IMI2

14th Call for proposals

Annex I to the 1st amended IMI2 JU Annual Work Plan and Budget for 2018 approved by the IMI2 JU Governing Board on 09 March 2018 per Decision n° IMI2-GB-DEC-2018-08

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Contents

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[1] 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[2].

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[3], 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)[4] 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.

Applicant consortia shall ensure that where relevant their proposals are in compliance with the General Data Protection Regulation (EU) 2016/679[5] and Clinical Trial Regulation (EU) 536/2014[6] (and/or Directive 2001/20/EC[7]) and any relevant legislation[8].

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[1] Council Regulation (EU) No 557/2014 of 6 May 2014 establishing the Innovative Medicines Initiative 2 Joint Undertaking (IMI2 JU).

[2] http://www.who.int/medicines/areas/priority_medicines/en/

[3] 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.

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

[5] 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.

[6] 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.

[7] 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.

[8] 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

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[9], 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).

[9] 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:

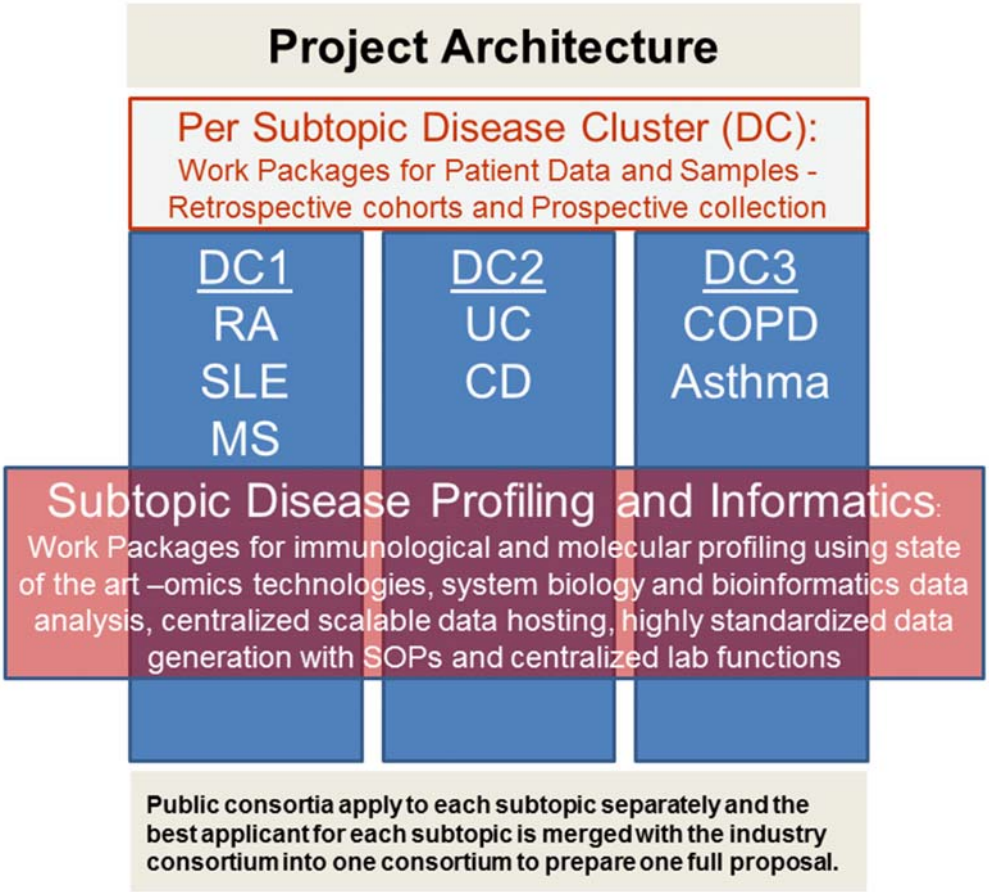
Subtopic 1: Disease profiling and informatics: state-of-the-art molecular and immune technologies in combination with cutting edge systems biology approaches to identify biomarkers predictive of treatment non-response, relapse and flare-up;

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.



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://www.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 ≥100, remission absolute CDAI < 150;
- Mayo Clinic Score (MCS): response defined as Δbaseline ≥ 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.

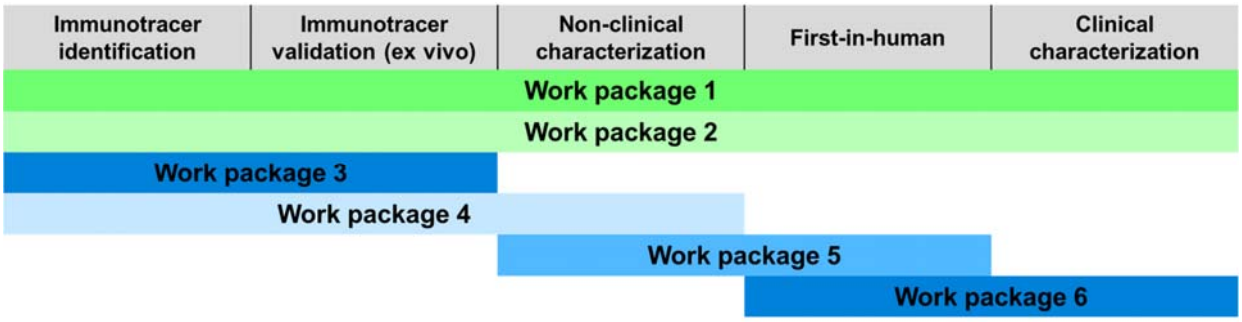
In the spirit of the partnership, and to reflect how IMI2 JU Call topics are built on identified scientific priorities agreed together with EFPIA beneficiaries/large industrial beneficiaries; these beneficiaries intend to significantly contribute to the programme and project leadership as well as project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



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.

1. 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.
2. 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.
3. 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%)[10]. 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.[11] 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[12] and IMI initiatives have already led to significant achievements in this area. For example, the first European Electronic Health Records data platform[13], 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.[14] 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.[15]

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.

[10] Center for Information & Study on Research Participation (CISCRP). Perceptions & Insights Study. 2017
[11] 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
[12] http://www.transceleratebiopharmainc.com/
[13] www.ehr4cr.eu
[14] 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
[15] 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),[16] Good Clinical Practices (GCP)[17], and EU clinical trials regulations[18]).

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.

[16] http://www.ich.org/home.html
[17] https://www.ich.org/fileadmin/Public_Web_Site/ICH_Products/Guidelines/Efficacy/E6/E6_R1_Guideline.pdf
[18] 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[19]). 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[20] and Clinical Trial Regulation (EU) 536/2014[21] (and/or Directive 2001/20/EC[22] 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.

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[19] 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

[20] 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

[21] 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.

[22] 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.

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;
  - 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[23];
- 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[24];
- CTTI[25];
- companies offering technology solutions that would support the implementation of the platform for running the pan-EU pilot remote DCT;

[23] 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)
[24] http://www.transceleratebiopharmainc.com/
[25] https://www.ctti-clinicaltrials.org/

- consortia of European clinical trial centres such as the European Clinical Trial Infrastructure Network (ECRIN)[26];
- relevant biotechnology consortia;
- relevant EFPIA groups (e.g. Clinical Development Expert Group…);
- national/local ethics committees or IRBs;
- consortia funded under ECSEL JU27 developing the technology required in the action.

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

[26] http://www.ecrin.org/
[27] http://www.ecsel-ju.eu/

- 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[28] 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:

- 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

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

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 CTR20-22 context;
- defining good practices and detailed SWOT on setting up 'remote DCTs' using individual partner experience in regard also to GDPR20 and CTR18 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 CTR20-22;
- 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 – remote 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 COUNTRIES AND APPLICABLE RULES FOR FUNDING

By way of derogation[29] from Article 10(1) of Regulation (EU) No 1290/2013, only the following participants shall be eligible for funding from the Innovative Medicines Initiative 2 Joint Undertaking:

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

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

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

(ii) secondary and higher education establishments;

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

(c) the Joint Research Centre;

(d) international European interest organisations.

Participating legal entities listed in (b) above established in a third country may receive funding from the IMI2 JU provided their participation is deemed essential for carrying out the action by the IMI2 JU or when such funding is provided for under a bilateral scientific and technological agreement or any other arrangement between the Union and the country in which the legal entity is established[30].

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 Call for proposals.

In addition, page limits will apply to proposals as follows:

At stage 1 of a two-stage Call, the limit for RIA/IA short proposals is 30 pages.

For stage 2 of a two-stage Call, the limit for RIA/IA full proposals is 70 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 Call for proposals.

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

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.[31]

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 Call for proposals.

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[29] 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

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

[31] 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"

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 Call for proposals.

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 Call for proposals:

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 innovation potential, and is beyond the state of the art; Mobilisation of the necessary expertise to achieve the objectives of the topic, ensure engagement of all relevant key stakeholders	The following aspects will be taken into account, to the extent to which the outputs of the project should contribute at the European and/or International level: The expected impacts of the proposed approach as mentioned in the Call for proposals Added value from the public private partnership approach on R&D, regulatory, clinical and healthcare practice as relevant; Strengthening the competitiveness and industrial leadership and/or addressing specific societal challenges; Improving European citizens' health and wellbeing and contribute to the IMI2 objectives[32].	The following aspects will be taken into account: Coherence and effectiveness of the outline of the project work plan, including appropriateness of the roles and allocation of tasks, resources, timelines and approximate budget; Complementarity of the participants within the consortium (where relevant) and strategy to create a successful partnership with the industry consortium as mentioned in the topic description in the Call for proposal; Appropriateness of the proposed management structures and procedures, including manageability of the consortium.
RIA and IA **Single stage, and 2nd stage**	The following aspects will be taken into account, to the extent that the proposed work corresponds to the topic description in the Call	The following aspects will be taken into account, to the extent to which the outputs of the project should contribute at	The following aspects will be taken into account: Coherence and effectiveness of the project work plan,

[32] 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
evaluation	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 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;[32] 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.	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.

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.

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.[33]

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[34] 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
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 Call for proposals.

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 Call for proposals.

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

[34] 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 Call for proposals.

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.[35]

In order to ensure excellence in data and knowledge management consortia will be requested to Disseminate scientific publications on the basis of open access[36] (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.

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[37] (e.g. IMI2 JU model Grant Agreement).

[35] Article 19 of Horizon 2020 Framework Programme and Articles 13 and 14 of the Horizon 2020 Rules for Participation.
[36] 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
[37] http://www.imi.europa.eu/apply-funding/call-documents/imi2-call-documents

LIST OF ACRONYMS

Acronym	Meaning
ATAC-Seq	Assay for Transposase-Accessible Chromatin using sequencing
AUC	Area under the curve
BAFF	B-cell Activating Factor
BAL	Bronchoalveolar Lavage
BCR	B-cell Receptor
CD	Cluster of differentiation
CD	Crohn's Disease
CDAI	Crohn's Disease Activity Index
ChIP	Chromatin Immunoprecipitation
CISCRP	Center for Information and Study on Clinical Research Participation
COPD	Chronic Obstructive Pulmonary Disease
CRO	Clinical Research organisation
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
EFPIA	European Federation of Pharmaceutical Industries and Associations
EMA	European Medicines Agency
EU	European Union
FDA	Food and Drug Administration
FEV1	Forced expiratory Volume
FMT	Fecal Microbiota Transplantation
FNIH	Foundation for the National Institutes of Health
GCP	Good Clinical Practices
HA	Health Authorities
HCP	Health Care Professionals/Providers
H2020	Horizon 2020
IBD	Inflammatory Bowel Disease
ICH	International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use
ICS	Inhaled corticosteroid
ICT	Information and Communication Technology
IMI2 JU	Innovative Medicines Initiative 2 Joint Undertaking

IP	Intellectual property
IT	Information Technology
LABA	Long-acting beta2-agonists
LAMA	Long-acting muscarinic antagonists
MRI	Magnetic resonance imaging
MS	Multiple Sclerosis
NK	Natural killer
PD	Pharmacodynamics
PET	Positron emission tomography
PHC	Personalised health care
POC	Proof of concept
POM	Proof of mechanism
R&D	Research and Development
RA	Rheumatoid Arthritis
ROC	Receiver operating characteristic
SABA	Short-acting beta-agonists
SLE	Systemic Lupus Erythematosus
SME	Small and Medium-sized Enterprise
SNP	Single Nucleotide Polymorphism
SOP	Standard Operating Procedure
SPECT	Single photon emission computed tomography
SVM	Support vector machine
TCR	T-cell Receptor
TNF	Tumor Necrosis Factor
UC	Ulcerative Colitis
VOC	Volatile Organic Compounds
WHO	World Health Organisation
WP	Work package