IMI2

18th Call for proposals

Annex II to the Decision of the IMI2 JU Governing Board No. IMI2-GB-DEC-2019-12 adopted on 21 June 2019

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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 2019 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.

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

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].

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

[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, OJ L 281, 23.11.1995, p. 31–50.

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

Topic 1: Central repository of digital pathology slides to support the development of artificial intelligence tools

Topic details

Topic code	IMI2-2019-18-01
Action type	Research and Innovation Action (RIA)
Submission and evaluation process	2 stages

Specific challenges to be addressed

Although pathology is the cornerstone of the workup of many diseases such as cancer, autoimmune diseases, and transplant rejection, it still relies heavily on the subjective interpretation of a histology sample by a qualified pathologist who captures observations and conclusions in a report. Once the observations are captured, the slides are archived and only the pathologist's report and diagnoses (considered as raw data in good laboratory practice (GLP) nonclinical studies) remain accessible. Therefore, significant information from the histology slides is no longer easily available. This hinders the discovery of new clinico-pathological entities that are relevant to patients' prognosis and treatment.

The recent developments of high-throughput slide scanners offer a possibility for making the entire information contained in the millions of glass slides produced every year, available for search. Ensuring storage and access to digital slides will overcome the current limitations to accessing and sharing pathology material together with the associated metadata. It will facilitate case consultation, help identify sub-types of diseases, assess the translatability of nonclinical safety observations and animal models, and thereby rationalise the design of clinical trials and the use of animal models.

The rise of deep learning and its unexpected ease at interpreting images offer unprecedented opportunities to develop tools for automated detection, classification and quantification of abnormalities in tissues. Hence, many initiatives are already looking at utilising histopathology slides in a digital format as a source of data for biomedical research. Current research focuses on a relatively reduced set of diseases and/or are fragmented and geographically limited, which may hinder their ability to deliver outside of much-targeted applications.

This is mostly because, although clinically relevant and efficient, disease-centric models cannot be easily expanded towards more general purposes.

However, the full transformative potential of deep learning applied to histopathology goes far beyond what is presently undertaken. In the future, it will provide the pathologist with smart suggestions regarding diagnoses and mechanistic or therapeutic hypotheses (predict patient's outcomes and responses to treatment), significantly improving overall patient safety and diagnosis. To achieve this ambitious goal, a much larger series of slides offering a broader coverage of tissues and lesions is required. Whereas such coverage may be difficult to achieve solely with clinical material, nonclinical toxicology studies provide an incredibly valuable and abundant source of histopathology slides, comprising all the normal tissues from multiple species, and a large diversity of lesions. As these lesions are similar to those seen in clinical practice, but in a more pure form, and at stages rarely encountered in humans, they will be a great help for the community developing artificial intelligence (AI). They will also likely offer an opportunity to expedite the development of assisted diagnosis tools applicable to nonclinical safety studies and clinical practice.

Need and opportunity for public-private collaborative research

The refinement of the pharmaco-therapeutic armamentarium requires the improvement of disease classification and of diagnostic and prognostic criteria. This is an ongoing effort in several areas of medicine. However, for many diseases, it is hampered by limited access to large histopathology series and the absence of reliable quantitative

methods. To overcome these obstacles, it is necessary to make large sets of histopathology slides accessible to the medico-scientific community in a digital form.

The current efforts in the field of machine learning and histopathology focus on the development of disease-specific models. Although their potential clinical utility is compelling, such models are limited to a particular tissue. The development of holistic models is necessary to support improvements in disease classification and translational research, which will in turn accelerate the discovery of new clinico-pathological entities and provide assisted diagnostics tools.

The magnitude of the challenges addressed by the Call topic is such that they cannot be addressed solely by the academic or industry sectors.

Firstly, it requires the collection of sufficiently large sets of histology data along with associated clinical information. The pharmaceutical industry will provide high-quality slides from nonclinical species obtained during toxicology testing. Public partners such as hospitals and pathology laboratories are an invaluable source of clinical slides and associated data, from clinical trials, observational studies and archives.

Secondly, the infrastructure to host such collections can only be the result of the combined efforts by public and private sectors. Moreover, the interactions between academic, pharmaceutical industry and small and medium-sized enterprise (SME) partners will constitute a significant factor of success for the development of innovative software tools and efficient end-user applications. Lastly, the involvement of representatives of health and regulatory authorities will allow frameworks for policies or roadmaps pertaining to the validation and qualification of digital slides and their use for peer review, primary read and adjudication of nonclinical studies and clinical cases.

Scope

The overall scope of the Call topic is to collect, host and sustain virtual slides along with associated data and to support the collaborative development of artificial intelligence in pathology.

The funded action will also address the regulatory, legal and ethical challenges associated with the collection, sharing and mining of the virtual slides.

Objective 1: Sustainable infrastructure

To deliver the infrastructure hosting several petabytes of digital slides and making the data accessible for research. It represents the hardware layer of the funded action and could take the form of a data centre, either centralised or decentralised. The key factors of success for this objective are the storage capacity and the possibility to exchange rapidly large amounts of data.

The achievement of this objective is also critical for sustainability and the long-term impact of the funded action. The ambition is that after the end of the funded action, the repository will be maintained and developed, following a model similar to public repositories for genomics (e.g. National Center for Biotechnology Information (NCBI) /Gene Expression Omnibus (GEO) — https://www.ncbi.nlm.nih.gov/geo/) and that it becomes the central place for hosting raw digital slides associated with scientific and medical publications. The planned infrastructure is expected to allow pathologists to concomitantly review difficult cases and to consolidate large case series including histopathology and clinical information in order to establish diagnostic criteria. The sustainability beyond the end of the funded action will take the form of a business model that leaves open access free of charge for non-profit purposes. This will represent a major advantage compared to the current approach of smaller databases.

Objective 2: Data

To compile digital histopathology slides from nonclinical safety studies, as well as from clinical series needed to populate the initial version of the repository, and contribute to developing tools and artificial intelligence models. The key factor of success is the diversity of lesions, tissues, and species while providing sufficient sample sizes. In addition, the slides will be made publicly available for the development of artificial intelligence in pathology in line with the sustainability model described in objective 1.

Objective 3: Tools

To deliver a mechanism of an honest broker (see 'Expected key deliverables' and 'Suggested architecture of the full proposal' sections) by developing a software ensuring the optimal and secure contribution of clinical and nonclinical material. Efforts will also be undertaken to propose a unified open digital slide format and tools to search, access, upload, register, download, view and homogeneously annotate information. In addition, AI models and tools, such as assistance to general diagnosis, screening for slides for lesions, and content-based image retrieval will be developed at a later stage of the funded action.

Objective 4: Regulatory framework

To advance the regulatory framework around the utilisation of digital pathology slides for nonclinical safety testing, evaluation of clinical trials and dissemination/discussion of difficult clinical cases. This will accelerate the adoption of roadmaps for the qualification of the usage of digital slides for peer-review or primary slide reading, as well for the development of artificial intelligence based tools for pre-screening and assisted diagnosis. This objective should be achieved by building on already existing and ongoing interactions and efforts between health and regulatory authorities, and professional societies.

Expected key deliverables

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

- mechanisms for adequate management of confidential information possibly associated with digital slides, through the establishment of a specific entity (further referred to as the honest broker);
- sustainable infrastructure to host a large series of digital slides (approximately three million during the lifetime of the project) ensuring confidentiality and privacy through the application of an honest broker concept. Meta-data and annotations will be provided in compliance with existing standards[10];
- nonclinical slide collection: approximately two million slides covering all tissues from several species and with the broadest spectrum of lesions should be collected. This material, obtained from toxicology studies, prospectively whenever possible, will represent a uniquely valuable asset for the fast development of models. Lesions elicited during toxicity testing are progressive and often in relatively pure form which is useful for developing models that recognise elementary lesions. Furthermore, such models developed initially on animal tissues can with little additional effort be expanded to clinical tissues and more complex lesions. It is required that the slides meet high standards of quality (e.g. orientation of samples, section thickness, staining) in order to optimally contribute to the development of AI models;
- clinical slide collection compliant with the quality and ethical standards: approximately one million digital slides should be provided from the archives and/or prospectively collected in the routine clinical practice over the project lifetime. They should be in a form of documented clinical series covering all the diseases areas such as (but not limited to):
    - oncology (e.g. breast, prostate and colon carcinoma, non-small cell and small cell carcinoma of the lung, hepatocellular carcinoma, or renal cell carcinoma, etc.);
    - dermatology (e.g. lupus, atopic dermatitis, melanocytic lesions, drug-induced skin reactions);
    - hepatology (e.g. autoimmune hepatitis, alcoholic and non-alcoholic steatohepatitis, drug-induced hepatitis, allograft rejection, tumours);
    - nephrology (e.g. glomerulonephritides, tubulointerstitial nephritides, drug-induced kidney injury, allograft rejection);

[10] For example: International Harmonization of Nomenclature and Diagnostic Criteria (INHAND — https://www.toxpath.org/inhand.asp), Standardization for Exchange of Nonclinical Data (SEND — https://www.toxpath.org/send.asp) or International Classification of Diseases (ICD — https://www.who.int/classifications/icd/en/)

- pneumology (e.g. idiopathic pulmonary fibrosis/usual interstitial pneumonia, nonspecific interstitial pneumonia).

- the established open-source data format for digital slides;
- developed open-source, cross-platform software tools to:
  - upload, search and access slides and associated metadata;
  - visualise and annotate the slides;
  - download slide for data mining and model development.
- AI models for:
  - identification of tissues and lesions;
  - generation of morphological and molecular signatures from slides.
- engagement with regulatory authorities for adapting guidelines to the new field of digital pathology;
- a sustainability plan for the maintenance and future development of the repository towards a central place gathering virtual slides from clinical cases series and raw data associated with publications. The plan should explore and propose a business model making the use of digital slides for commercial developments subjected to fees, while open access for research purposes should remain free of charge. Besides funding the storage of a massive amount of slides, the plan should also include the activities related to the control of the high quality of slides and validation of new slides while enriching future collection.

Expected impact

Applicants should describe how the outputs of the project would contribute to the following impacts and include baseline, targets and metrics to measure impact:

- catalyse research in digital pathology by providing a unique combination of animal and human histopathology. By offering the first complete coverage of tissues and elementary lesions, this repository will offer an unprecedented opportunity to build holistic models and allow generic mining of histopathology, irrespective of a particular tissue or indication;
- enable the development of artificial intelligence tools for rare diseases and uncommon conditions, which currently are left out of the models because of the paucity of cases;
- help identify sub-types in common diseases, possibly unveiling new clinico-pathological entities amenable to specific therapeutic interventions. It could also contribute to assessing the translatability of animal models for disease modelling, safety and efficacy studies, and thereby rationalise the design of clinical trials and the use of animal models. Ultimately, it should accelerate and improve patient treatment and management, thereby enhancing patient health along with the more efficient use of healthcare resources;
- clear the way for the use of digital slides in nonclinical safety and clinical consultation, and facilitate the approval of AI-based tools for slide screening and assisted diagnosis;
- in the long term, the repository delivered by the consortium will be maintained through sustainability mechanisms defined by the consortium and will provide the community with an infrastructure to host additional digital slides (e.g. associated with the publication of case reports, cases series for disease stratification and clinical trials).

Applicants should indicate how their proposal will impact 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.

Therefore, the applicants should explore possibilities of synergies with a similar past and ongoing IMI1 and IMI2 as well as upcoming IMI2 projects.

Industry consortium

The industry consortium is composed of the following EFPIA companies:

- Novartis (Lead)
- Janssen (Co-lead)
- Bayer
- Boehringer Ingelheim
- Novo Nordisk
- Pfizer
- Roche
- Sanofi
- Servier
- UCB

The industry consortium will contribute the following expertise and assets:

- the major part of the contribution will consist approximately in two million digital slides, mostly prospectively collected from high-quality nonclinical safety studies. These activities will be crucial to gather sufficient critical mass of high-quality slides needed for achieving the planned objectives;
- digital slides from clinical trials will be brought in. However, the vast majority of the clinical collection will be provided by the applicant consortium (see work package 3 ‘expected applicant consortium contribution’);
- experience and guidance for the harmonisation of metadata associated with digital slides;
- experience and guidance for the interaction with health authorities with respect to the qualification of digital and computational pathology in drug development.

Indicative duration of the action

The indicative duration of the action is 72 months.

Indicative budget

The indicative in-kind and financial contribution from EFPIA partners is EUR 37 771 260.

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 32 320 000.

Applicant consortium

The applicant consortium will be selected on the basis of the submitted short proposals and it 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 and capabilities:

- proven expertise in the management of digital slides in various formats including mastering of tools/mechanisms to collect/extract digital slides from various places (e.g. sponsors, contract research organisations (CROs)), transferring them securely to a central repository, and ensuring derived data can be returned to the contributor on demand;
- expertise in developing large databases for digital slides and related metadata, and tools to interact with them. Metadata correspond to various modalities associated with digital slides accessible for example via clinical registries, electronic health records, e.g. tabulated summaries of elementary lesions for non-clinical toxicology studies, summaries of information on the diagnosis, clinical presentation, genetic abnormalities and/or biomarker values for clinical samples;
- expertise in developing end-user applications for the visualisation, annotation, and analysis of digital slides;
- expertise in managing large clinical databases and large amounts of data;
- proven mastering of methodologies in creating tools for editing labels, anonymising/coding digital slides, encrypting individual files, and other methodologies required to set up the mechanism of the honest broker;
- the expertise of developing and training large-scale deep learning models for histopathology, such as convolutional neural networks, and evaluating the performance thereof;
- expertise in generating, annotating and sharing digital slides;
- solid scientific, medical, and clinical (including pathologist) expertise and knowledge in the research areas targeted by the topic text;
- legal, ethical and regulatory expertise related to patient privacy, informed consent, data anonymisation, and electronic submission of trial/safety data;
- professional project data management and communication capabilities with previous experience in large European public-private partnership settings.

In their proposal, applicants should demonstrate access to the following resources:

- proven access to large and well clinically documented collections of digital slides from clinical and diagnostic cases (e.g. from well-established pathology department(s)) relevant to disease areas enumerated under 'Key deliverables', organised in series with appropriate informed consent and preferred molecular biomarker annotation (e.g. next generation sequencing (NGS) oncogene panels or whole exome sequencing);
- adequate infrastructure and computing power to train deep-learning models, host and make accessible large amounts of data (approximately 3 peta-bytes for three million digital slides);
- infrastructure to scan a large number of slides (approximately one million).

Suitable SMEs can, for instance, be considered for the following activities: infrastructure management, honest broker mechanism, end-user interfaces and slide scanning.

The 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 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.

The proposal should be articulated around the following phases, which may overlap as needed to allow the optimal utilisation of resources and production of deliverables:

Phase 1: Establish an honest broker and infrastructure.

Phase 2: Data collection, tools for access and visualisation.

Phase 3: Artificial intelligence models and tools for morphological data mining and assisted diagnosis.

The architecture outlined below for the full proposal is a suggestion. The architecture of the full proposal should be designed to fulfil the objectives and key deliverables within the scope of this topic.

Work package 1 – Project management, coordination, and sustainability

This work package will address the strategy and implementation of project management. This will encourage regular meetings and interaction between sub-groups and teams to coordinate and follow up on the work effort. The applicant consortium with input from industry partners will develop the sustainability plan. Its objective should be to provide an infrastructure to host additional digital slides contributed by authors of case reports, clinical series or clinical trials, with the same level of annotation, anonymisation and accessibility for model development, as during the research phase. The plan should comprise financial, legal, ethical and structural aspects as well as scalability of the storage/access capacity.

Industry contribution:

Assurance of the coherence of consortium activity, and involvement in project management including planning, budgeting, follow-up and tracking of the work packages' progress, and consolidation of the reports. Project risk management and comprehensive communication and dissemination of the project's progress and its milestones will also be provided.

Expected applicant consortium contribution:

Providing detailed follow-up and tracking, via regular work package reports, early reports of any unexpected organisational or structural issues or delays with respect to the project deployment and intermediate objectives.

Work package 2 – Infrastructure and database hosting

This work package consists of the development of the infrastructure that will host approximately three million digital slides shared during the course of this project, and ensure that they are easily accessible to other project participants through available internet servers. The applicant consortium will ensure that the proposed infrastructure is amenable to expansion and is coordinated with the sustainability plans. The choice of the infrastructure will be coordinated with the industry partners and other consortium partners to ensure compatibility with the tools.

Industry contribution:

Advice for the harmonisation of metadata associated with the digital slides provided.

Expected applicant consortium contribution:

Building an infrastructure (data centre) to host three million digital slides and implement a database to register the corresponding files and associated metadata.

Work package 3 – Data collection & management

To support the other work packages, a data management system/database, able to register the digital slides contributed to by the industry partners and the applicant consortium, is needed. It will ensure the encoding of the data and compliance with patient privacy legislation and the confidentiality agreements established with the industry partners through an honest broker mechanism. The data management should also ensure that contributed digital slides, stripped from all proprietary information, are coded while retaining links with associated metadata (e.g. species, staining, tissue), and possibly complementary data such as clinical pathology, biomarkers, omics profiles, when shared by the contributor. Metadata will use controlled terms from the International Harmonization of Nomenclature and Diagnostic Criteria (INHAND) or International Classification of Diseases (ICD) classifications. This work package also comprises the handling, shipping and scanning of cases contributed as glass slides.

Slide scanners currently deliver the file in a proprietary format, which has limited compatibility outside the product family. In addition to data management, this work package will deliver a common, unique file format for virtual slides that are compatible with open-source visualisation software, where images associated with the virtual slide such as the label or the overview can be edited in order to remove confidential information.

Industry contribution:

Approximately two million glass or digital slides from nonclinical toxicology studies, animal models of diseases, or clinical trials, along with metadata, compliant with INHAND/ICD nomenclature, whenever possible, and structured under the standardisation for exchange of nonclinical data (SEND) format.

Expected applicant consortium contribution:

- honest broker mechanism: to allow all participants to share data comfortably in a secure environment, the applicant consortium should include an organisation with a proven track record of acting as an independent honest data broker from a legal and historical perspective. The mechanism and expected contribution should consist of:
    - setting up the database, encoding mechanisms and registering digital slides accordingly;
    - ensuring that digital slides contributed by members of the consortium are stripped from any information that could link them back to a specific study or patient when made available for the project (including elements of the digital slides themselves such as pictures of the original label);
    - ensuring information security and managing access rights between members of the consortium and the public, at the level of the individual digital slides through encryption;
    - keeping the possibility for a contributor to link scientific results (e.g. model predictions) to the contributed slide, if requested at the time of the submission of the digital slide;
    - if glass slides are submitted, organising their physical transfer to scanning facility, registration in the repository and return to the contributor.
- digital or glass slides from clinical series and archives: the clinical partners of the applicant consortium will provide approximately one million digital or glass slides from clinical case series obtained from the archives and/or prospectively collected from routine clinical practice in pathology laboratories, with accompanying diagnostic and clinical data using a controlled vocabulary (e.g. ICD);
- scanning of glass slides.

Work package 4 – Tools for accessing, annotating and mining digital slides

This work package intends to develop the following tools:

- tools for accessing slides: software tools to interact with the database will be developed to enable access to the virtual slides and the related metadata through search functionalities;
- tools for visualisation and annotation: the annotation of virtual slides refers to the delineation of regions of interest representing particular tissues, features, structures or lesions. Currently, available tools offer some of the required functionalities, which are usually insufficient to perform complex annotation tasks required for the training of deep-learning based models. Cross-platform, open-source tools will be developed to visualise and navigate fluently virtual slides of various file formats hosted in the database, including possible original formats developed in this project. The software tool will offer annotation functionalities for the optimal annotation of slides by pathologists and histologists.

Industry contribution:

- defining the functionalities required;
- guiding the development of tools to ensure implementation according to required functionalities;
- testing tools and providing feedback.

Expected applicant consortium contribution:

- providing tools to interact with said databases and managing metadata along with the digital slides;
- setting up end-user applications for the visualisation, annotation, and analysis of digital slides;
- providing large-scale deep learning models for histopathology, such as convolutional neural networks.

Work package 5 – Regulatory framework for digital slides and AI-based methods

The consortium is expected to have a strategy for the translation of the relevant project outputs such as policies or frameworks for the qualification of the use of digital pathology slides for peer-review and primary reading in nonclinical safety assessment and evaluation of clinical efficacy. It will explore the optimal utilisation of the digital slides from patients to develop AI in pathology in compliance with the General Data Protection Regulation (GDPR). It will also envisage the roadmap for the qualification of AI-based tools for the pre-screening of normal tissues in nonclinical safety and possibly selected domains of clinical practice. A plan for interactions with regulatory agencies/health technology assessment bodies with relevant milestones and allocated resources should be proposed to ensure that at least qualification advice or opinions are provided on the proposed methods during the course of the funded action.

Use of digital slides: the project will provide a platform to exchange and publish virtual slides from nonclinical and clinical studies. Although professional associations and some regulatory bodies have already developed guidance or opinions regarding the use of digital pathology techniques for regulated laboratory work, their applicability is still limited. This project will ideally accelerate the dialogue and create an interface between health authorities, regulatory bodies, clinicians and the pharmaceutical industry regarding the use of digital slides for the primary assessment of nonclinical safety studies, clinical trials and diagnosis.

AI-based methods: the ambition of the project generated from this topic is to catalyse the development of artificial intelligence in pathology by facilitating access to digital slides, a critical resource for training deep-learning based models. These models could serve as prediction engines for assisted diagnostics tools. This project should provide a platform for interaction between the scientific experts and health authorities aiming towards defining a framework for the qualification of these complex tools for clinical and regulatory use, e.g. the project's central repository could be used as a clinical reference or external quality assessment tool for pathologists.

Industry contribution:

Guidance for the interaction with health authorities with respect to the qualification of digital and computational pathology in drug development.

Expected applicant consortium contribution:

- engaging with health authorities representatives to get input to be discussed in the different governance structures of the funded action;
- organising and leading discussions for the adoption of frameworks or roadmaps for the qualification of the usage of digital slides and AI tools as described in the topic text, the use of clinical slides from archives and for the sharing of rare cases or published cases series. Therefore, the overall contribution should consist of:
    - contribute to the evolution of the use of digital slides as a surrogate of glass slides in nonclinical safety assessment (peer-review, primary read);
    - establishing a framework for or a roadmap towards the validation/qualification of artificial intelligence tools for nonclinical safety applications such as screening, lesion detection and grading, and for routine clinical use such as support for lesion detection, qualification/quantification of events, clinical decision-making support tools;
    - contribute to the evolution of the regulatory framework around the use of clinical slides from archives and AI tools in clinical trials;
    - defining the regulatory context for the sharing of rare cases or published cases series.

Topic 2: Health Outcomes Observatories – empower patients with tools to measure their outcomes in a standardised manner creating transparency of health outcomes

Topic details

Topic code	IMI2-2019-18-02
Action type	Research and Innovation Action (RIA)
Submission and evaluation process	2 stages

Specific challenges to be addressed

Patient outcomes and their experience of healthcare, and thus their overall care, could be improved through systematic capture of the patient voice and perspective.

There is general agreement on the need for increased patient centricity in healthcare provision. Current conceptualisations and measures of disease and clinically relevant disease outcomes have generally been developed from the perspective of the clinician and often fail to completely capture the totality of the disability, the symptoms of the disease and the impact on a patient's health-related quality of life (HRQOL) and a patient's experience of their healthcare from the patient's perspective. Important patient-to-patient variations in disease presentation and symptomology may also be lost in the effort to develop a generalisable framework for the disease.

It is important to complement existing clinical outcome measurements with patient-generated measures of disease and HRQOL to ensure that the patient perspective of disease and the impact of healthcare interventions are more completely captured and that disease heterogeneity is better understood. Patient-reported outcomes (PROs) are significant indicators for quality of life and quality of treatment. Their medical and psychological impact has been described for a broad range of diseases. A fine balance must be struck between maintaining authenticity and faithfully capturing the voice of the patient and making the data collected interpretable and generalisable.

In order to achieve this, it is essential to provide patients with tools that have the ability to better capture the entirety of the impact of a disease and treatments (e.g. signs, symptoms, tolerability), allowing them to document their disease more completely and in a structured manner. To be effective, these tools should be built on the basis of accepted standards, developed in partnership with all relevant stakeholders and accepted and integrated into the existing healthcare ecosystem.

A reward system that truly focuses on value requires measurement and transparency of patient outcomes.

Healthcare systems that have the goal of rewarding innovators and service providers on the basis of the value they create for patients need to collect transparent and reliable data on outcomes. Disease registries have already been established in a wide range of diseases. However, these registries tend to measure a non-standardised set of outcomes, are rarely interoperable, focus on clinical measurements, and have varying terms and conditions for access to the data captured. As a result, they often fall short of providing sufficient transparency of patient outcomes in specific diseases to inform scientific and policy decisions.

At the level of the individual patient, the data generated, once structured and subjected to a degree of standardisation, will enable patients to have more productive interactions with their healthcare provider. At the level of the healthcare system, this data will allow a systematic measurement of health outcomes and the possibility to set up a reward system based on value – which can be defined as the level of health outcomes achieved for a given cost.

There is a lack of models for capturing and managing patient-reported health data in an ethical and sustainable way.

Structured health data is invaluable for all stakeholders, from the individual patient, healthcare professionals (HCPs), the life science industry, and policy makers to the patient advocacy groups. There have been a few successful examples of approaches to integrate patient-reported health data into clinical care. In an era of greater focus on the patient, it is thus critical for a society that patient-reported health and experience data is captured and managed in an ethical manner ensuring broad and appropriate access while safeguarding patients' privacy and building high levels of trust.

Need and opportunity for public-private collaborative research

Despite rapid advances in medical science and a revolution in health technology, the lack of standardisation and integration of data remains an obstacle to fully realising the promised benefits of the digital revolution[11]. Measurement methodologies and outcome standards need to be endorsed by those both generating the data and those using the data, and be part of the broader healthcare ecosystem in order to be trusted and accepted. The complexity of the challenges is such that it requires action that is collective, innovative and nurtured in an environment where sensitive information can be shared securely.

- patient associations need to engage actively to develop tools and approaches, and to build trust and patient engagement.;
- regulatory authorities need to be part of the dialogue regarding novel endpoints, data requirements, and acceptability of evidence from patient-generated data;
- privacy and legal experts need to set up the appropriate governance models, consent forms and access terms in order to allow data sharing, ensure trust and, therefore, support sustainability;
- life sciences companies are critical, not only for bringing in expertise, commitment to long-term research, innovation and evidence generation in the disease areas, but also for providing funding and ensuring that the model can be made sustainable over the long term;
- small and medium-sized enterprises (SMEs) and other innovators such as digital companies need to be involved to develop the appropriate tools and technologies;
- public sector experts including medical experts, ethicists, social scientists, biostatisticians and researchers are required to identify or develop the appropriate measurements and the right methodologies for capturing and analysing the data;
- data custodians and data management experts are also essential.

Scope

The goals of this topic are as follows:

1. identify appropriate standards for capturing the patient perspective when measuring health outcomes and patients' experience of healthcare, and obtain support for these standards among relevant stakeholders. Where appropriate the partners will give preference to standards already being developed (e.g. International Consortium for Health Outcomes Measurement - ICHOM) and will follow the Observational Medical Outcomes Partnership Common Data Model (OMOP CDM) developed through Observational Health Data Sciences and Informatics (OHDSI);
2. implement appropriate technology solutions (including adopting existing technology where appropriate) that would allow individual patients to record and measure their outcomes according to these standards and use the information for a more structured dialogue with their HCPs. The technical solution developed will

[11] As acknowledged by the OECD in their paper: Fujisawa, R. and N. Klazinga (2017), "Measuring patient experiences (PREMS): Progress made by the OECD and its member countries between 2006 and 2016", OECD Health Working Papers, No. 102, OECD Publishing, Paris, https://doi.org/10.1787/893a07d2-en

make extensive use of smartphones and/or other commercially available wearable devices to collect both patient outcome measures and objective measures of patient function;

3. establish the appropriate platform to collect, process and manage data in the best interest of patients, patient organisations, health authorities, healthcare professionals, the research community and health care payers, and in compliance with General Data Protection Regulation (GDPR) and other relevant rules and regulations;
4. create a sustainable, socially acceptable and ethical model for the continuous collection of data and an appropriate model for providing access to the identifiable or anonymised or aggregated data to researchers with a legitimate interest in analysing them.

These goals can be achieved through the creation of a consortium whose mission will be to establish health outcomes observatories in three selected disease areas, collecting health data in (at least) three different European countries[12] for each disease area. It would be desirable for the three countries selected to reflect variability across Europe in order to provide experience and guidance for scaling the initiative more effectively to other countries in the future.

The observatories should be designed according to the following principles:

- full integration within the respective countries' healthcare systems;
- consistency in design across observatories to allow for comparability of patient outcomes across countries;
- a sustainable model for the observatories;
- robust patient consent and engagement;
- standardisation and interoperability across countries.

The disease areas selected are:

- diabetes type 1 and type 2;
- inflammatory bowel disease (IBD);
- cancer (side effects of chemotherapy and immuno-oncology).

Criteria considered for this selection were: (a) their prevalence in the European population; (b) their chronic and progressive nature; (c) their significant impact on patients' quality of life; (d) their compatibility with patients' digital literacy; (e) the patients have sufficient autonomy and motivation to become engaged in self-management of their disease; and (f) the investment in novel medicines and disease management tools for these diseases by EFPIA members and IMI Associated Partners. The disease areas will focus on adult patients.

Expected key deliverables

The overall aim is the creation and operation of observatories in (at least) the three disease areas identified collecting health data in (at least) three different European countries. The deliverables from the project funded under this topic would all be made public and a key objective is to set up the observatories on a sustainable basis.

To achieve this, the applicants will have to focus on the following deliverables:

- an appropriate, societally accepted, governance and sustainability model for the observatories in three different European countries that allows inclusion in the respective national health ecosystem, and develops revenue streams to fund the continued operation of the observatories beyond the life of the initial project term;

[12] European Union and H2020 Associated countries

- all legal and ethical analysis required to ensure appropriate consents for data collection, data management and access terms and conditions;
- the legal set up and operation of the observatories, sustainable beyond the life of the initial project term;
- the design and set-up of the appropriate infrastructure leveraging where possible existing technological solutions that would allow the collection of patient-generated data using an accepted common data model (e.g. OMOP CDM);
- the design of a methodology for identifying the appropriate measurements of outcomes for respective diseases taking into consideration the need to also ensure broad stakeholder acceptability and comparability of these measurements;
- the identification of the appropriate measurements of outcomes for the focus diseases of this project and the creation of an adequate digital tool leveraging as much as possible existing solutions;
- the launch of the respective digital tools;
- the publication of annual reports after the third year comparing health outcomes in the three European countries and identifying lessons learned and opportunities for improvement.

For the three specific disease areas, the work will focus on the following deliverables:

- identification and validation of key outcome measures to inform health economic evaluations in the disease area;
- analysis of patient outcome data in combination with electronic health records by means of advanced methodologies for patient stratification to determine ideal levels of care;
- a digital decision-making system based on the stratification above to allow personalised treatment.

Expected impact

Applicants should describe how the outputs of the project will contribute to the following impacts and include baseline, targets and metrics to measure impact:

- enable individual patients to:
    - receive close to real-time information on their disease status;
    - hold more informed discussions with healthcare professionals about their health status and options;
    - better understand how their status compares with other patients with a similar condition;
    - share their data and help the broader patient community.
- allow healthcare professionals to:
    - track the evolution of their patients;
    - enable a different outcome-based conversation;
    - better inform and enhance clinical decisions based on the patient perspective.
- allow patient organisations to:
    - assess the status and dynamics of their patient population;
    - increase engagement with other healthcare stakeholders in evidence-based advocacy;
    - further contribute to improving the healthcare system.
- allow health authorities and healthcare providers to:
    - improve the quality of care through better and more transparent evidence of patient measures and outcomes;
    - drive research agendas and investments in the right areas;

- ensure the sustainability of healthcare systems in finding ways to improve the allocation of resources.

- allow pharmaceutical companies and other innovative companies to use data to:
  - enable ethical utilisation of the observatory data as legally appropriate;
  - generate insights that can be used to support the design and direction of the development of new treatments;
  - generate robust evidence that can be used in submissions to regulators, health technology assessment (HTA) agencies and other decision makers.

It is also expected that the pool of harmonised data that will be generated can be shared with other institutions and consortia (see section 'Potential synergies with existing Consortia'). Standardised data across geographies can eventually enable comparison of outcomes among different healthcare systems.

Finally, applicants should indicate how their proposal will impact 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.

Collaboration agreements

There is the potential for important synergies between the consortium selected under this topic and the one selected under IMI2 JU Call 18 topic 3 (*Improving patient access, understanding and adherence to healthcare information: an integrated digital health information project*). In particular, on the one hand, for instance it could be possible for the consortium selected under topic 2 to leverage the observatory platform in order to to obtain access to and analyse relevant electronic health record (EHR) data, in compliance with applicable regulation, gathered under topic 3. On the other hand, the consortium selected under topic 3 could become an additional important use-case for the observatories and improve their usefulness. Additionally, the perspectives brought by the consortium selected under topic 3 can contribute to development of the governance and operational model of the observatories, under topic 2. It could also help future-proof them as a neutral guardian of patients' health data which could then be made available in the future with the appropriate safeguards for applications, such as those envisaged under topic 3.

To explore these potential synergies between actions funded under these two topics, the selected consortia are expected to cooperate in common boards/structures and provide access to their results for specific activities when relevant. Therefore the grants awarded under IMI2 JU Call 18 topics 2 and 3 will be complementary grants. The respective options under Article 2, Article 31.6 and Article 41.4 of the IMI2 JU Model Grant Agreement[13] will apply. Accordingly, the relevant consortia will conclude collaboration agreement(s) to ensure the exchange of relevant information, exploration of synergies, collaboration where appropriate.

Other potential synergies

The project funded under this topic will build on applicable methodologies and principles established in particular (but not limited to):

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

- Projects from the IMI2 Big Data for Better Outcomes (BD4BO) programme such as:
  - EHDEN – for infrastructure and principles of data standardisation;
  - BD4BO disease-specific projects – for their principles of establishing the usefulness of PROs and real world evidence (RWE) in decision making and establishing the value of interventions;
  - DO-IT – for its informed consent principles and recommendations amongst others Patient
- engagement projects such as EUPATI and PARADIGM;
- OMOP CDM (OHDSI) can provide a common model to encode data as well as important analytical tools.
- Projects suggesting novel treatment options and establishing patient survey mechanisms (e.g. BIOCYCLE).

Industry consortium

The industry consortium is composed of the following EFPIA companies:

- Takeda (lead)
- AbbVie
- Eli Lilly
- Hoffmann-La Roche Ltd
- Medtronic
- Pfizer
- Sanofi
- Novartis

In addition, the industry consortium includes the following IMI2 JU Associated Partners:

- Juvenile Diabetes Research Foundation (JDRF)
- Trial Nation

The industry consortium will contribute to the 'horizontal phase' of the project by providing the following expertise:

- medical knowledge for the disease areas;
- regulatory expertise;
- health outcomes and RWE expertise;
- legal expertise;
- financial and business planning expertise;
- digital technologies expertise;
- expertise in public-private partnerships related to clinical research in the health care ecosystem.

This expertise will be provided for the following tasks to be executed in collaboration with the public consortium:

- identification/ design of the underlying requirements (medical, legal, regulatory, etc.);
- business plan including governance model, structure, and sustainability;
- interactions with regulators and health care authorities for the acceptability of the PROs and of the observatories;
- selection of the digital technologies to measure PROs;

- development of methods to analyse the PROs.

Moreover, the industry consortium will contribute to the disease-specific 'vertical phase' by providing medical and regulatory experts for the disease areas, as well as expertise in digital technologies, health outcomes and RWE.

Indicative duration of the action

The indicative duration of this action is 60 months.

Future project expansion

Potential applicants must be aware that the Innovative Medicines Initiative 2 (IMI2) Joint Undertaking 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 and progress the results and achievements by extending action duration and funding. The consortium will be entitled to open to other beneficiaries as it sees fit.

In the context of this topic, a restricted Call may be launched as part of a future IMI2 JU Annual Work Plan to expand the work to include additional data sources, therapeutic areas and/or health economic analysis, leveraging the success achieved. This would help to maximise the long-term impact of the project and to engender continued future successes in making outcomes and value concepts and their application in healthcare and clinics being more fruitful and efficient.

Indicative Budget

The indicative in-kind and financial contribution from EFPIA partners and IMI2 JU Associated Partners is EUR 11 435 000.

This contribution comprises an indicative EFPIA in-kind contribution of EUR 10 385 000, of which EUR 900 000 financial contributions, and an indicative IMI2 Associated Partners in-kind contribution of EUR 1 050 000, of which 882 000 financial contributions.

The allocation of the financial contribution from EFPIA partners and Associated Partners to the beneficiaries receiving JU funding will be decided by the full consortium at stage 2 when preparing the full proposal.

Due to the global nature of the participating industry partners and IMI2 JU Associated Partner, 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 10 478 000.

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 to 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 the applicant consortium to mobilise, as appropriate, the following expertise:

- solid experience in measuring health outcomes, creating appropriate methodologies that allow the capture of patient insights and integrating these methodologies appropriately to gain broad acceptance;
- access to existing real-world data and technology to query the data, together with experience in creating and operating patient registries that capture patient's input and preferences;

- demonstrated ability to build strong relationships with the health authorities and patient organisations of at least three different European countries where there is desire and willingness to co-create these observatories together with the industry;
- strong legal skills including GDPR / data governance aspects but also in broader healthcare law;
- digital architecture and technical skills, including data linkage skills, to set up and/or adapt and operate the appropriate infrastructure in full compliance with GDPR and cybersecurity requirements;
- technical capabilities to create the right digital solutions that will allow individual patients to monitor their outcomes in accordance with the agreed standards;
- expertise in data mining, machine learning, computational biology and modelling expertise and resources;
- biostatisticians and epidemiologists to combine and analyse the data and publish regularly on the outcomes;
- medical expertise across the disease areas;
- social scientists to ensure a robust and socially acceptable model for the collection of data;
- expertise in planning, developing and drafting communications to a range of audiences (including, but not limited to, medical, patient, academic and policy maker audiences);
- strong project management expertise.

Very importantly, the applicant consortium should include among their participants, either as members of the consortium or demonstrated willingness to contribute as experts:

- patient advocacy groups in the respective disease areas and the respective countries to ensure that the patient voice is appropriately heard, captured and interpreted;
- national bodies, such as regulatory agencies and/or HTA agencies and/or health authorities in the respective countries/regions to ensure that the observatories will become part of the national/regional healthcare ecosystems.

Data management

In their short proposal, applicants should give due visibility to ‘data management’. At stage 2, applicants should include a draft data management plan (DMP) in the full proposal, outlining how research data will be handled and made available during the project and after it is completed.

Dissemination, exploitation and communication activities

In their short proposal, applicants should give due visibility to the dissemination, exploitation and communication of the project's results. At stage 2, in their full proposal, applicants should further develop these activities.

Partnership with the industry consortium

In their short proposal, applicants should outline a strategy to create a successful partnership with the industry consortium.

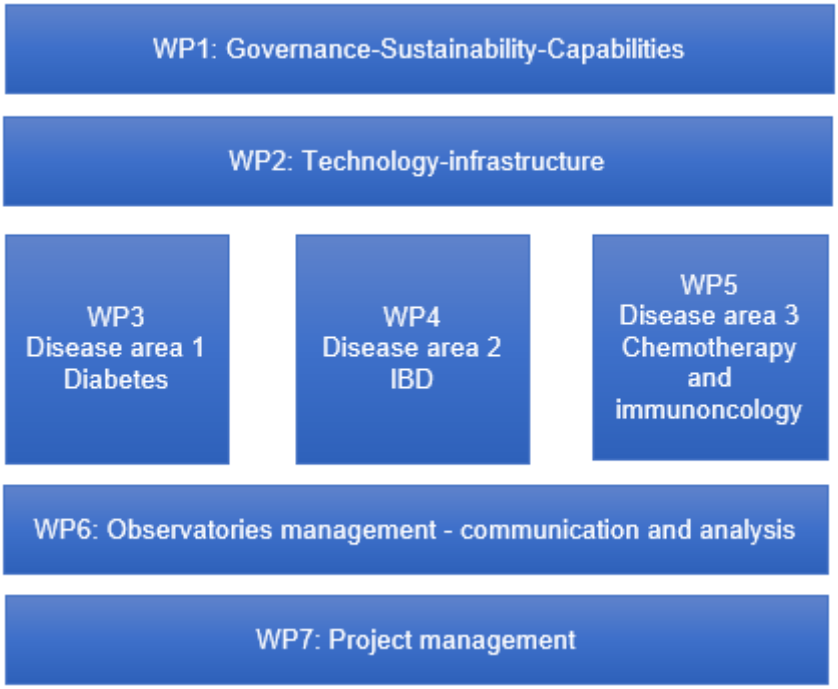
Suggested architecture of the full proposal

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 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 should 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 architecture outlined below for the full proposal is a suggestion. The architecture of the full proposal should be designed to fulfil the objectives and key deliverables within the scope of this proposal.



Work package 1: Governance - Sustainability - Capabilities

- design of the specific governance principles and structures including legal structures, funding and operating model in the given countries in a way to ensure long-term sustainability. This should include the governance and operating procedures for the creation and maintenance of the observatories, including their relationship with patient organisations, health authorities both at regional/national and above country level and commercial entities. Important elements for the design of the appropriate governance model would be:
    - the long-term sustainability of the model;
    - the possibility to scale it to further disease areas;
    - the interoperability of the data collected with health data derived from EHRs, registries, academic researchers, etc.;
    - the development of a robust consenting process in compliance with the GDPR and other relevant legal and regulatory requirements;
    - the creation of an ethics council to watch over the observatories to build strong trust levels among patients and society.
- methodology for identifying the appropriate measurement standards ensuring they reflect patients' priorities and validating them. In order for any measurement/reporting tool to be truly useful to patients, it should

offer them the opportunity to improve their communication with their HCP and/or the healthcare system more broadly. It is therefore an important part of the mission of the observatories to choose standards that reflect patients' priorities but also integrate these standards with the broader stakeholders in order to gain broader acceptability;

- identify the capabilities and capacity required for the collection, analysis and dissemination of health data in the observatories, including the required capabilities for data analysis and administration, and staff the observatories appropriately.

Work package 2 – Technology – Infrastructure

Identify the appropriate technology that will allow the capture of relevant information from patients and enable real-time information sharing with patients. Set up or adapt the appropriate technology, including tools and a platform, that would allow the collection and management of patient-generated data taking into consideration the possible scalability of the project as well as the interoperability of this data with health data derived from other sources (EHR, registries etc.).

Work packages 3 – 5

These work packages will focus on each disease area, aiming to enhance the value of treatment and care for patients through the collection of patient-generated data, the analysis of best care practices as well as the development and validation of digital e-health tools and technologies. The ultimate aim is to increase the wellbeing of patients through improvements in patient care that have been developed with greater insights from patients generated by the observatories.

Specific common objectives are:

- identify the appropriate measurement standard for the respective disease/outcome and ensure validation by the stakeholder community;
- create the methodology to answer the specific research questions identified by the consortium as the most pertinent to the respective disease;
- provide input to the design of technologies in WP2.

Work package 3 – Diabetes types 1 and 2

- to focus on the analysis and validation of key outcomes measures and assess their usefulness for diabetes care and contribution to health economic aspects of the healthcare system;
- to use state of the art analytical techniques to demonstrate ideal levels of care based on the validated outcomes data together with other data types such as EHR and patient-generated data;
- to stratify people with diabetes according to outcomes to improve the understanding of diabetic endotypes;
- to develop a digital decision-making system which can be used by healthcare professionals in clinical practice for more personalised treatment of people with type 1 and type 2 diabetes.

The following sub-work packages are proposed to achieve WP3's goals:

- WP3.1: Collecting, refining and validating existing outcome measures to enable solid assessment of the value of a treatment:
    - weighting outcome measures and understanding their impact on the quality of life and care of patient segments;
    - weighting outcome measures and understanding their appropriateness for the cost of care analyses;

- development of a digital decision-making tool, based on outcomes that could be used by HTA bodies to aid in the assessment of new therapies and treatments.

- WP3.2: Analysing and validating clinical, patient-reported and real-world data to enable the development of a novel segmentation of patients to attribute to them the right level of care:
  - deployment of computational biology approaches for assessment and analysis of large multivariate datasets (e.g. outcomes-data derived from both EHRs and clinical trials) to divide patients into more precise and personalised segments;
  - development and validation of new recommendations of treatment, care and approaches for the newly-defined patient segments based on the comparative assessment of the performance of established treatments for type 1 and type 2 diabetes.
- WP3.3: Development of a clinical digital decision-making tool, based on outcomes and healthcare experience, for healthcare providers to aid in the assessment of treatment choice.

Work Package 4 – Inflammatory bowel disease

- to establish and validate a key set of key outcomes and healthcare experience measures that matter to patients in IBD, especially related to the assessment of disease severity based on patient-reported outcomes;
- to develop digital tools to collect these data directly from patients;
- to assess the acceptance and usability of these tools in patients suffering from IBD;
- to collect a set of patient-generated data using these tools and assess how these outcomes data sets compare to and complement other measures of patient outcome derived from clinical assessments, registries and EHR data;
- to better understand patient endotypes in IBD;
- to better understand how outcomes vary with patient endotypes and clinical practice and assess their potential use for improving patient care and system efficiency in the care of IBD;
- to utilise the PRO data to develop a simple scoring algorithm to indicate a patient's risk of not showing an adequate response to their existing IBD therapy (and which could prompt his/her treating physician to re-evaluate the treatment strategy);
- to support the development of digital decision-making tools which can be used by healthcare professionals in clinical practice for more personalised treatment based on patient and disease characteristics, treatment history and risk factors.

Work Package 5 – Side effects of chemotherapy and immuno-oncology

- to establish and validate a key set of core, patient-relevant, outcomes and health care experience measures that matter to patients with chemotherapy and immune-oncology side effects, and to develop digital tools to collect these data directly from patients;
- to assess the acceptance and usability of these tools in patients suffering from the side effects of chemotherapy or immune-oncology;
- to collect a set of patient-generated data using these tools and assess how these outcome data sets compare to and complement other measures of patient outcomes derived from clinical assessments, registries and EHR data;
- to better understand how outcomes and experience with healthcare vary across patients and across clinical practice and assess the potential for improving patient care and system efficiency in the care of cancer patients;
- to better understand patient segments across chemotherapy or immuno-oncology side effects;

- to support the development of digital decision-making tools which can be used by healthcare professionals in clinical practice for more personalised treatment of patients with side effects of chemotherapy or immune-oncology.

Work Package 6 – Observatory management: communication and analysis

- establish the operation of the observatories, including continuous support to patients and other stakeholders for using the technology, collecting feedback and data;
- generate regular publications to demonstrate the value added of the observatories and the lessons learned;
- manage the gateway for users of the data (including patient-level data, whether identifiable or anonymised, and aggregated data) to be able to access the data;
- define the appropriate operational and maintenance plan to ensure the technical, organisational and financial sustainability after completion of the project. Explore with partners possible expansion into additional diseases as well as possible integration with EHR and registry data.

Work Package 7 – Project management

Take responsibility for overall project management of the project, including (but not limited to) finance management for the project as a whole; meeting management and organisation (for the project as a whole); administration of communication activities; and supporting the reporting to and communication with the IMI office. WP7 will not be responsible for managing the activities of the individual work packages.

Topic 3: Improving patient access, understanding and adherence to healthcare information: an integrated digital health information project

Topic details

Topic code	IMI2-2019-18-03
Action type	Research and Innovation Action (RIA)
Submission and evaluation process	2 stages

Specific challenges to be addressed

The ability to access and understand high-quality health information is central to health literacy, and this affects the day-to-day decisions citizens make in the management of their health and care [1] that will ultimately determine adherence to treatment [2]. A lack of adherence is an established public health concern, with significant effects on the individual patient, as well as healthcare systems as a whole [3].

A multitude of health-related information resources are now available to patients, tapping into demands for greater engagement with personal healthcare. This digital era, however, is compromised by two major concerns. Firstly, the sheer volume of information available has become disorientating to users, many of whom have poor health literacy [4] to start with, and do not know which source to trust for up-to-date guidance. Distribution of this information across different source locations only compounds the issue. Secondly, existing health-related resources are generally not personalised to their specific needs or health literacy level, and therefore large amounts of the information available are irrelevant to the patient[14]. Indeed, product information is a prime example of this phenomenon, with little direct evidence to suggest that patients are actively reading, understanding and adhering to details in the patient leaflet (PL)[15]. Bearing in mind that the product information is considered for most products to be the primary risk minimisation measure, this paradigm clearly needs to change.

There is therefore the need to lay the foundations for the application of digital technologies to health information in order to transform citizens' understanding of their health and care, thereby promoting adherence to prescribed treatments, and ultimately contributing to better outcomes. The topic is consistent with the EU Digital Single Market Strategy, which highlights the need and opportunity to introduce a digital transformation of health and care[16], and is aligned with the IMI Strategic Research Agenda under Axis 4 'Patient Tailored Adherence Programmes'[17]. The topic is also consistent with the key benefits noted in the European Medicines Agency (EMA) Action Plan on e-Product Information (ePI)[18] and subsequently in the draft key principles for electronic product information published by EMA[19] following an EMA/HMA/EC stakeholder workshop.[20] During the workshop, this topic was presented alongside other initiatives in the context of a future vision for electronic product information in the broader digital

[14] The most frequently quoted example of this is pregnancy information for male patients.
[15] The authoritative source of information provided to patients about their medicine is the patient leaflet which must be provided unless all information can be included on the outer packaging (Directive 2001/83/EC Article 58). This single document is provided to all patients irrespective of their health literacy, patient profile, medical history, or preference. In addition, the current format of the package leaflet is widely acknowledged to need improvement (Report from the European Commission on the shortcomings of product information published 22 March 2017)
[16] Communication on Transformation of Health and Care in the Digital Single Market (April 2018)
[17] IMI Strategic Research Agenda.
[18] EMA Product Information Action Plan was published on 10 October 2017
[19] Electronic-product-information-human-medicines-european-union-draft-key-principles - consultation period 31-Jan-19 to 31-Jul-19
[20] European Medicines Agency (EMA) / Heads of Medicines Agencies (HMA) / European Commission (EC). Stakeholder presentations and the workshop report including details of the mapping of ongoing initiatives have been published. See: https://www.ema.europa.eu/en/events/european-medicines-agency-ema-heads-medicines-agencies-hma-european-commission-ec-workshop

health landscape, and the EMA also shared details of their mapping of ongoing ePI initiatives, illustrating the very considerable degree of interest and activity in this area at the present time.

Need and opportunity for public-private collaborative research

While there are already digital tools available that enable patients to access product information electronically (e.g. electronic Medicines Compendium (eMC) in the UK, LIF in Denmark, FASS in Sweden, and the Gebrauchsinformation 4.0 project in Germany)[21], and ePI texts may also be available via health authority websites, these do not at this time comprehensively address the broader information needs noted above, there is limited flexibility to tailor the information available to individual needs, and equivalent digital tools are not available to all patients in all countries.

To address the challenges and undertake a project of such a transformational nature, an active partnership from a range of contributors across the public and private sectors is necessary. The project must balance the need for interoperability with national healthcare systems, align with other key principles mentioned in the EMA ePI draft key principles document, address concerns from industry to enhance the effectiveness of the ePI as a primary risk minimisation measure, and provide all of this in an intuitive and user-friendly design which meets citizens' unmet needs as noted above. This includes:

- perspectives from patient and healthcare professional organisations to understand patient health information/literacy needs and ensure that proposed solutions are fit-for-purpose, acceptable to all stakeholders and truly value-added from the user perspective, and to enable measures to be defined of relevance to these stakeholders;
- academic and research institutions and appropriate health literacy experts who can support the development of appropriate methodology to test patient understanding and impact and contribute to development of appropriate key performance indicators (KPIs) in relation to the project objectives;
- current providers of ePIs and associated product information to enable existing best practices/expertise to be leveraged, and other technology organisations who can develop and integrate the envisaged technology platform and digital applications that will be needed for the proof of concept testing, including considerations for data integration;
- public sector partners who can contribute to the identification of trusted sources of product information, electronic health records and health education materials for use within the project framework;
- contributors with appropriate expertise in the gathering/use/analysis of real-world data and risk-benefit assessment, to measure the effectiveness of the platform as a risk minimisation tool;
- advice from regulators (i.e. EMA, national competent authorities) to consider alignment with wider telematics initiatives and the impact of the proposed approaches on the current/future regulatory framework for the provision of health information to patients;
- contributors with legal and data privacy, as well as social science and ethical expertise to ensure that questions in relation to these areas can be addressed.

The establishment of a public-private partnership offers a unique mechanism for these diverse stakeholders to engage to deliver the range of input and expertise necessary for achieving the project aims and ensuring that a practical and sustainable solution is found.

[21] For example, see the Swedish FASS website at http://www.fass.se; mp3 audio files on http://www.laakeinfo.fi, videos on https://www.indlaegssedler.dk, and the 'Gebrauchsinformation 4.0' project in Germany: https://www.ema.europa.eu/en/documents/presentation/presentation-product-information-40-gebrauchsinformation-40-gi-40-g-lang_en.pdf

Scope

The principle objective of this topic is to demonstrate how the use of an integrated, digital, user-centric health information solution could enable a tangible improvement in the ability of citizens to access and understand reliable, relevant health information from different sources.

Access to and understanding of health information are key components determining health literacy, and the health literacy level of a citizen underlies their decision-making in regarding to management of their health and care, including adherence to treatment. Accordingly, a secondary objective will be to measure how improved access to and understanding of health information translates into higher levels of treatment adherence, safer use of medicines and consequently better health outcomes, with new insights into how health information can be optimised to act as an effective risk minimisation measure.

The topic objectives will be achieved by a phased approach, in which later stages build on the outputs of the earlier research activities in an agile manner:

1. **Establishing stakeholder needs and development of appropriate KPIs**

Research will be conducted to establish an in-depth understanding of citizens'[22] expectations and aspirations for the provision of healthcare information in a digital setting to form the basis for future project activities and design-planning for technology development. Specific contexts/patient journeys will be mapped at this stage either on specific therapy areas or other product-type scenarios, such as non-prescription medicines or vaccines. The needs of different patient populations, including vulnerable patients, will also be considered. KPIs will be developed in relation to the two key objectives outlined above to enable the measurement of the success of the proposed integrated digital health information approach versus the current paradigm (which typically relies on paper-based product information for the patient and/or fragmented digital sources).

2. **Technology platform and digital solution**

Development of an **underlying open source technology platform,** and a **digital solution** to enable testing and measurement of the effectiveness of a digital approach to meet defined user needs.

The initial focus will be on product information, electronic health records (EHRs) and a two-way communication channel with the patient. Appropriate, trusted data sources will be linked to the platform taking into account applicable data security and General Data Protection Regulation (GDPR[23]) considerations. A digital solution with tailored information in line with patient needs will be developed for the proof of concept testing of understanding and acceptability. Alignment with the key principles on the common standard for ePI coming from the EMA Action Plan will also be taken into account[24].
Depending on technical progress with product information and EHRs, the latter stages of the project may include a wider range of trusted health educational materials (HEMs) within the platform, with the aim of further enhancing patient understanding.

3. **Evaluation of the ability of digital solutions to enhance risk minimisation approaches through the generation of real-world evidence**

Feedback gathered via the digital tool can be used to assess understandability and options can be evaluated for how to further assess the effectiveness of the platform as a risk minimisation tool.

Ongoing: Development and execution of a sustainability plan

[22] Including patients, healthcare professionals and members of a patients' support network.
[23] See https://ec.europa.eu/info/law/law-topic/data-protection_en.
[24] EMA Product Information Action Plan was published on 10 October 2017.

A sustainability plan will be developed over the life of the project which details recommendations for how successful concepts/technology approaches will be carried forward and implemented into the digital healthcare ecosystem at the national/regional level in a sustainable and practical manner. The draft plan will be developed early in the life of the project and adapted in an agile manner based on the project outcomes.

Any form of promotional materials will **not be in scope** for this project.

Expected key deliverables

The key deliverables will be an **open-source technology platform** and **digital technology solution**(s) that have been developed for testing.

- The open-source technology platform will integrate information from regulator-approved product information and electronic health records in the wider context of digital health. The platform will aim to make such information available via an application programming interface (API) to allow other companies/developers to use this as a basis for further market-specific applications, offering flexibility for the future evolution of the digital ecosystem.
- The digital technology solution will allow digital information to be presented to the patient in a tailored, user-friendly manner to more effectively serve the needs of patients in the management of their own health and care. A range of digital functionality will be built into the digital solution and tested with user groups to measure the effectiveness in improving understanding, adherence to treatment, and health outcomes.
- For example:
    - a user-friendly view of the patient's medical history and other pertinent characteristics;
    - tailored versions of the ePI dependent on patient circumstances and health literacy needs. A variety of formats will be made available based on the approved PLs, and integration across PLs for different products to generate a single 'treatment ePI' will also be investigated;
    - the solution will incorporate additional digital functionality to enhance the user experience and support understanding, adherence and health outcome measures. These features will be fully defined during the research studies but may include features such as dosage reminders, comprehension tests, linkage to healthcare systems to receive e-prescriptions or book appointments, and other off-the-shelf capabilities that already exist in different EU Member States;
    - users will have the ability to send information to the platform to be aggregated and analysed to improve outcome measures;
    - depending on progress with EHRs and ePI, the platform may also look to identify defined health educational materials at different health literacy levels that will help the patient understand their health, medical diagnosis, and prescribed treatments.

Other deliverables will include the following:

- a series of study reports will be published presenting the outcomes of research studies which seek firstly to demonstrate the benefit that this integrated digital approach offers to patients in accessing and understanding health information from the identified sources (primary objective), and in turn to applying this to enable improved adherence to treatment and health outcomes (secondary objective). Details of the KPIs developed for measurement of success in relation to these two objectives will be described;
- an evaluation will be completed to assess the potential ability of digital solutions to enhance risk minimisation approaches through the generation of real-world evidence;
- at the end of the project, the project team will publish a white paper that outlines the next steps that should occur in the EU to take advantage of the research findings from the proof of concept test phases. Depending on the results and demonstration of the success of different concepts, this may include a recommendation on adoption of the technology platform/digital solution as the starting point for national or regional implementation (with appropriate modifications), adoption of elements of the solution for further development, and what changes (if any) would be needed to EU legislation/regulation to allow for introduction of these elements;

- identification and publication of key stakeholder needs and preferences in terms of information, personalisation and functionality, which will then be used as a basis for design planning for a suitable digital solution;
- identification and publication of a set of data source specifications for integration into the digital solution via:
    - identification of the data standards for, and key elements of, electronic medical records and medical alerts for inclusion;
    - utilisation of regulator-approved product information in the appropriate data standard according to emerging ePI standards.
- report on the key features of future data standards for ePIs that would optimise functionality in relation to the provision of health information for consideration by regulators[25].

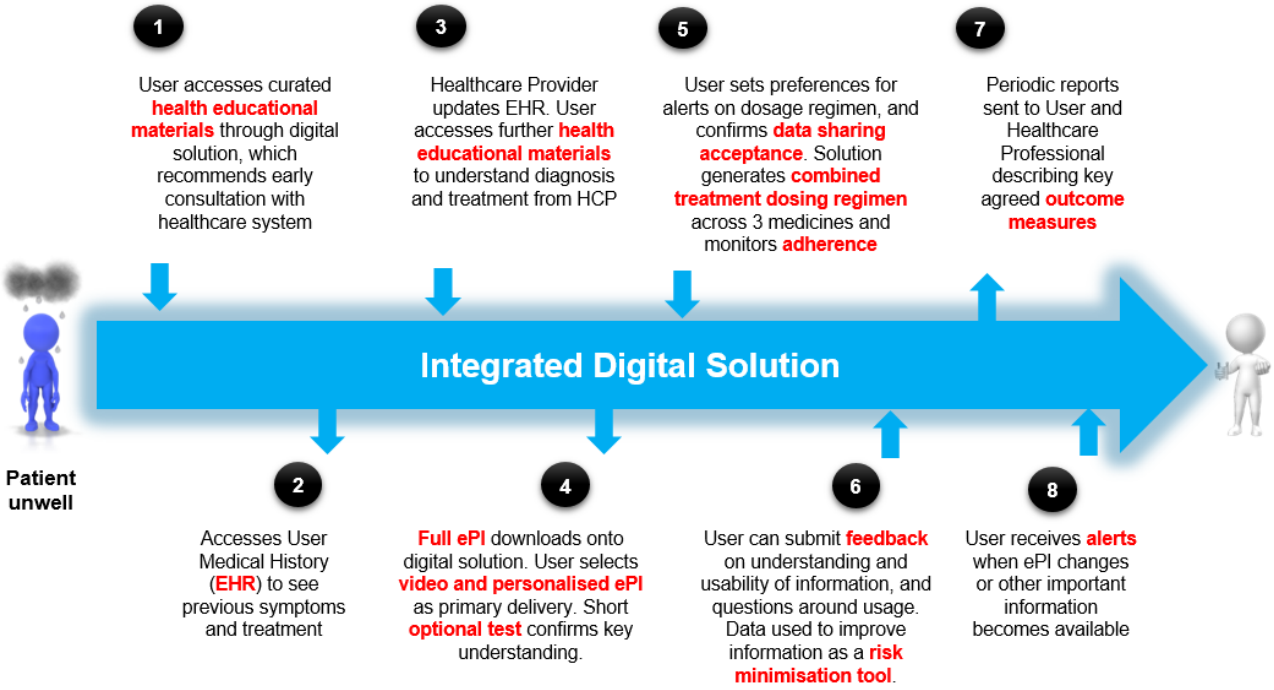
Expected impact

Applicants should describe how the outputs of the proposed project will contribute to the following impacts and include baseline, targets and metrics to measure impact:

- allow individual patients to easily access trusted health information, tailored to be relevant to their specific needs. Empower these patients and better prepare them for informed interaction with national healthcare systems;
- further build patients' (digital) health literacy, so allowing for better decision-making concerning their health care, disease prevention and health promotion, to maintain or improve quality of life throughout the course of life;
- positively impact healthcare at a societal level through enhanced adherence, better use of resources, and improved overall patient outcomes; the approach may offer particular benefits in complex scenarios, for example where patients are managing multiple morbidities;
- improve the effectiveness of ePIs as a primary risk minimisation measure by surfacing greater insights on access, understanding and the usability of the information provided to them;
- the technology platform/tools developed for the purposes of the project will be made available open-source, and will be accessible to other companies/developers to use this as a basis for further market-specific applications which can accommodate the specifics of local digital ecosystems, allowing flexibility to best support longer-term implementation of the integrated digital healthcare approach;
- the implementation will enable relevant and approved updated trusted health information to be pushed in a timely manner to ensure adherence with changes in safety or usage information to continue to enhance patient adherence and safety after and with patient permission to receive alerts pertinent to them;
- the digital approach and technology developed under the project has the potential to transform the patient experience as they engage with and manage their health and care throughout their healthcare journey. The figure below illustrates how such a journey may be envisaged in the future, in an environment in which digital information sources are integrated effectively and tailored to the needs of the individual.

[25] Accordingly, the option of Article 28.2 IMI2 JU Grant Agreement regarding results contributing to standards should be activated and included in the text of the future funded action's Grant agreement.

Figure 1. Illustrative use case (prescription scenario)



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

This proposal is expected to develop synergies, build on results, and avoid duplication of efforts with existing consortia and current e-PI/EHR initiatives at national, EU, and international level. The development of the global IDMP (ISO)[26] standard for the product database can further be regarded as a potential synergy to this project. Applicants should assess existing opportunities for synergies with other ongoing initiatives at a regional or national level, in particular in the fields of ePI and EHR and demonstrate in their proposals how they will synergise with such initiatives in order that the project can leverage relevant expertise to the maximum degree

Collaboration agreements

There is the potential for important synergies between the consortium selected under this topic and the one selected under IMI2 JU Call 18 topic 2 (Health Outcomes Observatories – empower patients with tools to measure their outcomes in a standardised manner creating transparency of health outcomes). On the one hand, for instance, while the consortium selected under this topic 3 should have access to sufficient EHRs and patients to meet its own objectives, this consortium could also leverage the observatory platform in order to obtain access to and analyse additional relevant electronic health record (EHR) data, in compliance with applicable regulation, gathered under topic 2. On the other hand, the consortium selected under this topic could become an additional important use-case for the observatories under topic 2 and improve their usefulness. Additionally, the perspectives brought by the consortium selected under topic 3 can contribute to development of the governance and operational model of the observatories, under topic 2. It could also help future-proof them as a neutral guardian of patients'

[26] Identification of Medicinal Products (International Organization for Standardization). See https://www.ema.europa.eu/en/human-regulatory/overview/data-medicines-iso-idmp-standards-overview

health data which could then be made available in the future with the appropriate safeguards for applications, such as those envisaged under topic 3.

To explore these potential synergies between actions funded under these two topics, the selected consortia are expected to cooperate in common boards/structures and provide access to their results for specific activities when relevant. Therefore the grants awarded under IMI2 JU Call 18 topics 2 and 3 will be complementary grants. The respective options under Article 2, Article 31.6 and Article 41.4 of the IMI2 JU Model Grant Agreement[27] will apply. Accordingly, the relevant consortia will conclude collaboration agreement(s) to ensure the exchange of relevant information, exploration of synergies, collaboration where appropriate.

Industry consortium

The industry consortium is composed of the following EFPIA companies:

- Pfizer (Lead)
- Astra Zeneca
- Bayer
- Grunenthal
- Lilly
- Medidata
- Mylan
- Novartis
- Roche
- UCB

In addition, the industry consortium includes the following IMI2 JU Associated Partners:

- Datapharm
- Medicines for Europe

The scope of the research proposed is wide-ranging, and hence the industry contributors are offering functional expertise across a range of disciplines aligned to the project scope and objectives. These areas of expertise include: knowledge of development and maintenance of product information, and its central place in pharmacovigilance and risk management/minimisation methodologies; the importance of health literacy and the provision of high quality medical information; the use of real-world data to improve understanding of product safety and effectiveness; business technology expertise concerning development of systems; processes, and data standards to support regulatory processes; and knowledge of development and implementation of EHR systems.

Indicative duration of the action

The indicative duration of the action is 60 months.

Indicative budget

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

The indicative in-kind and financial contribution from EFPIA partners and IMI2 JU Associated Partners is EUR 9 280 000

This contribution comprises an indicative EFPIA in-kind contribution of EUR 9 070 000 and an indicative IMI2 JU Associated Partners in kind contribution of EUR 210 000.

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

The financial contribution from IMI2 JU is a maximum of EUR 9 280 000.

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.

This may require mobilising, as appropriate the following expertise:

- patient groups/healthcare professional groups to ensure that the perspective of the end user is taken into account fully in the research scope, the development of appropriate KPIs relating to the two key objectives, and also for the proof of concept testing;
- academic and research institutes specialising in the provision/use/understanding of health information, who can support the definition of appropriate KPIs relating to the two key objectives, and development of an appropriate methodology for testing to demonstrate patient understanding and impact;
- expertise in gathering/use/analysis of real-world data and risk-benefit assessment, to consider the effectiveness of the platform as a risk minimisation tool;
- expertise on the legal, ethical, social science and GDPR questions arising from the proposed work;
- technology partners, including SMEs, who have proven experience in electronic health records, provision of health information (for example current leaders of national electronic product information initiatives), platform integration and development of user-centric solutions within a highly secure environment, and provision of business/regulatory information technology. User-centric solutions need to be designed with the patient journey in mind, covering measures which will improve patient adherence to treatment (e.g. adherence checks), patient understanding of the product information (e.g. novel interactive question and answer features), and the delivery of novel forms of personalised product information (e.g. video, pictorial, digital assistant) based on defined criteria coming from EHRs or other data-entry methods. Interest from SMEs who can offer technical expertise that could support the development of the technology envisaged under the project is welcomed;
- ideally, national competent authorities would be part of the applicant consortium to ensure alignment with national initiatives.

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

- applicants should demonstrate access to appropriate data sources spanning product information and EHRs in at least one country. It is proposed to conduct the study in several markets;
- existing relevant digital technologies that can be further developed during the project.

Experience and engagement with relevant digital health initiatives

Applicants should demonstrate how they will seek to take advantage of established/planned digital health initiatives within relevant member states, in particular in relation to ePIs and EHRs.

Interaction with regulators

In their proposals, applicants should have a plan for engaging with regulators (for example, seeking scientific advice from the European Medicines Agency and/or national competent authorities). This is to ensure alignment with any new e-labelling principles across the region, but also to consider the potential impact on legislation to allow the development of recommendations for the introduction of successfully proven solutions in due course. At a minimum, it is anticipated this will occur prior to initiation of testing activities in the specific Member States and during the development of implementation recommendations in the later phases of the project. Suitable resources should be dedicated to these activities.

Data management

In their short proposal, applicants should give due visibility to 'data management'. Applicants should include proposals for how concerns relating to data privacy/GDPR may potentially be addressed. At stage 2, applicants should include a draft data management plan (DMP) in the full proposal, outlining how research data will be handled and made available during the project and after it is completed.

Dissemination, exploitation and communication activities

In their short proposal, applicants should give due visibility to the dissemination, exploitation and communication of the project's results. At stage 2, in their full proposal, applicants should further develop these activities.

Partnership with the industry consortium

In their short proposal, applicants should outline a strategy to create a successful partnership with the industry consortium.

Sustainability planning

In their short proposal, applicants should outline how they have considered the longer-term sustainability of the project outputs.

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 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.

The architecture outlined below for the full proposal is a suggestion. The architecture of the full proposal should be designed to fulfil the objectives and key deliverables within the scope of this topic.

The proposed project should be phased with an initial focus on product information, then moving on to linkages with electronic health records, and the development of a two-way communication channel to the patient to assess the potential of the platform as an effective risk minimisation tool. A final phase of the proposed project should focus on the expansion of content within the platform to include a wider scope of health educational materials will

be considered after the project has proven the utility of the integrated platform across product information and EHRs. In each phase of the proposed project, attention will be paid to ensuring that the platform is delivering a *meaningful* effect on patient understanding and adherence before moving to the next stage.

Phase 1: Establishing stakeholder needs and development of appropriate KPIs

Research activities to define key patient/user needs and preferences in terms of information, personalisation and functionality as described above across product information and EHRs. Testing scenarios will be assessed during this phase. In addition, technology contributors/partners will be assessing the feedback and analysing its feasibility and complexity for consideration in technology development planning. KPI development will begin to enable measurement of enhanced understanding/adherence during the planned studies.

Phase 2: Sourcing, developing, testing, and measuring the effectiveness of digital solutions to meet defined user needs through a series of proof-of-concept projects

Work packages across both of the initial information areas (product information & EHR) will manage the next phase of activities during which technologies will be built and tested in initial proof–of-concept studies.

In parallel, the technical development and evaluation of the ability of digital solutions to enhance risk minimisation approaches through the generation of real-world data will begin, so that this element of functionality can be incorporated into the digital tool as a basis for further testing. The work packages will proceed in parallel.

Phase 3a: Sourcing, developing, testing, and measuring the integrated digital solutions to meet defined user needs in a proof-of-concept study

Proof-of-concept testing of the fully integrated prototype digital solution to demonstrate a benefit on identified measures relevant to patient health.

Phase 3b: Extension to include health educational materials

This last phase will only proceed if Phase 3a is successful and will look to identify and include trusted sources of health educational material to further enhance patient understanding. The methodology will be developed to define how such sources may be identified, assessed, and included (either linked or embedded) within the platform and tested with users.

Ongoing: Development and execution of a sustainability plan

A sustainability plan will be developed over the life of the project, and then executed to allow the development of recommendations based on project outputs that would consider how successful concepts will be carried forward and implemented. The initial plan will be developed at an early stage of the project, and then adapted in an agile manner in response to project outcomes. Horizon-scanning/landscape mapping to allow for identification of relevant digital health initiatives will also occur during the life of the project to ensure that the project outputs can be integrated successfully into the wider digital health ecosystem. Explore future case scenarios and drive thought leadership for next generation activities relevant to product information.

References

[1] Sabate E (2003). World Health Organization. Adherence to Long Term Therapies. Evidence for Action. Geneva. WHO. Available at: https://www.who.int/chp/knowledge/publications/adherence_report/en/

[2] Medication adherence is defined as 'the extent to which the patients' behaviour matches agreed recommendations from the prescriber' and thus illustrates the importance of the patients' decisions. See: Horne RWJ, Barber N , Elliot R , et al. Concordance, adherence and compliance in medicine taking. Report for the national coordinating centre for NHS service delivery and organization R & D (NCCSDO), 2005. http://www.netscc.ac.uk/hsdr/files/project/SDO_FR_08-1412-076_V01.pdf

[3] Viswanathan M, Golin CE, et al. Interventions to Improve Adherence to Self-administered Medications for Chronic Diseases in the United States: A Systematic Review, 4 Dec. 2012. https://doi.org/10.7326/0003-4819-157-11-201212040-00538

[4] Health literacy entails 'people's knowledge, motivation and competencies to access, understand, appraise, and apply health information in order to make judgments and take decisions in everyday life concerning healthcare, disease prevention and health promotion to maintain or improve quality of life during the life course'. Sorensen K et al. (2012), Health literacy and public health: A systematic review and integration of definitions and models BMC Public Health 12:80 https://doi.org/10.1186/1471-2458-12-80

Topic 4: Establishing international standards in the analysis of patient reported outcomes and health-related quality of life data in cancer clinical trials

Topic details

Topic code	IMI2-2019-18-04
Action type	Research and Innovation Action (RIA)
Submission and evaluation process	2 stages

Specific challenges to be addressed

Patient-centeredness is increasingly identified as a critical component of quality health care [1]. As such, health-related quality of life (HRQOL) and other patient-reported outcomes (PRO) that quantify how a patient feels or functions during treatment are increasingly considered as important endpoints in cancer clinical trials. Data on these endpoints are increasingly used to inform benefit-risk evaluations for regulatory marketing authorisation purposes. These endpoints are also useful in the context of reimbursement decision-making, where they are instrumental in evaluation of added therapeutic benefit and documentation of the value of surrogate endpoints such as progression-free survival (PFS) or overall response rate (RR). Moreover, information on HRQOL and PROs may also be used to enable better communication and shared decision making between patients and their treating physician, improving outcomes, treatment satisfaction and care.

Numerous efforts have been undertaken to standardise the way HRQOL and PRO data are conducted and reported in cancer clinical trials. These include recommendations to standardise reporting and drafting of clinical trials [2][3], translations in clinical trials [4], and how to develop and standardise measures for use in clinical trials [5]. However, there are no agreed standards on how to analyse HRQOL and PRO data in clinical trials and subsequently, interpret the findings. The various ways data are analysed and interpreted make it difficult to compare results across trials, and hinder the application of research findings to inform physicians, patients, caregivers, policy makers, reimbursement authorities and other stakeholders. Lack of standardisation can lead to variation in the analysis of results and could result in two near-identical trials being analysed in different ways, leading to potential differences in data interpretation.

A number of systematic reviews from randomised controlled trials (RCTs) have highlighted the current lack of standardisation in this field and reported the following key findings [6][7][8]:

- a lack of clear HRQOL and PRO research objectives;
- a lack of standardisation of basic statistical terms such as compliance and completion rates;
- the use of suboptimal statistical practices and a variety of statistical methods not well justified with respect to analysing HRQOL and PRO data;
- the use of a variety of approaches to handling missing data.

There is an urgent need to develop clear standards and guidelines, endorsed by a broad range of stakeholders, to improve how HRQOL and PRO data are analysed in cancer clinical trials. This would also help promote HRQOL and PROs as potential primary or co-primary endpoints (when relevant) in cancer clinical trials. Such standards will support the full use and understanding of HRQOL and PROs in drug development and drug and device approval by regulators and health technology assessment (HTA) bodies, but importantly it will also support better communication of PRO results to clinicians and patients with the potential to inform and improve shared decision-making.

Need and opportunity for public-private collaborative research

This initiative aims to establish a multi-stakeholder consortium with the overall objective to standardise and develop recommendations for the analysis and interpretation of HRQOL and PRO data in cancer clinical trials. The focus of this topic is to achieve a consensus on the analysis methods of HRQOL and PRO data in RCTs. However, as other study designs (e.g. single arm studies, basket trials) are also starting to play an important and innovative role in cancer drug development, there is general agreement that guidelines and best practices also need to be developed for these trial designs. Moreover, once these new standards and guidelines are developed, it is critical to validate them using existing data from academic and pharma-led clinical trials. Finally, PRO findings based on these recommended analyses must be communicated in a simple and accurate way to clinicians, patients and other stakeholders.

To be able to address this challenge, the concerted efforts of different experts from various organisations are needed. It is critical to have a broad based consortium to include a wide range of experts and organisations. For instance, patient groups and their representatives, healthcare decision makers, regulators and representatives from HTA authorities and other public health bodies are needed, as well as experts from the pharmaceutical industry. Small and medium-sized enterprises (SMEs) may also play a role in the development of data visualisation software which should demonstrate added value to the regulatory and HTA bodies.

Scope

The scope of this Call topic is to develop recommendations for the different analyses and interpretations of HRQOL and PRO endpoints in cancer clinical trials that will be tailored towards addressing specific research objectives within each clinical trial. This Call topic aims for a global scope and is of strong interest to individuals from various regulatory and HTA bodies, key cancer organisations, the pharmaceutical industry, specialised vendor organisations, academic societies and international patient organisations. The buy-in of these various key stakeholders is crucial, as this will help identify a set of similar expectations, facilitate the implementation of these recommendations, and harmonise the analysis and interpretation of HRQOL and PRO data on a global scale.

The main objectives are to:

- achieve international consensus, across stakeholders, on the optimal use of HRQOL and PRO data in cancer clinical trials;
- improve the quality of statistical analysis of HRQOL and PRO data in cancer clinical trials;
- improve the standards of reporting of HRQOL and PRO data, and as such the interpretability of the data. It is hoped that this will result in more reliable interpretation, and ultimately faster dissemination, of HRQOL and PRO findings, as well as cross-referencing within and between different cancer settings, whenever this is deemed feasible.

Expected key deliverables

The work should lead to several important key deliverables and consensus documents that are aligned with relevant stakeholders; alignment with regulatory and HTA bodies will be especially important as this will be critical to successful implementation. Continuous collaboration throughout the project with representatives from patient advocacy groups is vital to ensure the patient-centricity of the research recommendations, dissemination strategies and patients' understanding of educational programmes.

The deliverables below should be achieved during the 48 months duration of the project.

- Work towards the development of internationally agreed consensus-based guidelines and recommendations for HRQOL and PRO analysis for RCTs, supported by relevant publications:
  a) recommendations to support the development of industry guidelines for the design, analysis and interpretation of HRQOL and PRO findings from cancer clinical trials;

b) recommendations to support the development of regulatory guidance, such as European Medicines Agency (EMA) Points to Consider, and HTA guidelines for the design, analysis and interpretation of HRQOL and PRO findings from cancer clinical trials;
c) recommendations to support the European Society for Medical Oncology (ESMO) and American Society of Clinical Oncology (ASCO) guidelines on assessing clinical benefit using HRQOL and PRO data from cancer trials;
d) recommendations for dissemination strategies and educational programmes designed specifically to improve patients' understanding of HRQOL/PRO and empower their abilities for shared decision making;
e) recommendations for clinically meaningful change for HRQOL/PRO instruments used in cancer clinical trials.

- Delivery of a case study database to retrospectively validate consensus recommendations;
- A freely accessible toolbox providing recommendations for the communication, presentation and visualisation of HRQOL and PRO findings from cancer RCTs, including templates that are freely available to all users and promoted in all literature;
- Evaluate the feasibility of developing recommendations for non-RCTs, using single-arm studies as a case study (this should be closely linked to the main recommendations for RCTs to ensure uniformity in terminology and synergy of complementary ideas);
- A sustainability and capacity building plan to ensure that recommendations for PRO analysis in cancer clinical trials remain constantly up to date and relevant, including establishing an ongoing governing advisory board (with defined roles and responsibilities) to give advice on future updates to the recommendations.

Recommendations will be widely disseminated, where appropriate, and made available through a publicly accessible website that also allows access to other deliverables; use of this website's resources, along with implementation of the recommendations by regulatory agencies and HTAs, will be instrumental in ensuring the success of this initiative.

Expected impact

A consensus and clear set of agreed methodological recommendations for the statistical analysis of HRQOL and PRO data in cancer studies will improve their interpretability. This is an important prerequisite for better adoption and increased use of these outcomes in various decision-making contexts (regulatory approval, HTA/reimbursement decisions, shared decision making between physicians and patients). Importantly, the expected outcomes of this initiative will be of mutual benefit to all stakeholders involved, including the most important beneficiary of healthcare, the patient. Reaching a broad international consensus is a prerequisite for a broader adoption of HRQOL and PRO data and is likely to result in:

- more reliable findings and faster dissemination of HRQOL and PRO data in cancer studies;
- advances in statistical science and improved statistical practice in cancer studies;
- improved interpretability of the data because of greater familiarity with standardised reporting;
- broader use and adoption of PRO data to inform benefit-risk evaluation in regulatory appraisals, added benefit evaluation in HTAs and reimbursement decision processes as well as shared treatment decision making contexts;
- better and improved shared decision making between patients and their treating physicians which may lead to improved patient satisfaction, an increased likelihood of adherence to treatment, higher likelihood of treatment success and a reduction in health-care cost;
- better and more efficient use of increasingly finite research and healthcare funding;
- improved and more efficient clinical trial designs that also investigate the cancer patient perspective on treatment outcomes.

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 and funding. Proposals should document how collaboration will be achieved.

Possible synergies and collaborations will exist with the following initiatives and it is vital for the success of this project that close collaboration and alignment with these institutions should be sought by the applicants:

- The Setting International Standards in Analysing Patient-Reported Outcomes and Quality of Life Endpoints Data (SISAQOL) Consortium, managed by the European Organisation for Research and Treatment of Cancer (EORTC), currently working on guidelines for the analysis of PRO data;
- The Standard Protocol Items: Recommendations for Interventional Trials (SPIRIT)-PRO/ Consolidated Standards of Reporting Trials (CONSORT)-PRO (https://www.equator-network.org/reporting-guidelines/spirit-pro/) who recently published standards and are collaborating on standards for designing clinical trials, including non-RCT cancer trials;
- The Critical Path Institute (C-PATH - https://c-path.org/): a group working on PRO in the United States and working on the important area of developing electronic PRO measurements;
- EMA who have developed guidelines on PRO assessment; [9]
- The Food and Drug Administration (FDA) who have recommendations on PRO assessment in label claims, although limited guidance in terms of statistical analysis or interpretation; [10]
- The International Society for Quality of Life Research (ISOQOL; http://www.isoqol.org/) and International Society for Pharmacoeconomics and Outcomes Research (ISPOR: https://www.ispor.org/) working groups;
- Health Canada (https://www.canada.ca/en/health-canada.html) and the Japanese Clinical Oncology Group (http://www.jcog.jp/en/) who are developing new efforts towards making PRO an important national endpoint;
- Oncology societies that have made major steps in oncology: ASCO (https://www.asco.org/) and ESMO (https://www.esmo.org/).
- Study data from existing EU-funded (from the FP6/FP7/H2020 research portfolio) RCTs and observational studies addressing palliative, end-of-life and survivorship care could be potentially used to validate the recommendations for statistical analyses developed in this initiative, if feasible.

Industry consortium

The industry consortium is composed of the following EFPIA companies:

- Boehringer Ingelheim (lead)
- AbbVie
- Bayer
- Bristol-Myers Squibb
- Merck KGaA
- Pfizer

The industry consortium will contribute the following expertise and assets:

- in-depth knowledge of the advantages and disadvantages of various statistical methods and how they can be matched to identified research objectives;

- contributing to the review of clinically important responders and clinically important differences for various instruments and developing best practice recommendations for future instruments including outcome item banks;
- participation at all consensus meetings; making proposals, discussing options and contributing to guideline drafting and review;
- validating guideline recommendations by re-analysing existing data-sets and implementing them in prospective case studies;
- discussing and assessing the operational feasibility of implementing guideline recommendations in future cancer studies;
- contributing to developing educational tools and dissemination materials.

Indicative duration of the action

The indicative duration of the action is 48 months.

Indicative budget

The indicative in-kind and financial contribution from EFPIA is EUR 2 900 000.

This contribution comprises an indicative EFPIA in-kind contribution of EUR 2 000 000 and EUR 900 000 as financial contribution to the beneficiaries receiving JU funding in the selected action.

At stage 1, applicants should provide a suggested allocation of the total financial contribution (EUR 3 182 000) in the budget of their short proposal in order to achieve the proposed objectives.

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 2 282 000.

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.

To be successful, the applicant consortium will need to effectively combine the expertise of the various stakeholders in order to harmonise and standardise HRQOL and PRO analysis for cancer RCTs. Therefore, the successful consortium should have representatives from these key stakeholders or demonstrate plans to bring in necessary stakeholders and in-depth knowledge, as appropriate:

- regulatory affairs expertise with a proven track record of interacting with key regulatory agencies;
- representatives from HTA agencies;
- biostatisticians, epidemiologists, psychologists, and HRQOL and PRO researchers with experience in cancer RCTs (mandatory as participants);
- clinicians and other health-care professionals with experience in the design and conduct of cancer randomised clinical trials;
- representatives from academic medical and methodological societies;

- experts in the visualisation and presentation of HRQOL and PRO data;
- cancer patient advocacy groups, with knowledge and experience in cancer clinical trials (for activities in work package 7).

Optional:

- representatives from key cancer/medical journals;
- experts (including SMEs) in communication and knowledge dissemination;
- experts in interaction and communication with an international, multi-disciplinary stakeholder group.

The applicant consortium is also expected to have access to closed, completed cancer randomised controlled trial datasets with HRQOL/PRO assessments. Ideally, such data sets will be international and collected in the academic based clinical trial setting. The applicant consortium is expected to possess the necessary project management skills suitable for the consortium activities including organising and conducting consensus meetings.

The resources allocated should be adequate for the complexity and size of the consortium.

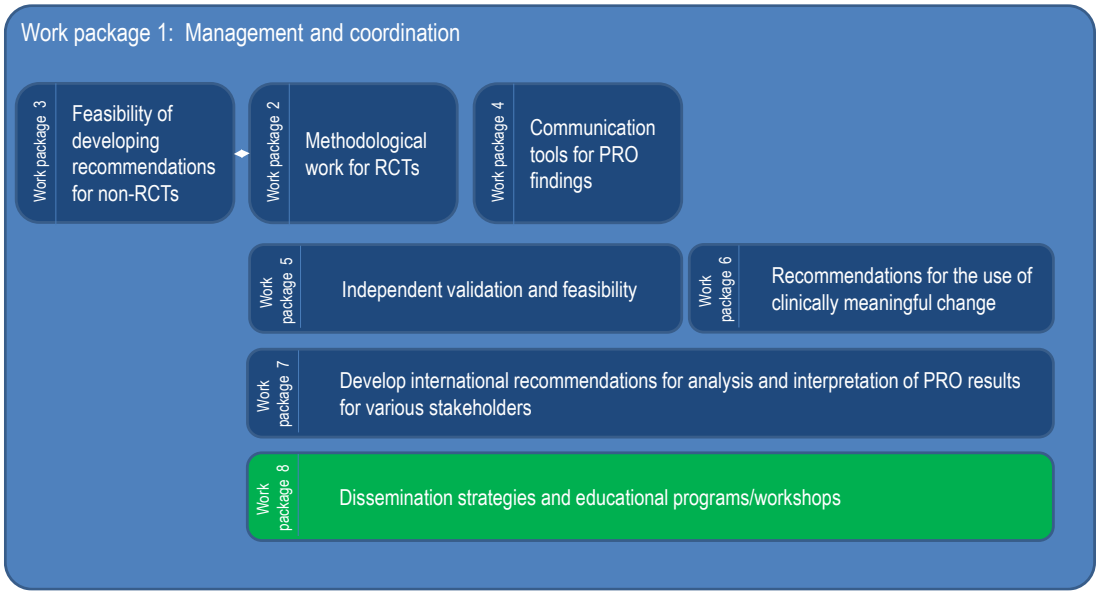
Suggested architecture of the full proposal

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 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.

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.

The below architecture for the full proposal is a suggestion. The architecture of the full proposal should be designed to fulfil the objectives and key deliverables within the scope of this call topic.



Work package 1 – Management and coordination

The goals of this work package are to:

- establish a working governance structure, ensuring that various key stakeholder groups are well-represented;
- establish an internal communication structure to ensure the harmonisation of work across project teams;
- organise project-wide meetings;
- budget administration;
- communicate with the project team and relevant external stakeholders to ensure alignment and uptake of recommendations;
- establish an independent ethics advisory task force to help ensure all ethical aspects of the research and their recommendations conform to H2020 standards and norms.

Industry contribution:

- project leader;
- coordination across different work packages (including overall scientific and strategic oversight).

Expected applicant consortium contribution:

- project coordinator;
- professional project management expertise (daily operational support with project meetings, reporting and internal communication), see also section on applicant consortium.

Work package 2 – Methodological work for cancer RCTs

The goals of this work package are to:

- identify and update valid PRO objectives for RCTs and translate them into estimands;
- set criteria to help design the timing and frequency of PRO assessments (including baseline), balancing the need for assessments at clinically relevant time points and reducing patient burden;

- set criteria to assess quality of collected PRO data, ensuring that there is enough good quality data available to respond to the PRO objectives;
- set criteria to identify appropriate statistical methods to analyse PRO data;
- match appropriate statistical methods to valid PRO objectives;
- provide recommendations on the interpretation of PRO findings based on the trial objectives, data quality and statistical methods used;
- ensure close communication with work package 3, ensuring that the key criteria needed for drawing conclusions of PRO findings are correctly represented in the communication tools for various stakeholders;
- provide guidelines on when an update of the methodological work would be needed.

Work package 3 – Feasibility of developing recommendations for non-RCTs, with single-arm studies as a case study

The goals of this work package are to:

- identify case studies in which PROs were used in single-arm cancer clinical trial studies;
- identify the needs of various stakeholders to assess PROs in single-arm studies;
- identify valid PRO objectives that can be addressed by single-arm studies and set criteria needed to evaluate PROs in single-arm studies as well as criteria to evaluate the potential bias for single arm, open-label studies;
- evaluate aspects of RCT recommendations that can be adapted to single-arm studies.

It is recommended that this work package be closely linked to the main work for RCTs to ensure uniformity in terminology and synergy of complementary ideas.

Work package 4 – Communication tools for PRO findings from cancer clinical trials

The goals of this work package are to:

- set criteria and general guidelines for presentation and visualisation of PRO findings from cancer RCTs – this should be done in close collaboration with work package 2;
- identify the needs of various stakeholders (regulatory, HTA, patients, clinicians, journals, academics) on how they want the PRO results from clinical trials to be reported;
- produce templates for the visualisation and presentation of PRO findings that would fit the needs of different stakeholders;
- provide guidelines on when an update of the communication tools would be needed.

Work package 5 – Independent validation and feasibility of methodological work and communication tools

The goals of this work package are to:

- manage and coordinate the use of research data including legal and ethical considerations;
- identify case studies for this project:
    - retrospective cancer clinical trials data with HRQOL/PRO assessment;
    - prospective cancer clinical trials that will include a HRQOL/PRO assessment.
- using the case studies, implement and assess the feasibility of the approaches from work packages 2–3, including identifying gaps and recommending solutions for each of these gaps;
- provide guidelines on when additional validation and feasibility checks would be needed.

Work package 6 – Develop international recommendations for the terminology and definitions of clinical meaningful change in cancer clinical trials

The goals of this work package are to:

- identify best practices to develop clinical meaningful change research objectives for the most commonly used HRQOL/PRO instruments in cancer trials that clearly differentiate group level differences and individual level differences. Recommendations need to recognise the wide-range of terminologies currently used in the literature which include, but are not limited to minimum clinically important differences (MCIDs) / minimum important differences (MIDs) and responder thresholds;
- investigate whether these approaches can be generalised to emerging new instruments and item banks;
- Develop final recommendations for the use of terminology and definitions in HRQOL/PRO assessments in cancer trials that are agreed by the main stakeholders including regulatory agencies, HTA agencies as well as ESMO and ASCO;
- Provide guidelines on when updates of recommendations would be needed.

Work package 7 – Develop international recommendations for analysis and interpretation of PRO results for various stakeholders

The goals of this work package are to:

- identify a procedure to ensure recommendations are based on a consensus and that key experts and stakeholder groups are well-represented;
- ensure that the needs of the various stakeholders are considered in the final recommendations including feedback from representatives of leading patient advocacy organisations;
- provide final recommendations based on the combined results from work packages 2, 4, 5 and 6 for the various stakeholders to:
    - support the development of industry guidelines for the design, analysis and interpretation of PRO findings from cancer clinical trials;
    - support development of regulatory and HTA guidelines for the design, analysis and interpretation of PRO findings from cancer clinical trials;
    - support ESMO and ASCO guidelines on assessing clinical benefit.
- provide guidelines on when an update of the recommendations would be needed.

Work package 8 – Dissemination strategies and educational programmes/workshops

The goals of this work package are to:

- provide a continuous dissemination and communication plan (including social media) to ensure that project results are communicated to both internal and external stakeholders;
- provide an educational tool based on the work from the different work packages for different stakeholders;
- ensure close collaboration with all Work package leaders to ensure proper and efficient dissemination of results from the various work packages are disseminated;
- a feasibility plan and guidelines for updating relevant PRO objectives, statistical methods and handling of missing PRO data based on future developments in methodology and changes in the cancer clinical trial environment. The goal is to have a live document that will be available for all stakeholders in the long-term;
- provide educational tools and develop required knowledge to assess, analyse and interpret PRO data in cancer clinical trials for all relevant stakeholders including patients.

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[3] Zikos, E., et al., *Health-related quality of life in small-cell lung cancer: a systematic review on reporting of methods and clinical issues in randomised controlled trials.* Lancet Oncol, 2014. **15**(2): p. e78-89.

[4] Koller, M., et al., *Translation procedures for standardised quality of life questionnaires: The European Organisation for Research and Treatment of Cancer (EORTC) approach.* Eur J Cancer, 2007. **43**(12): p. 1810-20.

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Topic 5: Accelerating research & innovation for advanced therapy medicinal products

Topic details

Topic code	IMI2-2019-18-05
Action type	Research and Innovation Action (RIA)
Submission and evaluation process	2 stages

Specific challenges to be addressed

Curative or near curative therapies for rare and orphan diseases have been a long-held desire for many in the biomedical research and development arena, including patients. Rare diseases are often very severe, genetically driven illnesses with high morbidity and mortality that place a large burden on families of patients and healthcare systems. Though these diseases are relatively rare, the costs of medicines are high, even for many that provide only marginal benefit. Gene therapy and cell therapy provide an opportunity for a curative, single treatment for many of these devastating diseases, eliminating the need for chronic treatment. This topic aims to accelerate the research and development of advanced therapy medicinal products (ATMPs) by filling gaps in our knowledge base in, and tools for, gene and cell therapy. This will provide medicines developers and regulators with the information they need to more swiftly move these potentially transformative medicines forward so that they can benefit patients in need.

The goal of gene and cell therapy is to provide, with a single treatment, sustained therapeutic levels of transgene expression or cell activity, with potentially life long duration. This can be achieved employing classical viral vectors and cells transformed using viral vectors, or by novel means based on non-viral technologies, cellular encapsulation, etc. [1][2] Challenges to this goal are immunological and non-immunological factors that may impact persistent expression and eligibility for treatment. [3] [4] [5] Patients with pre-existing neutralising antibodies (nAbs) due to natural viral infections that result in cross-reactive antibodies, or perhaps due to prior exposure to viral gene therapy capsids, are typically excluded from treatment [6][7]. After treatment, patients are also excluded from redosing due to the high titer nAb response to the dose of vector [8]. Additionally, some patients, when treated systemically with gene/cell therapy, mount an immune response to transduced cells that have resulted, in some instances, in damage to targeted liver and muscle tissues [9]. Molecular features, such as concatemer state and integration mechanism, may influence persistence which in turn may be impacted by age and tissue target [10]. Consequently, the potential dilutional impact of tissue division and growth on persistence requires deeper molecular understanding to develop efficacious and long-lasting gene/cell therapy products.

Conventional medicinal product characterisation, clinical safety/efficacy, and regulatory requirements already pose challenges to developing treatments for rare monogenic diseases. These challenges are amplified for gene and cell therapies due to knowledge gaps in our understanding of these ATMPs for viral or non-viral approaches. By addressing these existing knowledge gaps, we hope to accelerate and improve the feasibility of product development and decrease development time and costs to bring effective new advanced therapies to patients. For many aspects of ATMP biology and safety, regulatory agencies have to consider theoretical concerns in this emerging field, largely due to a lack of supporting data and evidence. This can be a major burden for the efficient development of ATMPs.

To streamline regulatory requirements, it would be highly beneficial to continue to build a greater understanding and evidence-base of essential performance parameters needed in the field of gene/cell therapy. Those parameters include: persistence of gene/cell therapy efficacy; potential for re-treatment; the impact of host immunology on patient inclusion and product efficacy; the molecular characterisation of common features of each delivery modality and the possibility of creating 'plug-and-play' platform approaches; and the delineation of the right balance between the standards for product characterisation, safety, and the value of the medicine.

Need and opportunity for public-private collaborative research

Collaboration between public and private partners is essential and will enable directed research to solve the challenges posed in this topic; provide learning opportunities for the next generation of scientists in the ATMP area; and foster open scientific interaction in the public domain. Much of the expertise in gene and cell therapy lies in academia, however, clear data important for ATMP development regarding host responses, persistence of efficacy, redosing, and safety is lacking. Working together in this public-private partnership, combining the deep expertise and innovation in vector design, adeno-associated virus (AAV) biology, cell biology, and immunology that resides in academia, with growing industry ATMP development expertise and data emerging from clinical trials, as well as regulatory expertise lying in regulatory agencies, will create synergies that will enable the building of a data-driven consensus around ATMP biology, immunology, and persistence. This in turn will support the development of guidance by regulators on the development of ATMPs.

Scope

The main focus of this topic is to develop a product characterisation framework and methodologies that are limited to the pre-competitive space. Though much of the work will be to understand aspects of gene or cell therapy in general without a particular disease focus, there may be some work that utilises disease models to accomplish the appropriate characterisation. The disease focus will be on non-oncological, monogenic rare diseases. Therefore, this topic intends to utilise both therapeutically relevant systems, as well as model systems that rely on the use of marker transgenes. In order to develop such a framework, there is a need for a coordinated and substantive effort to acquire and analyse the currently available data and then design preclinical and clinical studies to fill the knowledge gaps. This information will help to address gene/cell therapy risks and also guide product developers and regulators to determine and implement an appropriate and effective characterisation framework to enable efficient and safe development of gene/cell therapies.

The main objectives of the topic, intended to address existing knowledge/data and tools gaps focused on viral-mediated gene therapy and cell therapy, are to:

1. develop better, standardised models for predicting product immunogenicity in humans;
2. build our understanding of gene/cell therapy drug metabolism inside a host and explore any loss of efficacy (persistence), particularly with non-integrating viral vectors or cell therapy;
3. understand the clinical factors around pre-existing immunity limiting patient access to ATMP therapy, and adaptive immune responses affecting product safety, efficacy and persistence, including for integrating vectors-based therapies;
4. engage regulators to ensure that the models and data generated through the funded action will provide the necessary information to support regulatory filings and to address regulatory and safety concerns.

Specifically, the scope of the project is expected to address the following points:

- Develop better, standardised models for predicting ATMP immunogenicity in humans: some aspects of human immunology are not adequately captured in current pre-clinical models. Improving these models would enable development of regimens for modulating humoral and cellular immune responses to cell and gene/cell therapy products. Specific areas to address for each ATMP type are:
    - Gene Therapy: predictive tools for testing immunogenic properties of viral or non-viral delivery systems, or their combinations, to enable the design of vectors that will evade immune recognition in order to: 1) treat a higher proportion of patients; 2) achieve successful transfer of the therapeutic gene protein to the target cells; and 3) mitigate the risk of immunotoxicity on target organs.
    - Somatic cell therapy: expand on current paradigms in transplantation immunology using innovative *ex vivo* and *in vivo* systems. Aim for a deeper understanding of mechanisms that influence acute immune responses at the site of implantation and how the nature of disease affects long term immunity against therapies using autologous, allogeneic, or xenogeneic non-germline cells.

- Tissue engineered products: develop new models to investigate the innate and adaptive immunity that contribute to the inflammatory response to natural and artificial scaffold structures.

- Characterise host, tissue, and target cell metabolic responses to gene/cell therapy vectors and transgene products to understand persistence: As many rare genetic diseases manifest in childhood and the cells in the target organs in young patients continue to divide, it is of interest to characterise the dilution of the therapeutic effect, which is most likely different depending whether viral or non-viral vectors may have been used. Specifically, it needs to be investigated whether there is a dilution effect in children and/or in specific organs or tissues. It is of interest to characterise the metabolism of the vector genome in different cell types to understand whether rates of degradation, episomal maintenance, or integration vary from cell to cell, and to define strategies to improve the persistence of vector genomes. Prospective paediatric samples may be obtained to explore how the levels of expression are affected by growth.
- Understand the clinical factors around pre-existing immunity limiting patient access to ATMP therapy, and adaptive immune responses to gene/cell therapy drug substance and product: in order to address challenges of potential immunologic barriers, the funded action is expected to:
    - develop novel protocols for the modulation of immune responses to capsids, cells, and transgene products, or induction of tolerance to expressed transgene products, as well as components and materials used for non-viral vectors, or induction of tolerance to expressed transgene products;
    - develop cohesive metrics for immunological characterisation applicable in gene and cell therapies, for both patient inclusion and post-treatment monitoring phases;
    - develop standardised pathways for the characterisation of pre-existing immunity to gene/cell therapy products, including memory T-cells and neutralising and binding antibodies;
    - establish a geographically diverse prospective biobank from treated and untreated donors with matching cell, serum, and plasma samples to enable the evaluation of the pre-existing and adaptive immunity, assuring that appropriate informed consent is obtained, and privacy maintained;
    - develop and standardise innovative characterisation/functional assessment methods for gene/cell therapy drug substances and products;
    - evaluate the safety risk of administering viral and non-viral vectors in the presence of humoral and/or cellular immunity;
    - evaluate novel approaches to allow for vector re-administration in order to re-establish therapeutic protein levels.
- Engage with regulators to ensure the results of the funded action will support regulatory filings and address regulatory and safety concerns: specifically, concerns such as insertional mutagenesis/carcinogenicity, vector shedding, viral clearance, material biocompatibility, degradability, safety, and persistence, need to be addressed. In addition, since large amounts of data are generated across the field it is important to explore, jointly with regulators, how to bring this information together in a meaningful way to potentially address issues across a class of products. It is expected that the models and data generated through this funded action will provide the information needed to support the alignment efforts and the development of harmonised guidance through the International Council for Harmonisation (ICH), and optimise the risk-benefit of the ATMPs covered in this initiative. Therefore, the funded action is expected to:
    - gather examples, develop criteria and evaluate options to standardise differences in regulatory requirements across countries;
    - identify and address scientific gaps in current knowledge and generate new evidence/systems to support the development of improved standards for safety, while enabling accelerated product development;
    - identify mechanisms for unified regulatory approaches to key issues in gene/cell therapy development, including environmental assessments, the characterisation of replication competent viruses, viral clearance/shedding, patient screening criteria, and long-term follow up for persistence and delayed adverse events;

- explore, and where feasible, enable developments that effectively and appropriately allow new developments to benefit from and utilise existing regulatory analogies or frameworks;
- conduct a comprehensive review of clinical data and prepare a package (or white paper) aimed at evaluating the theoretical risk of insertional mutagenesis and formulating recommendations to the regulatory agencies.

Expected key deliverables

The expected key deliverables to be achieved during the duration of the funded project are:

- in vitro, ex vivo, and animal models with better translatability of the immune responses to gene/cell therapy; once in place these models should be sustainable;
- deep understanding of how host cells and tissues metabolise gene/cell drug products and how this affects persistence;
- identification of immunogenicity hurdles and potential solutions, for de-immunisation or immunomodulation that can improve overall efficacy and minimise patient risk along with a standardised vector characterisation platform;
- during the first year, the consortium is expected to develop a plan for which issues will benefit the most from a comprehensive database(s) to address regulatory needs;
- a sustainable, beyond the timeframe of the action, prospective biobank of samples obtained with appropriate informed consent and privacy from healthy volunteers and patients treated with gene or cell therapies;
- optimised and validated specific methods and models, which will increase regulatory acceptance and thereby facilitate the regulatory success of future gene therapy projects;
- standardised methods and gold standards to better characterise the products, such as potency, dose, and various quality properties.

Expected impact

Primarily, the action funded under this topic will fill gaps in our knowledge base around gene/cell therapy host responses which will allow for the data-driven development of a product characterisation framework to aid researchers, developers and regulators to more rapidly move effective and safe gene/cell therapies forward.

Understanding the host immune responses and the prevalence of pre-existing immunity in humans in broad geographic areas will be instrumental for finding the best immune-modulating regimens, thus increasing patient access to advanced medicines. Understanding the determinants of immunogenicity may enable re-dosing with gene/cell therapy products, while studying the mechanisms of persistence will help to define the optimal age for gene/cell therapy intervention.

Finally, joint efforts across pharma, biotech, academia, and regulatory functions will inform patient inclusion criteria, limit sub-therapeutic dosing, and define the impact of the pre-existing and adaptive immunity on the efficacy and persistence of gene/cell therapy. This broad understanding will help to focus industry resources on actual (not theoretical) risks and will facilitate the harmonisation of regulatory requirements. These improvements will, in turn, enable accelerated cures for rare diseases via a defined regulatory framework.

Applicants should also 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 and funding.

Industry Consortium

- Pfizer (lead)
- Astellas
- Bayer
- Janssen
- Lonza
- Novartis
- NovoNordisk
- Sanofi
- Spark Therapeutics
- Takeda
- Viscofan

The industry consortium will contribute the following expertise and assets:

- Anonymised existing or prospective data from clinical trial cohorts from industry partners supplementing the academic cohorts;
- Personnel with in-depth knowledge in the fields of experimental and clinical immunology, cell and *in vivo* biology, virology/vectorology, histology, genetic toxicology, omics, chemistry manufacturing and controls (CMC) analysis, medical affairs, statistics, regulatory, bioethics, epidemiology and non-clinical development;
- Know-how and means to support the establishment of the federated database including legal advice, setting up the database, and making analysis feasible, accessible and sustainable over time;
- A cash contribution, detailed in the indicative budget section, for supporting the derivation of a novel methodology for the modulation of immune responses to capsid and transgene products, and autologous or allogeneic gene-modified or unmodified transplanted tissues and cells. Similarly, develop protocols to induce tolerance to expressed transgene products or to autologous or allogeneic gene-modified or unmodified cell products. Also, for the design of improved hybrid vectors that have a higher efficiency of concatermerisation, and full-length vector genome reconstitution, and to accommodate transgenes that exceed the packaging capacity of AAV. Details will be decided by the full consortium at stage 2 when preparing the full proposal.

Indicative duration of the action

The indicative duration of the action is 60 months.

Indicative budget

The indicative in-kind and financial contribution from EFPIA partners is EUR 15 752 500.

This contribution comprises an indicative EFPIA in-kind contribution of EUR 14 500 000. The total financial contribution available from the EFPIA partners for activities in relation to the objectives of this action is EUR 1 252 500. The allocation of the EUR 1 252 500 financial contribution will be decided by the full consortium at stage 2 when preparing the full proposal.

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

The financial contribution from IMI2 JU is a maximum of EUR 11 773 000.

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. Therefore, the consortium should mobilise all relevant expertise, skillsets and stakeholders to implement proposed activities in order to achieve the objectives of the topic. This may require mobilising, as appropriate the following:

- groups with experience and relevant skillsets in research and development and regulation of gene and cell therapy ATMPs, including experience with AAV biology and production, drug delivery, tissue engineering, predictive organ-tissue models, *in silico* simulation, cell biology and production, cell biology and production, transgenic animals, immunology, virology/vectorology, histology, omics, and *in vivo* experimentation;
- state-of-the-art experience and expertise in the establishment of databases, data harmonisation, database management and data security;
- experience in translating and conveying data for regulatory purposes;
- access to clinical cohorts and samples from patients dosed with gene or cell therapies.

The applicant consortium should engage with relevant patient organisations and incorporate patient input and active involvement into the project.

In addition to academic groups, relevant small and medium-sized enterprises (SMEs) are encouraged to participate in the applicant consortium.

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

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 provided above and 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.

The consortium is expected to have a strategy for the translation of the relevant project outputs into regulatory and clinical practice. A plan for interactions with regulatory agencies / health technology assessment bodies with relevant milestones and resources allocated should be proposed.

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. The architecture of the full proposal should be designed to fulfil the objectives and key deliverables within the scope of this proposal.

Work package 1 – Management, coordination, and dissemination

The goals of this work package will be as follows:

- general oversight and coordination;
- dissemination of research results and data amongst the consortium and into the public domain via workshops, publications, and presentations.

Expected applicant consortium contribution: project management including coordination of work package deliverables, periodic reporting and budget administration, dissemination of scientific results.

EFPIA consortium contribution: overall leadership of project goals, communication, and dissemination of project results.

Work package 2 – Develop better, standardised models for predicting product immunogenicity in humans

The goals of this work package will be as follows:

- develop models for evaluation of the impact of pre-existing immunity or of adaptive immunity on product efficacy and/or safety using *in vitro* cell-based assays and/or various routes of administration in relevant animal species, in combination with immune phenotyping methods (e.g. IgG profiling on protein arrays and multiplexed targeted protein profiling for innate and adaptive immunity key factors);
- expand on current mechanistic understanding of innate immune response during initial ATMP exposure, the priming of the adaptive response, and the maturation of the immune response against targeted tissues that can provide a basis for the rational design of immunomodulation protocols that can be evaluated in work package 4 for clinical application.

Expected applicant consortium contribution:

- innovative models of interactions between immune cells and target cells;
- next generation technologies for assessing immunity in those models across a breadth of immune cells and receptor repertoires;
- identification of cellular and/or protein biomarkers that could contribute to potential stratification of patients in order to reduce the risk of deleterious immune responses;
- application of the most relevant models (e.g. humanised rodent, non-human primates) already in use or under development;
- strategies for investigating the role of patient genotype on the anti-ATMP response, with consideration for how to mitigate for small numbers of subjects;
- translation of mechanisms learned from *in vivo* and *in vitro* systems to clinical approaches for immunomodulation or immunosuppression of the response to ATMP (in alignment with WP4);
- using the knowledge and patient samples from work package 4, develop methods to determine the predictive value of *in vivo* and *in vitro* models.

EFPIA consortium contribution:

- selection and prioritisation of models with an emphasis on those dealing with cellular immune responses;
- models, including *in vitro* and *in vivo* for evaluation;
- expertise in cellular immune assays including assay development, validation, and data interpretation;
- scientific input for innovative approaches to develop additional models;

- data management / bioinformatics infrastructure.

Work package 3 – Build our understanding of gene/cell therapy drug metabolism inside a host and explore any loss of efficacy (persistence), particularly with non-integrating viral or non-viral vectors or cell therapy

The goals of this work package will be as follows:

- WP3 broadly aims to understand the molecular stability and metabolism of AAV-derived therapeutic vector genomes, both wild type size and oversized, in target tissues, as well as that of non-viral approaches. This provides a unique opportunity to identify the main advantages and disadvantages of both systems, and to integrate their use to modulate response for a more effective and safe treatment. Characterisation of the effect of vector genome dilution, as a consequence of target tissue growth, and thereby therapeutic potential, will be addressed. Additionally, characterisation of the metabolism of the therapeutic vector genome in different cell types will be explored. Finally, strategies to improve the persistence of vector genomes as well as to generate hybrid vectors to accommodate transgenes that exceed the packaging capacity of AAV or non-viral counterparts will be investigated.
- identify strategies to mitigate loss of vector genomes and explore the idea of stabilising non-integrated AAV or non-viral vector genomes within the target cell;
- characterise the metabolism of the vector genome in different cell types to understand whether rates of degradation, episomal maintenance, or integration vary from cell to cell;
- design improved hybrid vectors that have a higher efficiency of concatermerisation, and full-length vector genome reconstitution.

Expected applicant consortium contribution:

- small and large animal models of disease. Focus on central nervous system (CNS), muscle and liver;
- development and utilisation of technology to measure vector copy number, vector genomic structure, monomers, concatemers, epigenetic status of vectors over time in relevant tissues;
- development of and utilisation of tools to analyse the cellular milieu to identify factors which govern vector stability and genomic structure.

EFPIA consortium contribution:

- disease relevant animal models;
- registry of results from pre-clinical data;
- prospective paediatric patient data and samples.

Work package 4 – Understand the clinical factors around pre-existing immunity limiting patient access to ATMP therapy, and adaptive immune responses affecting product safety, efficacy and persistence, including for integrating vector-based therapies

Objective: Perform translational and clinical research with the intent of standardising existing analytics based on biobanked samples, and the development of the new immune-modulatory protocols.

The goals of this work package will be as follows:

- establish a geographically diverse prospective biobank from treated and untreated donors with matching cell, serum, and plasma samples to enable evaluation of the pre-existing and adaptive immunity; assure that informed consent is properly obtained and strict adherence to privacy is maintained;
- develop standardised pathways for characterisation of pre-existing immunity to gene/cell therapy products, including macrophages, natural killer (NK) cells, memory T-cells, and other cells, and neutralising and binding antibodies;

- develop cohesive metrics for immunological characterisation, applicable for gene and cell therapies, for both patient inclusion and post-treatment monitoring;
- standardise assays for use in safety and persistence biomarker monitoring;
- develop and standardise innovative characterisation methods for the analytical evaluation of therapeutic drug substance to assess function, potency, quality, and microbiological load;
- establish novel protocols for the modulation of immune responses to capsid and transgene products, non-viral vector components, and autologous or allogeneic gene-modified or unmodified transplanted tissues and cells. Similarly, develop protocols to induce tolerance to expressed transgene products or to autologous or allogeneic gene-modified or unmodified cell products;
- evaluate safety risks when dosing viral gene therapies in the background of humoral and/or cellular immunity against the virus.

Expected applicant consortium contribution:

- organisation of biobanking from healthy volunteers and recipients of cell and gene therapies from broad geographic areas;
- characterisation of the relationship between binding antibodies and neutralising antibodies. Define the interplay between humoral immunity, complement activation, and cell-mediated immunity. Establish models to allow prediction of innate immune responses. Discern mechanisms of activation of memory T-cell and NK-cell activation and their role in loss of transgene expression. Expand knowledge regarding non-antibody mediated neutralisation;
- define metrics for immunological characterisation, applicable for gene and cell therapies, for both patient inclusion and post-treatment monitoring;
- develop and standardise of innovative characterisation methods for the analytical evaluation of therapeutic drug substance (characterisation/functional assessments of potency, quality, and microbiological load), especially for products used in cell-based assays and *in vivo* models from WP2;
- use animal models developed in WP2 to access modulatory/intervention strategies. The learning and knowledge derived from WP2 will be used to inform this goal of developing novel animal models and establishing novel protocols for the modulation of immune responses to capsid and transgene or cell products, as well as induction of tolerance to vectors, expressed transgene products, and autologous or allogeneic gene modified or unmodified cell products;
- conduct nonclinical studies to identify potential adverse events when dosing the presence of viral vector immunity.

EFPIA consortium contribution:

- prospective data from clinical samples;
- alidation of immunosuppressive protocols in animal models.

Work package 5 – Engage regulators to ensure that the models and data generated through this project will provide the necessary information to support regulatory filings and to address regulatory and safety concerns

The goals of this work package will be as follows:

- enable data-driven regulatory requirements. Identify and address scientific gaps in current knowledge in order to generate improved and data-driven standards for safety while enabling accelerated product development. This may include key issues in gene/cell therapy development, including environmental assessments, characterisation of replication competent virus, viral clearance in the manufacturing process, genetically-modified organism (GMO) issues such as viral shedding after administration, patient screening criteria, and long-term follow up for persistence and delayed adverse events such as those related to insertional mutagenesis. This will enable a move from theoretical concerns to data driven risk assessments that can be used to update regulatory requirements;

- identify opportunities for regulatory harmonisation. Conduct a landscape analysis of regulatory requirements and gather examples, develop criteria and evaluate options to standardise differences in regulatory requirements across countries. Utilise project efforts to guide the development of ATMP specific ICH guidelines;
- perform a landscape analysis of regulatory requirements and identify differences in existing requirements in order to develop recommendations for regulatory harmonisation;
- publish a white paper(s) outlining the results of the data analysis and regulatory landscape analysis with specific recommendations for updated regulatory requirements;
- participation in meetings or workshops with regulators to drive acceptance of consortium-recommended regulatory harmonisation;
- create predictable regulatory pathways for innovation. Work with regulators to develop a more predictable path to implementing innovative systems and technology such as the qualification of novel biomarkers (e.g. transgene expression) for use as endpoints in clinical trials, the use of standardised manufacturing platforms, improved comparability strategies and the utilisation of predictive immunogenicity strategies, engage with health authorities, take advantage of regulatory tools and procedures such as Innovation Task Force (ITF); the European Medicines Agency (EMA) (including the committee on Advanced Therapies) scientific advice (SA) and qualification advice as well as national scientific advice.

Expected applicant consortium contribution:

- based on the plan generated, develop a prospective database where non-competitive data can be collected such as replication competent virus testing, vector shedding, and long-term follow up. The database should be set up to ensure patient confidentiality and protect competitive corporate intelligence. Compile data and perform cross-sectional analysis to determine actual experience related to the unique risks of cell and gene therapy to enable a move from theoretical to data-driven recommendations for regulatory requirements.

EFPIA consortium contribution:

- share non-competitive data related to regulatory requirements such as replication competent virus testing, vector shedding, and long-term follow up to allow for a cross-sectional analysis of data to enable a move from theoretical to data-driven recommendations for regulatory requirements;
- contribute to landscape analysis of regulatory requirements and develop recommendations for regulatory harmonisation.

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Topic 6: Supporting the development of engineered T cells

Topic details

Topic code	IMI2-2019-18-06
Action type	Research and Innovation Action (RIA)
Submission and evaluation process	2 stages

Specific challenges to be addressed

Despite recent advances in cancer treatment, the unmet medical need in oncology remains high. In the European region, cancer causes 20 % of deaths and is the second cause of death after cardiovascular diseases, with 3 million new cases and 1.7 million deaths each year. Cancer is also a leading cause of death in children and adolescents around the world [1].

Engineered T cells, including chimeric antigen receptor (CAR) and T-cell receptor (TCR) engineered T cells, combine features of cell therapy, gene therapy, and immunotherapy. With two distinct autologous CD19 CAR-T-cell therapies approved by Food and Drug Administration (FDA) in 2017 and European Medicines Agency (EMA) in 2018, cellular immunotherapy is emerging as a promising new treatment modality for a broad range of cancers. Allogeneic approaches are also being developed in order to overcome some of the challenges of autologous therapies. Although CAR-T-cell therapies have been largely successful in treating haematological malignancies, they have not been as effective in treating solid tumours [2].

These complex medicinal products have the unique ability to self-amplify and persist in treated patients. Their translation from basic and pre-clinical research to clinical trials therefore poses many challenges that slow down clinical development [3]. They have been associated with unique specific acute toxicities, with cytokine release syndrome (CRS) and neurotoxicity being two most commonly observed toxicities. Animal models often fail to predict toxicities associated with the use of CAR-T cells and frequently overestimate the efficacy of the treatment, as they do not accurately reflect the tumour microenvironment (TME). Although new mouse models have recently been shown to be able to recapitulate human efficacy, CRS and neurotoxicity of anti-CD19 CAR-T cells, efforts are still needed to optimise and extend these models to other tumour antigens [2][3][4][5][6][7]. The use of alternative, non-genotoxic and non-myeloablative methods to induce lymphodepletion or better schemes for administrating existing regimens may also contribute to decreased toxicity associated with engineered T cells [3][8].

The need for good manufacturing practice (GMP)-compliant manufacturing may also constitute a specific hurdle in the timely translation to the clinic. Issues may be related to the consistency of clinical batches, the characterisation of the final product, and definition and evaluation of specific potency criteria. The standardisation of analytical procedures would improve comparability of CAR-T-cell batches and of clinical results from patients included in different trials and/or receiving CAR-T cells from different origins [3].

In addition, there is an increasing consensus among stakeholders that patient engagement is critical to fostering patient access to innovative therapeutic solutions and delivering better patient health outcomes.

Need and opportunity for public-private collaborative research

Advancing therapeutic T-cell engineering requires progress on multiple fronts, including the development of pre-clinical models with high translational potential to predict the safety and efficacy of engineered T cells; the optimisation of lymphodepletion regimens and better understanding of their impact on the safety and efficacy of engineered T cells; and better control and industrialisation of cell manufacturing sciences and regulatory compliance in the development of engineered T cells.

To address such a wide range of complex issues, there is a need for strong cooperation amongst industry, biotechs, academia, patient organisations, policymakers, public health experts and regulators, bringing their diverse expertise in the following fields:

- development of relevant pre-clinical models of safety and efficacy;
- standardisation of analytical methods;
- collection of public or existing biological and clinical data related to engineered T cells and lymphodepletion;
- modelling (pharmacokinetics/pharmacodynamics (PK/PD) / lymphodepletion);
- biostatistics;
- quality profiles and regulatory aspects of the manufacturing of engineered T-cell therapies;
- patient access to treatments.

This Call topic also represents an opportunity to enable patients to better reflect their perspectives in CAR and TCR engineered T-cell development. Through meaningful patient engagement, all stakeholders involved in the development of medicinal products should benefit from each other's expertise and develop a better understanding of how diverse viewpoints can positively drive better medicines.

Scope

The overall objective of the call topic is to support the development of autologous and allogeneic engineered T-cell therapies, including CAR and TCR engineered T cells. The Call topic addresses both haematological and solid tumours.

The objectives of the Call topic are:

- Optimisation of existing pre-clinical models, tools and pharmacodynamic (PD) markers to predict toxicities associated with engineered T cells, such as CRS, neurotoxicity, graft-versus-host disease (GvHD), off-target toxicity of gene editing technologies and insertional mutagenesis linked to the use of viruses. Development of new models and tools if needed.
- Optimisation of existing pre-clinical models, tools and PD markers to predict the efficacy of engineered T cells, including assessment of anti-tumour activity, pharmacokinetics (PK) (trafficking, homing, infiltration, persistence) and PK/PD modelling. Development of new models and tools, such as patient derived xenograft (PDXs) models relevant for the heterogeneity of the tumour and potentially to study the role of TME in the case of haematological malignancies, as well as syngeneic models.
- Comparison of existing analytical methods used pre- and post-infusion of engineered T cells to define gold standard methods. New technologies may also be developed. Methods related to quantification and characterisation of engineered T cells pre-infusion (product), assessment of the clinical fate of engineered T cells (homing, persistence, expansion and efficacy), immune monitoring of patients (kinetics of reconstitution of immunity, profiling of engineered T cells and immune response to engineered T cells), and assessment of off-target toxicity of gene editing technologies and insertional mutagenesis linked to the use of viruses, both pre- and/or post-infusion.
- Creation of a database with historical existing clinical and biological data from patients receiving lymphodepleting regimens. Modelling of the impact of the different lymphodepleting agents on immune cells. Development of relevant *in vivo* models to evaluate new lymphodepleting regimens.
- Expert discussion on the implementation of regulatory guidance for engineered T cells, including European Pharmacopoeia and GMP for advanced therapy medicinal products (ATMPs) to define standard product profiles.

- Determination of the role(s) of patients in each research and development (R&D) stage. Development of patient-friendly communication tools to improve the patient journey, and materials to facilitate the training of healthcare providers (HCPs) on engineered T-cells to better respond to patient needs.
- Expert discussion on the best path to ensure broad patient access to engineered T cells.

Expected key deliverables

The expected key deliverables will be public and should include the following:

- Deliverable 1: Pre-clinical models, pharmacodynamic markers or tools with high translational potential to predict safety of engineered T cells, including CRS, neurotoxicity, GvHD and off-target toxicity of gene editing technologies and insertional mutagenesis linked to the use of viruses.
- Deliverable 2: Pre-clinical models, pharmacodynamic markers or tools with high translational potential to predict efficacy of engineered T cells and the role of TME, including anti-tumour activity and pharmacokinetics (trafficking, homing, infiltration, persistence) and PK/PD modelling.
- Deliverable 3: Gold standard analytical methods used both pre- and post-infusion of engineered T cells, including quantification and characterisation of engineered T cells pre-infusion (product), assessment of clinical fate of engineered T cells (homing, persistence, expansion and efficacy/potency), immune monitoring of patients (kinetics of reconstitution of immunity, profiling and immune response to engineered T cells) and assessment of genetic modifications pre- and/or post-infusion (off-target toxicity of gene editing technologies and insertional mutagenesis linked to the use of viruses).
- Deliverable 4: Optimised lymphodepletion regimens for engineered T cells, based on analysis/modelling of existing lymphodepletion data and development of new *in vivo* models to evaluate the impact of different lymphodepleting regimens on engineered T-cell expansion and persistence.
- Deliverable 5: Customised European Pharmacopoeia and GMP for ATMPs for engineered T cells to achieve standard product profiles.
- Deliverable 6: Communication tools for patients and healthcare providers on engineered T cells, including tools to increase the capability of patients to understand and contribute to R&D of engineered T cells, reliable and patient-friendly communication tools to improve the patient journey and to raise awareness among HCPs of patient concerns.
- Deliverable 7: White paper on equitable patient access to engineered T cells across EU member states.

Expected impact

Applicants should describe how the outputs of the project will contribute to the following impacts and include baseline, targets and metrics to measure impact.

At the levels of the R&D process, regulatory pathways and/or health technology assessment (HTA), patient access processes, clinical and healthcare practices, the impact would be:

- the development of safer and more effective engineered T-cell therapies;
- the opportunity to compare data generated from standardised analytical methods;
- increased industrial competitiveness;
- broader patient access to engineered T-cell therapies;
- an increased awareness among HCPs of patients' concerns.

In addition, patients will benefit from the project outputs by:

- better understanding the mode of action and procedures of their treatment;

- having a better consideration of their perspectives by being a key actor of the whole R&D process;
- facilitated interactions with HCPs.

For society, the impact could be:

- a better understanding of these complex therapies by the public (complexity, efficacy and safety);
- a better understanding and evidence-based development of engineered T cells might also contribute to decreasing their cost;
- improved synergies between industry, small and medium-sized enterprises (SMEs) and academic organisations.

Applicants should indicate how their proposal will impact 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.

In particular, potential applicants should consider any relevant work/result from other IMI2 JU projects as far as these are accessible (e.g. IMI2 - Call 15, topic 4: Emerging translational safety technologies and tools for interrogating human immuno-biology).

Industry consortium

The industry consortium is composed of the following EFPIA companies and partners:

- Servier (lead)
- Bayer
- Janssen Pharmaceutica
- Nanostring
- Takeda.

In addition, the industry consortium includes the following IMI2 JU Associated partners:

- European Hematology Association (EHA).

The industry consortium will contribute with major assets such as:

- clinical experience of engineered T-cell therapies;
- chemistry manufacturing and controls (CMC);
- regulatory issues;
- communication & dissemination;
- education & training;
- managing expert boards;
- standardisation of monitoring tools/systems.

Moreover, the industry will also contribute with the following expertise:

- project management;
- legal/compliance;
- modelling;
- IT support;
- biostatistics;
- bioinformatics;
- molecular biology;
- cell biology;
- market access;
- patient advocacy / engagement.

Indicative duration of the action

The indicative duration of the action is 60 months.

Indicative budget

The indicative in-kind and financial contribution from EFPIA partners [and IMI 2 JU Associated Partner] is EUR 8 733 000.

This contribution comprises an indicative EFPIA in-kind contribution of EUR 6 158 000 and an indicative IMI2 JU Associated Partner in kind contribution of EUR 2 575 000.

Due to the global nature of the participating industry partners and IMI2 JU Associated Partner, 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 8 733 000.

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.

This may require mobilising, as appropriate, the following expertise and contribution with a major focus on:

- development of pre-clinical models and tools (*in vitro* and *in vivo* models);
- cellular and molecular biology;
- pharmacometrics (PK-PD) / modelling;
- regulatory / HTA;
- health economics.

In their short proposal, applicants should demonstrate that they have access to historical data, as well as existing cohorts, of patients treated with engineered T-cells and/or receiving lymphodepletion regimens.

Patient organisations will be considered as key partners of the funded action. They will contribute by collecting concerns and needs from patients and caregivers, actively taking part in the R&D process and ensuring patient-friendly communication.

Moreover, the applicant will also contribute with the following expertise:

- imaging;
- immunology;
- CMC/GMP;
- clinicians with lymphodepletion experience;
- project management.

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 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.

The architecture outlined below for the full proposal is a suggestion. The architecture of the full proposal should be designed to fulfil the objectives and key deliverables within the scope of this proposal.

In the short proposal, 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.

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

Description:

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

Proposed objectives:

- define work expectations of different work streams, deliverables, dates and activities, and review progress regarding adherence to budget, timelines and quality (by all consortium members);
- ensure legal and contractual management;

- ensure the set-up of a joint governance structure (by all consortium members);
- quality assessment of documents;
- define project interdependencies, stakeholders and risks;
- ensure ethics management;
- ensure appropriate communication within the consortium;
- ensure dissemination of the project progress and outcomes (project website, conference talks, social media presence, a project newsletter, abstracts, publications);
- communication to the wider public.

Industry contribution: will include co-leading this work package, including management of legal, contractual, ethical and quality assessment aspects, and contributing to the definition of the dissemination and communication plan.

Expected applicant consortium contribution: will co-lead in partnership with industry consortium and work together to define the governance structure and full work plan, will participate in communication and data dissemination.

Work package 2 – Patient involvement

Description:

The goal of this work package is to guarantee that the patient perspective is taken into account.

Proposed objectives:

- promote engagement of patients all along the R&D process;
- ensure adequate communication on engineered T-cell therapies to patients and their family/caregivers;
- ensure that HCPs are sensitised to patient needs;
- propose solutions for equitable patient access to engineered T cells;
- propose solutions to guarantee broad patient access to engineered T cells.

Industry contribution: communication and dissemination, education and training, collaboration with patient advocacy groups, management of expert boards, knowledge of pharmaceutical life-cycle process, market access.

Expected applicant consortium contribution: patient expertise, communication, national health care authorities and societies, health economics.

Work package 3 – Models and tools to assess safety of engineered T cells

Description:

The goal of this work package is to optimise and/or develop pre-clinical models, pharmacodynamic markers and tools with high translational potential to predict the safety of engineered T-cell therapies.

Proposed objectives:

- map existing pre-clinical models relevant to assess the safety of engineered T cells and identify gaps/needs;
- optimise existing models and develop new models or tools to better predict the safety of engineered T cells;
- preclinical models may include models of CRS, neurotoxicity, GvHD;

- off-target toxicity of gene editing technologies and insertional mutagenesis linked to the use of viruses could also be addressed.

Industry contribution: clinical knowledge of engineered T-cell safety concerns, preclinical models.

Expected applicant consortium contribution: pre-clinical models including *in vivo* and *in vitro* models, technologies, immunology.

Work package 4 – Models and tools to assess efficacy of engineered T cells

Description:

The goal of this work package is to optimise or develop models, pharmacodynamic markers and tools with high translational potential to predict the efficacy of engineered T-cell therapies.

Proposed objectives:

- map existing pre-clinical models relevant to assess the efficacy of engineered T cells and identify gaps/needs;
- optimise existing *in vitro* and *in vivo* models and develop new models and biomarkers to better predict efficacy of engineered T cells; the development of new models relevant to studying the impact of tumour heterogeneity and the role of TME would be a plus;
- Efficacy parameters may include the assessment of anti-tumour activity (predictive *in vitro* assays and *in vivo* models) for haematological and solid tumours or any other relevant biomarkers for engineered T cell expansion and persistence;
- the development of tools and models to assess the pharmacokinetics of engineered T cells, including trafficking, homing, infiltration and persistence could also be included (imaging, molecular biology);
- immunocompetent mouse models to study epitope spreading;
- PK/PD modelling based on the data generated in the different models (and if possible, on clinical data available).

Industry contribution: expertise in modelling, *in vivo* and *in vitro* preclinical models, PK.

Expected Applicant consortium contribution: pre-clinical models including *in vivo* and *in vitro* models, imaging, PK data, cell therapy PK/PD modelling.

Work package 5 – Gold standard analytical methods used both pre- and post-infusion of engineered T cells

Description:

The goal of this work package is to optimise/develop analytical methods and define gold standard analytical methods to be used for both pre- and post-infusion of engineered T cells.

Proposed objectives:

- Analytical methods to be standardised may include but are not limited to the assessment/quantification of engineered T cells, rapid and less product consuming assays to assess microbiological safety, assessment of the clinical fate of engineered T cells (homing, persistence and efficacy), immune monitoring of patients (kinetics of reconstitution of immunity, profiling of engineered T cells and immune response to engineered T cells) and assessment of off-target toxicity of gene editing technologies and insertional mutagenesis linked to the use of viruses.
- Technologies such as quantitative polymerase chain reaction (qPCR), antibody – and targeted protein (via protein-microarrays, and targeted multiplex bead-arrays), flow cytometry, next generation sequencing (NGS), single cell analysis, replication competent lentivirus (RCL), omics may be addressed.

- Development of new tools and methods if needed.
- Technologies could be first developed using relevant *in vitro* models and could then be validated on batches/clinical samples that may be provided by clinicians treating patients with commercially available or academic engineered T cells.

Industry contribution: CMC, translational, analytics, bioinformatics, standardisation of monitoring tools/systems.

Expected applicant consortium contribution: Molecular biology, imaging, immunology.

Work package 6 – Development of optimal lymphodepletion /conditioning regimen

Description:

The goal of this work package is to develop lymphodepletion models to better understand the impact of lymphodepletion on engineered T-cell safety and efficacy, and to optimise or develop new conditioning regimens.

Proposed objectives:

- collect existing biological and clinical data from patients who received lymphodepleting regimens in the context of allograft transplantation and/or CAR-T cells and create an easy to access database by pooling collected data;
- meta-analysis of the data;
- modelling of the different existing lymphodepleting regimens (based on collected data);
- development of relevant *in vivo* models (preclinical) to optimise or test new conditioning regimens and address key questions.

Industry contribution: clinical expertise, *in vivo* and *in vitro* preclinical models, PK, bioinformatics and IT.

Expected applicant consortium contribution: historical data, literature review, bioinformatics, modelling, pre-clinical models, immunology.

Work package 7 – Data integration

Description:

The goal of this work package is to create and manage an IT platform where all data collected and generated in the context of the consortium will be stored.

Proposed objectives:

- develop an IT platform to allow easy, compliant and secured access to all the data collected or generated during the project to all members of the consortium and will be made publically accessible at the latest stage;
- consider the sustainability of the platform.

Industry contribution: IT platform accessible to all members of the consortium.

Expected applicant consortium contribution: IT and suitable data sets.

Work package 8 – Customised European Pharmacopoeia and GMP for ATMPs for engineered T cells

Description:

The goal of this work package is to address some regulatory and quality aspects of manufacturing in order to achieve a standard product profile.

Proposed objectives:

- biological and pharmaceutical characterisation of the products (i.e. potency activity, release assays, appearance);
- critical quality attributes;
- quality control, including safety tests such as RCL;
- recommendations on the practical implementation of GMP for ATMPs and pharmaceutical requirements;
- some technologies developed in WP5 could also be applicable for this work package.

Industry contribution: CMC, regulatory.

Expected applicant consortium contribution: Academic Centres, contract development and manufacturing organisations (CDMOs) or any other organisations that are interacting with regulatory health authorities, CDMOs, with access to academic centres.

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[8] Turtle CJ, Riddell SR, Maloney DG. CD19-Targeted chimeric antigen receptor-modified T-cell immunotherapy for B-cell malignancies. Clin Pharmacol Ther. 2016 Sep;100(3):252-8.

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 18 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-IMI2-2019-18-two-stage**
Type of actions	**Research and Innovation Action (RIA)**
Publication Date	**26 June 2019**
Stage 1 Submission start date	**26 June 2019**
Stage 1 Submission deadline	**26 September 2019 (17:00:00 Brussels time)**
Stage 2 Submission deadline	**26 March 2020 (17:00:00 Brussels time)**

Indicative Budget

From EFPIA companies and IMI2 JU Associated Partners	EUR 85 871 760
From the IMI2 JU	EUR 74 866 000

Call Topics

IMI2-2019-18-01 Central repository of digital pathology slides to support the development of artificial intelligence tools	The indicative contribution from EFPIA companies is EUR 37 771 260 The financial contribution from IMI2 JU is a maximum of EUR 32 320 000	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.

IMI2-2019-18-02 Health Outcomes Observatories - empower patients with tools to measure their outcomes in a standardised manner creating transparency of health outcomes	The indicative contribution from EFPIA companies is EUR 10 385 000 The indicative IMI2 JU Associated Partners contribution is EUR 1 050 000 The financial contribution from IMI2 JU is a maximum of EUR 10 478 000	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.
IMI2-2019-18-03 Improving patient access, understanding and adherence to healthcare information: an integrated digital health information project	The indicative contribution from EFPIA companies is EUR 9 070 000 The indicative IMI2 JU Associated Partners contribution is EUR 210 000 The financial contribution from IMI2 JU is a maximum of EUR 9 280 000	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.
IMI2-2019-18-04 Establishing international standards in the analysis of patient reported outcomes and health-related quality of life data in cancer clinical trials	The indicative contribution from EFPIA companies is EUR 2 900 000 The financial contribution from IMI2 JU is a maximum of EUR 2 282 000	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.
IMI2-2019-18-05 Accelerating research & innovation for advanced therapy medicinal products	The indicative contribution from EFPIA companies is EUR 15 752 500 The financial contribution from IMI2 JU is a maximum of EUR 11 773 000	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.
IMI2-2019-18-06 Supporting the development of engineered T cells	The indicative contribution from EFPIA companies is EUR 6 158 000 The indicative IMI2 JU Associated Partners contribution is EUR 2 575 000 The financial contribution from IMI2 JU is a maximum of EUR 8 733 000	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.

The following general conditions shall apply to the IMI2 JU Calls for Proposals. They are based on the General Annexes to the Horizon 2020 Work Programme 2018-2020[28].

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

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;
- at 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[31] applies:

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

[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"

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.

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 with the following additions:

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.

The Award criteria, scores and threshold for IMI2 JU Call 18 are as follows:

Type of action	Excellence *The following aspects will be taken into account, to the extent that the proposed work corresponds to the topic description in the call for proposals and referred to in the IMI2 JU annual work plan:*	Impact *The following aspects will be taken into account:*	Quality and efficiency of the implementation *The following aspects will be taken into account:*
RIA 1st stage Evaluation IMI2 JU Call 18	▪ Level to which all the objectives of the Call topic text are addressed; ▪ Soundness of the concept and credibility of the proposed methodology; ▪ Extent that the proposed work is beyond the state of the art and demonstrates innovation potential; ▪ Appropriate consideration of interdisciplinary approaches and use of stakeholder knowledge.	▪ Demonstration of how the outputs of the project will contribute to each of the expected impacts mentioned in the relevant Call topic text; ▪ Outline of how the project plans to leverage the public-private partnership model to achieve greater impact on innovation within research and development, regulatory, clinical and healthcare practices, as relevant; ▪ Impacts on competitiveness and growth of companies including SMEs; ▪ Quality of the proposed outline to: ○ Disseminate, exploit and sustain the project results; ○ Manage research data; ○ Communicate the project activities to relevant target audiences.	▪ Quality and effectiveness of the work plan outline, including extent to which the resources assigned to work packages are in line with their objectives and deliverables; ▪ Appropriateness of the outline management structures and procedures; ▪ Appropriateness of the allocation of tasks, ensuring that all participants have a valid role and adequate resources in the project to fulfil that role; ▪ Complementarity of the participants and extent to which the consortium as whole brings together the necessary expertise; ▪ Strategy to create a successful partnership with the industry consortium as mentioned in the Call topic text.

Type of action	Excellence *The following aspects will be taken into account, to the extent that the proposed work corresponds to the topic description in the Call for proposals and referred to in the IMI2 JU annual work plan and, for two stage procedures, is consistent with the stage 1 proposal:*	Impact *The following aspects will be taken into account:*	Quality and efficiency of the implementation *The following aspects will be taken into account:*
RIA 2nd stage Evaluation IMI2 JU Call 18	▪ Level to which all the objectives of the Call topic text are addressed; ▪ Soundness of the concept and credibility of the proposed methodology; ▪ Extent that the proposed work is beyond the state of the art and demonstrates innovation potential; ▪ Appropriate consideration of interdisciplinary approaches and use of stakeholder knowledge.	▪ Demonstration of how the outputs of the project will contribute to each of the expected impacts mentioned in the relevant Call topic text; ▪ Demonstration of how the project plans to leverage the public-private partnership model to achieve greater impact on innovation within R&D, regulatory, clinical and healthcare practices, as relevant; ▪ Impacts on competitiveness and growth of companies including SMEs; ▪ Quality and effectiveness of the proposed measures to: ○ Disseminate, exploit and sustain the project results; ○ Manage research data; ○ Communicate the project activities to relevant target audiences.	▪ Quality and effectiveness of the work plan, including extent to which the resources assigned to work packages are in line with their objectives and deliverables; ▪ Appropriateness of the management structures and procedures, including management of risk and innovation; ▪ Appropriateness of the allocation of tasks, ensuring that all participants have a valid role and adequate resources in the project to fulfil that role; ▪ Complementarity of the participants and extent to which the consortium as whole brings together the necessary expertise; ▪ Clearly defined contribution and effective integration of the industrial partners to the project.

The scheme above is applicable to a proposal in a two-stage submission procedure under IMI2 JU Call 18. 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.

Under the IMI2 JU Call 18, for the evaluation of proposals under a two-stage submission procedure, at both stages (Stage 1 and Stage 2):

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

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

The full evaluation procedure is described in the IMI2 JU Manual for submission, evaluation and grant award in line with the Horizon 2020 Rules for Participation.[32]

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

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

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

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

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

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

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

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

INDICATIVE TIMETABLE FOR EVALUATION AND GRANT AGREEMENT

	Information on the outcome of the evaluation (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.

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 online, before the call deadline, by the coordinator via the Submission Service section of the relevant topic page available under Funding & tender opportunities – Single Electronic Data Interchange Area (SEDIA).

No other means of submission will be accepted.

OTHERS

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

http://ec.europa.eu/research/participants/data/ref/h2020/other/legal/templ/h2020_tmpl-clinical-studies_2018-2020_en.pdf

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

Ethical issues should be duly addressed in each submitted proposal to ensure that the proposed activities comply with ethical principles and relevant national, Union and international legislation. Any proposal that contravenes

ethical principles or which does not fulfil the conditions set out in the H2020 Rules for Participation, or in the IMI2 JU Call for proposals shall not be selected. [34]

In order to ensure excellence in data and knowledge management consortia will be requested to Disseminate scientific publications on the basis of open access[35] (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.

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

Applicants intending to submit a proposal in response to the IMI2 JU Calls should also read the topic text, the IMI2 JU Manual for submission, evaluation and grant award, and other relevant documents[36] (e.g. IMI2 JU model Grant Agreement).

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

LIST OF ACCRONYMS

Acronym	Meaning
AAV	Adeno-associated virus
AI	Artificial Intelligence
API	Application Programming Interface
ASCO	American Society of Clinical Oncology
ATMPs	Advanced Therapy Medicinal Products
CAR	Chimeric Antigen Receptor
CMC	Chemistry Manufacturing and Controls
CNS	Central Nervous System
CONSORT	Consolidated Standards of Reporting Trials
C-PATH	Critical Path Institute
CROs	Contract Research Organisations
CRS	Cytokine Release Syndrome
DMP	Data Management Plan
EC	European Commission
EFPIA	European Federation of Pharmaceutical Industries and Associations
EHR	Electronic Health Record
EMA	European Medicines Agency
eMC	electronic Medicines Compendium
EORTC	European Organisation for Research and Treatment of Cancer
ePI	electronic Product Information
ESMO	European Society for Medical Oncology
EU	European Union
FASS	Farmacevtiska specialiteter i Sverige
FDA	Food and Drug Administration
GDPR	General Data Protection Regulation
GLP	Good Laboratory Practice
H2020	Horizon 2020
HEMs	Health Educational Materials
HMA	Heads of Medicines Agencies
HRQOL	Health-Related Quality of Life
IBD	Inflammatory Bowel Disease
ICD	International Classification of Diseases
ICH	International Council for Harmonisation
ICHOM	International Consortium for Health Outcomes Measurement
IDMP	Identification of Medicinal Products
IMI2 JU	Innovative Medicines Initiative 2 Joint Undertaking
INHAND	International Harmonization of Nomenclature and Diagnostic Criteria
ISOQOL	International Society for Quality of Life Research
ISPOR	International Society for Pharmacoeconomics and Outcomes Research
IT	Information Technology
ITF	Innovation Task Force
MCID	Minimum clinically important difference
MID	Minimum important differences
nAbs	neutralizing antibodies
NGS	Next Generation Sequencing
NHP	Non-human primates
NK	Natural killer
OHDSI	Observational Health Data Sciences and Informatics
OMOP CDM	Observational Medical Outcomes Partnership Common Data Model

Acronym	Meaning
PD	Pharmacodynamics
PFS	Progression-free survival
PK	Pharmacokinetics
PRO	Patient-Reported Outcome
QoL	Quality of life
qPCR	quantitative Polymerase Chain Reaction
R&D	Research& Development
RCL	Replication Competent Lentivirus
RCTs	Randomized controlled trials
RIA	Research and Innovation Action
RIs	Research Infrastructures
RR	Response rate
SA	Scientific Advice
SEND	Standardization for Exchange of Nonclinical Data
SISAQOL	Setting International Standards in Analysing Patient-Reported Outcomes and Quality of Life Endpoints Data
SMEs	Small and Medium-sized Enterprises
SPIRIT	Standard Protocol Items: Recommendations for Interventional Trials
SRA	Strategic Research Agenda
TCR	T Cell Receptor
WHO	World Health Organisation
WP	Work package