- reorganise the patient journey and the clinical environment;
- redefine the clinical trial framework in compliance with the EU regulations.[20-22]

Other expected impacts include:

- increase the participation of more diverse populations in clinical trials and reduce drop out;

- collaborating with specialty patient networks to decrease patient burden;

- support patients in managing better their disease(s) and their treatment(s) and increasing their knowledge[48];

- increase digital literacy among healthcare providers, facilitating later development of telehealth;

- provide evidence for supporting the European policy on telehealth and telemedicine applied to remote patient monitoring in Europe, beyond the scope of clinical trials.

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

Potential synergies with existing consortia

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

The synergies should be explored with:

- consortia utilising electronic health records for recruiting patients;

- consortia developing informed consent forms to be used across the EU;

- consortia involved in digital monitoring of patients, including endpoints, outcomes and quality of life;

- consortia involved in disease-specific research at international and European level (to be determined based on indication(s) selected);

- Transcelerate[49];

- CTTI[50];

- companies offering technology solutions that would support the implementation of the platform for running the pan-EU pilot remote DCT;

- consortia of European clinical trial centres such as the European Clinical Trial Infrastructure Network (ECRIN)[51];

- relevant biotechnology consortia;

- relevant EFPIA groups (e.g. Clinical Development Expert Group…);

- national/local ethics committees or IRBs;

- consortia funded under ECSEL JU[52] developing the technology required in the action.

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[48] Example of a Danish research monitoring at home patient suffering from diabetic foot ulcers; though non statistically significant, patients who used the sensors had healed wounds and less pain after 6 months, and did not need to travel to outpatient clinic. The majority of patients using this new type of care gained more knowledge about the treatment of their wounds, were very satisfied with their home care and satisfied with the collaboration between their care providers (2015 eHealth in the WHO European region report)
[49] http://www.transceleratebiopharmainc.com/
[50] https://www.ctti-clinicaltrials.org/
[51] http://www.ecrin.org/
[52] http://www.ecsel-ju.eu/

Industry consortium

The industry consortium is composed of the following EFPIA partners:

- Sanofi (lead)
- Allergan
- AstraZeneca
- Bayer
- Boehringer Ingelheim
- Covance
- IQVIA
- Janssen
- Medtronics
- Nokia
- Novartis
- Pfizer
- Takeda
- Teva
- UCB

In addition, the industry consortium includes JDRF as an IMI2 JU Associated Partner.

The industry partners will bring the following expertise:

- clinical operations
- clinical statistics
- supply chain / IP distribution
- telemedicine, medical technology and digital health
- telecom-, cloud-platform- and IoT (Internet of Things) architecture and deployment
- IoT security and end-point (connected device) security
- connectivity- and device management
- quality control and quality assessment
- legal matters for DCT (patients' rights, data collection, data transfer, data analysis)
- regulatory matters (including GDPR, CTR)
- public affairs
- patient advocacy
- patient engagement.

In addition, the industry partners will bring at least 5 remote DCT case studies (either as hybrid or fully remote DCTs). The organisational elements of these DCTs in terms of activity flows and quality criteria will be analysed in the funded action to establish best practices for running remote DCTs in Europe.

Indicative duration of the action

The indicative duration of the action is 60 months.

Following the delivery of the technology package, a project review will be held to review the proposed technology package (see expected deliverables) and ensure the action is on track to deliver the expected impacts within the five year period.

Future project expansion

Potential applicants must be aware that the IMI2 JU may, if exceptionally needed, publish at a later stage another Call for proposals restricted to the consortium already selected under this topic, in order to enhance their results and achievements by extending their duration and funding. The consortium will be entitled to open to other beneficiaries as they see fit. The decision for this will be based on progress of the action and decisions made in the sustainability work stream of the action. This process could be envisioned to build upon this running pan-EU pilot remote DCT with the following objectives (not all inclusive):

(i) add complementary modules that required public-private collaborations such as block chain approach,

(ii) extend the country representativeness in the pan-EU pilot, or

(iii) even deploy the pan-EU pilot for other therapeutic areas not selected in the initial action.

These objectives are developed to generate additional evidence of the reliability of the remote DCT approach that could be required for extending the acceptance at EU level of remote DCTs.

Indicative budget

The indicative in-kind contribution from EFPIA partners and the IMI2 JU Associated Partner is EUR 21 600 360. This contribution comprises an indicative EFPIA in-kind contribution of EUR 21 512 860 and an indicative IMI2 JU Associated Partner contribution of EUR 87 500.

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.

The financial contribution from IMI2 JU is a maximum of EUR 19 037 000.

Given the rapid speed of technological innovation in the telemedicine field, it is likely that technology available at project start will be outdated by the time the pilot remote DCT is planned to start (indicatively at month 42). Therefore, in order to ensure access to state-of-the-art technologies for the launch of the pilot DCT at month 42, the consortium may consider enrolling additional technology participants to fulfil the tasks identified in the technology package delivered at month 24. This technology package and proposed additional technology participants should be selected through an open call[53] by the funded consortium and approved by the independent review panel during the project review at month 26. To allow for these state-of-the-art technologies to be incorporated following this review, 30 % of the overall IMI2 JU funding should be reserved for such tasks and expertise.

Applicant consortium

The applicant consortium is expected to address all the topic objectives and make key contributions to the defined deliverables in synergy with the industry consortium.

The consortium shall include all relevant stakeholders involved in the clinical trial environment including SMEs to build the remote DCT Centre of Excellence:

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

- regulatory agencies to contribute to the definition of guidance for remote DCTs and to ensure the alignment with the updating of the ICH guidelines;

- standards organisations on good clinical practices to implement the guidance in an ethical and legal manner;

- SMEs with past and present experience on remote DCTs and deep expertise in Good Clinical Practice (GCP) using technology for recruiting and monitoring patients;

- telemedicine, medical technology companies to contribute to the new integrated mobile environment of patients including expertise in data validation, approved medical devices into clinical trials for data capture and continuous monitoring and their associated devices;

- patient associations and patient groups to ensure the co-design approach of patients in the remote DCT design and execution, as members or potentially as advisors to work on guidance and the patient-specific challenges;

- academics/clinical trial centres to co-design and implement the remote DCT, managing already trial programmes that could be adapted to DCT approach;

- academics involved in medical devices to contribute particularly in the technology scan of the remote DCT in an end-to-end journey and the subsequent deployment of the pan-EU pilot;

- health insurance organisations to support the telemedicine at patients' homes.

When planning the set-up of the pan-EU remote DCT pilot, the applicant consortium should consider more than a single EU country to ensure the wider acceptance of this model.

Suggested architecture of the full proposal

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

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.

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

The consortium is expected to have a strategy on the translation of the relevant project outputs into regulatory, clinical and healthcare practice. A plan for interactions with regulatory agencies/health technology assessment bodies with relevant milestones and resources allocated should be proposed to ensure the deployment and acceptance of the remote DCT concept at a pan-EU level for clinical development.

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

The below architecture for the full proposal is a suggestion; different innovative project designs are welcome, if properly justified.

All work package activities described below **should comply** with all EU regulations and more particularly with GDPR[20] and CTA Regulations[21].

Work package 1 – Collecting and analysing study information on previous and ongoing experiences of remote DCTs (benefits, process, patient's surveys, process data) and compilation of best practices / recommendations (liaise with WP3)

The goals of this work package will be as follows:

- defining criteria for analysing the DCTs model and processes, including the set-up, recruitment, enrolment, informed consent process, and data collection, data quality and relevance;

- analysing process information from 'individual partner studies' (either US or EU if any) including challenges confronted and solutions, e.g. Science37 model including provisions from GDPR and CTR[20-22] context;

- defining good practices and detailed SWOT on setting up 'remote DCTs' using individual partner experience in regard also to GDPR[Error! Bookmark not defined.] and CTR[43] context;

- upgrading the 'individual partner studies' using the good practices developed in this funded action';

- guidelines to set up the pan-EU pilot remote DCT including compliance with GDPR and CTR[20-22];

- analysing protocol suitability for remote DCT including how to establish criteria for selecting trials for the remote DCT model.

Expected key deliverables

The expected key deliverables will be as follows:

- definition of criteria to analyse each case study (either hybrid/fully decentralised) and report to build up the remote DCT approach in the EU;

- review of previous case studies (remote decentralised clinical trials/home monitoring) available from industries and investigation sites (public/private) to date to define and share challenges and solutions in remote DCT/home monitoring for application in an EU setting;

- definition of first best practices using individual partner case studies;

- definition of first recommendations for remote DCTs (to be implemented in the pan-EU pilot remote DCT – cf. work package 2);

- criteria defined for selection of appropriate trials.

Industry contribution

Clinical operational experts; statisticians; IT experts (telemedicine activities and digital health); quality control; pharmaceutical research scientific domain experts; legal experts; patient engagement experts. Experience from previous or on-going remote DCT case studies to build up the best practices (mainly from US) and upscaling the best practices into case studies for setting-up the EU DCT model; data validation; expertise on using approved medical devices in clinical trials for data capture (mainly for pharmaceutical sponsors and mainly continuous monitors and their associated devices).

Expected applicant consortium contribution

Principal investigators; hospitals; clinicians; experts in the conduct of multisite clinical trials as a minimum, preferably in remote DCT trials including home monitoring; clinical statisticians; IT experts in the development of platforms for patients; supply chain / IP distribution; legal experts; previous or ongoing case studies to be used to build up the best practices regarding EU regulations[20-22] and any subsequent updates.

Work package 2 – Pan-EU 'remote DCTs' pilot (liaise with WP3)

The goals of this work package will be as follows:

- design a pan-EU pilot using guidelines developed in WP1, potentially in a way that allows for comparison with a 'traditional' study – for example run part of the same study in a remote DCT model, while the rest is traditional, or find a previously conducted study / studies that allows for some comparison – and integrate & tailor the 'technology package' approved by the external review panel for the pan-EU pilot remote DCT;

- set-up and run the pan-EU pilot remote DCT;

- analysing process information from the pan-EU pilot to define the scientific and operational quality of the pilot and proposed optimisations;
- refining key performance indicators (KPIs) to qualify and quantify the flow of activities in the pan-EU pilot, e.g. (but not limited to) recruitment rate, retention rate, patient burden/satisfaction, data quality, confidentiality and integrity compared directly during a trial (half traditional and half DCT) or retrospectively through benchmark data.

Expected key deliverables

The expected key deliverables will be as follows:

- setting-up of a pan-EU pilot study or multisite study. Pilots should be private-public collaborations to the extent possible, and organised by a referenced public centre;
- final evaluation of the pan-EU pilot regarding the KPI defined including conditions of DCT use compared to traditional trial and acceptability of the model at pan-EU level.

Industry contribution

Clinical operational experts; statisticians; IT experts (telemedicine activities and digital health); quality control; pharmaceutical research scientific domain experts; supply chain / IP distribution; legal experts; patient engagement experts; investigate and design new technologies/logistics for distant monitoring in DCT; medical technology experts; upgrading the best practices on remote DCT in their respective trials; regulatory experts.

Expected applicant consortium contribution

Principal investigators; hospitals; clinicians; experts to set up and run the pan-EU remote DCT pilot including home monitoring (if feasible); IT experts in the development of platforms for remote DCTs; regulators in agencies; patient associations; medical technology experts.

Work package 3 − Technologies – identification of barriers and enablers and data management

The goals of this work package will be as follows:
- data quality and management (WP1 and 2) - activity flows;
- assessment of a wide range of 'technology packages' (as defined in the deliverable section) either as available or as a validated proof-of-concept including all supporting services that are likely going to be required ('virtual site' with phone / email / chat support, logistics, home or online nurses…);
- recommendations on technologies evaluated and data quality/data relevance including evaluation of some technologies available as well as in a validated proof-of-concept;
- propose refinement of work package 3 activities after the selection of the 'technology package';
- tailor the technology package to be used for the pan-EU pilot remote DCT.

Expected key deliverables

The expected key deliverables will be as follows:

- technology scan for remote DCT in an end-to-end journey assessing e.g. quality and data integrity, security, connectivity, communication interface, stakeholders' feedbacks such as patients, principal investigators, regulators, sponsors. The scan on 'remote DCT technologies' will include an assessment of a broad technology range (available or with a validated proof-of-concept) in order to enable seamless communication, data monitoring and collection from distant locations (described in the specific deliverable section);
- tailored 'technology package' for running the pan-EU pilot to be deployed in the pan-EU pilot remote DCT.

Industry contribution

Clinical operational experts; statistical experts (telemedicine activities and digital health); legal experts including data privacy experts; experts in clinical outcomes; patient engagement experts; experts in data flows and app developments for home monitoring of patients; expertise in using approved medical devices in clinical trials for data capture, continuous monitors and associated devices.

Expected applicant consortium contribution

Principal investigators; hospitals; clinicians; IT experts on digital health; patient engagement experts; experts in data flows and app developments for home monitoring of patients; platform developers and services related to technologies used for remote DCTs; regulatory experts; regulators in agencies; expertise in approved medical devices into clinical trials for data capture; continuous monitors and associated devices.

Work package 4 – Ethics, data privacy, legal, GCP, regulatory issues and recommendations

The goals of this work package will be as follows:

- continuous assessment of EU environment and the EU regulation (including digital policy, GDPR, CTR…) to be implemented for remote DCT approach;
- ethics organisation of remote DCTs in EU;
- defining the legal, GCP and data management for 'remote DCT' approach including data quality and regulatory acceptability of DCT approach;
- upgrading using regulation changes;
- stakeholders' working group to align the strategy of remote DCTs with ethics, data privacy.

Expected key deliverables

The expected key deliverables will be as follows:

- SWOT analysis of the barriers and enablers for the implementation of remote DCTs in EU for ethics, data privacy, regulation…;
- best practices on remote DCTs (first and final version) in EU and US;
- final recommendations on remote DCTs in the EU including intermediary model (hybrid studies).

Industry contribution

Legal and data privacy experts; regulatory experts on the use of digital tools in clinical trials; GCP experts.

Expected applicant consortium contribution

Regulatory experts (including from agencies); ethics experts; GCP experts; legal and data privacy experts.

Work package 5 – Communication, dissemination and stakeholders' engagement in changing the paradigm of remote DCTs

The goals of this work package will be as follows:

- interviews of stakeholders on the EU view and EU experience in remote DCTs (patients, regulatory agencies, ethics committees, principal investigators, study coordinators, hospitals, pharmaceutical companies…) to reassess the barriers and enablers;
- mapping of paradigm change on patients and HCPs between current approach and induced changes in remote DCTs;
- assess and tailor the related services of the 'technology package' for the communication activities;
- check-list on best practices for setting-up a remote DCT in EU (public deliverable);
- training kits for deploying pan-EU 'remote DCTs' for principal investigators, HCPs, patients, inspectors, pharmaceutical companies, clinical research organisations;
- company providers/developers of technologies to be deployed for remote DCTs.

Expected key deliverables

The expected key deliverables will be as follows:

- mapping of paradigm changes in the relationships between HCPs and patients;

- report on changing stakeholders' roles and responsibilities and proposals from stakeholders to overcome any challenges;

- set of tools for remote DCT including training materials for stakeholders (e.g. principal investigators, patients, regulatory representatives and inspectors…), and contract templates for 'remote DCT';

Industry contribution

Representatives for stakeholder engagement at regulatory, HCP and patient engagement and data privacy levels; communication experts; clinical outcomes experts.

Expected applicant consortium contribution

Experts in stakeholder engagement and communication for the relevant fields of this future action; patients organisations; IT and communication tools to support paradigm changes in remote DCTs; training to engage relevant stakeholders.

Work package 6 – Project management

This work package will establish effective governance and internal communication procedures to allow for the flow of information within the project. It will also fulfil the administrative tasks associated with management of this project. It will also take into account the particular conditions relative to the 'technology package' and inclusion of new technology partners.

Industry contribution

Project management expertise.

Expected applicant consortium contribution

Project management expertise.

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 14 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-IMI2-2018-14-two-stage**
Type of actions	**Research and Innovation Action (RIA)**
Publication Date	**15 March 2018**
Stage 1 Submission start date	**15 March 2018**
Stage 1 Submission deadline	**14 June 2018 (17:00:00 Brussels time)**
Stage 2 Submission deadline	**11 December 2018 (17:00:00 Brussels time)**
Indicative Budget	
From EFPIA companies and IMI2 JU Associated Partners	EUR 84 920 360
From the IMI2 JU	EUR 82 357 000

Call Topics

| IMI2-2018-14-01 **Targeted immune intervention for the management of non-response and relapse** | The indicative contribution from EFPIA companies is EUR 40 320 000

 The financial contribution from IMI2 JU for each subtopic is :

 Subtopic 1 (Profiling & Informatics): a maximum of EUR 16 128 000.

 Subtopic 2 (DC1 - SLE, RA, and MS): a maximum of EUR 12 096 000.

 Subtopic 3 (DC2 - UC and CD): a maximum of EUR 8 064 000.

 Subtopic 4 (DC3 – Asthma and COPD): a maximum of EUR 4 032 000. | Research and Innovation Action (RIA)

 Two-stage submission and evaluation process.

 At stage 1, applicant consortia to this topic will submit short proposals to address one of the four subtopics. Applicants can submit proposals to any of the subtopics. If applicant consortia wish to submit for more than one subtopic, separate short proposals should be submitted. Applicants are not obliged to apply for all.

 For each subtopic, only the applicant consortium whose proposal is ranked first at the first stage is invited for the second stage. At stage 2, the first ranked consortium from each subtopic shall merge into a single consortium with the industry consortium. |

IMI2-2018-14-02 **Non-invasive clinical molecular imaging of immune cells**	The indicative contribution from EFPIA companies is EUR 15 000 000 The financial contribution from IMI2 JU is a maximum of EUR 15 000 000	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.
IMI2-2018-14-03 **Development of a platform for federated and privacy-preserving machine learning in support of drug discovery**	The indicative contribution from EFPIA companies is EUR 8 000 000 The financial contribution from IMI2 JU is a maximum of EUR 8 000 000	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.
IMI2-2018-14-04 **Centre Of Excellence – decentralised clinical trials**	The indicative contribution from EFPIA companies is EUR 21 512 860. The indicative IMI2 JU Associated Partners contribution is EUR 87 500 The financial contribution from IMI2 JU is a maximum of EUR 19 037 000.	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.

LIST OF ACRONYMS

Acronym	Meaning
ABAC	Accrual Based Accounting System
AD	Alzheimer's disease
AD (HR)	Administrator
AER	Average error rate
AMR	Antimicrobial Resistance
AST	Assistant
ATAC-Seq	Assay for Transposase-Accessible Chromatin using sequencing
AUC	Area under the curve
AWP2018	Annual Work Plan 2018
BAFF	B-cell Activating Factor
BAL	Bronchoalveolar Lavage
BCR	B-cell Receptor
CA (Budget)	Commitment Appropriation
CA (HR)	Contractual Agent
CD	Cluster of differentiation
CD	Crohn's Disease
CDAI	Crohn's Disease Activity Index
CDISC	Clinical Data Interchange Standards Consortium
CEOi	Global CEO Initiative
CFAST	Coalition for Accelerating Standards and Therapies
CFS	Certificates on Financial Statements
ChIP	Chromatin Immunoprecipitation
CISCRP	Center for Information and Study on Clinical Research Participation
COPD	Chronic Obstructive Pulmonary Disease
C-Path	Critical Path Institute
CPD	Continuing professional development
CRO	Contract research organisation
CRO	Clinical Research organisation
CSC	Common Support Centre
CT	Computed tomography
CyTOF	Cytometry by Time of Flight
DCT	decentralised clinical trial
DC1	Disease cluster 1 - SLE, RA, and MS
DC2	Disease cluster 2 - UC and CD
DC3	Disease cluster 3 - Asthma and COPD
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)
DPO	Data protection officer
E&T	Education & Training
EBiSC	European induced pluripotent stem cell
EC	European Commission
ECA	European Court of Auditors
EDPS	European Data Protection Supervisor
EEG	Electroencephalograph
EFPIA	European Federation of Pharmaceutical Industries and Associations
EHR	Electronic Health Record
EMA	European Medicines Agency
ESFRI	European Strategy Forum on Research Infrastructures

Acronym	Meaning
EU	European Union
FDA	Food and Drug Administration
FEV1	Forced expiratory Volume
FG	Function Group
FMT	Fecal Microbiota Transplantation
FNIH	Foundation for the National Institutes of Health
FTE	Full-Time Equivalent
fNIH	Foundation for the National Institute of Health
FP	Full Proposal
FP7	Seventh Framework Programme
FWC	Framework Contract
GA	Grant Agreement
GAP	Global Alzheimer's Platform
GB	Governing Board
GCP	Good Clinical Practices
H2020	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
HA	Health Authorities
HCT	Human challenge trials
HCP	Health Care Professionals/Providers
Helmsley Charitable Trust	Leona M. and Harry B. Helmsley Charitable Trust
HR	Human resources
HTA	Health Technology Assessment
IAC	Internal Audit Capability
IAPO	International Alliance of Patients' Organisations
IAS	Internal Audit Service of the European Commission
IBD	Inflammatory Bowel Disease
ICC	Internal Control Coordinator
ICH	International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use
ICS	Internal Control Standards
ICS	Inhaled corticosteroid
ICT	Information Communications Technology
ILG	Industry Liaison Group
IMI 1 JU	Innovative Medicines Initiative 1Joint Undertaking
IMI 2 JU	Innovative Medicines Initiative 2Joint Undertaking
IMI JU	Innovative Medicines Initiative Joint Undertaking
IP	Intellectual property
iPS cells	Induced pluripotent stem cells
ISA	Information System for Absences
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
LABA	Long-acting beta2-agonists
LAMA	Long-acting muscarinic antagonists
MAPPs	Medicines adaptive pathways to patients
MEP	Member of the European Parliament
MRI	Magnetic resonance imaging
MS	Multiple sclerosis

Acronym	Meaning
MTA	Material transfer agreement
ND4BB	New Drugs for Bad Bugs
NIMH	National Institute of Mental Health
NK	Natural killer
OECD	Organisation for Economic Co-operation and Development
OLAF	European Anti-Fraud Office
PA	Payment Appropriation
PD	Pharmacodynamics
PET	Positron emission tomography
PHC	Personalised health care
PM	Person/month
PMDA	Pharmaceuticals and Medical Devices Agency
POC	Proof of concept
POM	Proof of mechanism
PPP	Public-private partnership
PRO	Patient reported outcomes
QST	Quantitative sensory testing
R&D	Research and development
RA	Rheumatoid arthritis
RAE	Risk assessment exercise
RCSA	Risk and control self-assessment
RepER	Representative error rate
ResER	Residual error rate
ROC	Receiver operating characteristic
SABA	Short-acting beta-agonists
SC	Scientific Committee
SEND	CDISC SEND Controlled Terminology
SGGs	Strategic Governing Groups
SLC	Solute carriers
SLE	Systemic Lupus Erythematosus
SMEs	Small and medium-sized enterprises
SNP	Single Nucleotide Polymorphism
SOFIA	Submission of Information Application
SOP	Standard operating procedure
SP	Short Proposal
SPECT	Single photon emission computed tomography
SRA	Strategic Research Agenda
SRG	States Representatives Group
SVM	Support vector machine
T1D	Type 1 diabetes
T2D	Type 2 diabetes
TA	Temporary Agent
TCR	T-cell Receptor
TNF	Tumor Necrosis Factor
TTG	Time to Grant
TTP	Time to Pay
UC	Ulcerative Colitis
US	United States
VOC	Volatile Organic Compounds
WHO	World Health Organisation
WP(s)	Work Package(s)