Topic: Innovations to accelerate vaccine development and manufacture

All information regarding future IMI Call topics is indicative and subject to change. Final information about future IMI Calls will be communicated after approval by the IMI Governing Board.

Topic details

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

Specific challenges to be addressed by public-private collaborative research

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

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

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

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

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

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

Next-generation in vitro systems (i.e. organoids and other self-organised *in-vitro*–derived tissue culture systems that exhibit human organ functionality) and assays related to them, have the potential to model and evaluate host-pathogen interactions in the mucosa; the tissue in which the majority of pathogens enter the human body [30]. Some of these in vitro systems utilise human induced pluripotent stem (iPS) cells, allowing the potential to evaluate human pathogens with consideration to particular predispositions in the donor [30]. Also, in vitro systems and assays are needed to phase out animal models [48].

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

Scope

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

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

Subtopic 1: systems-immunology platform for model development

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

- Immune responses to vaccines and pathogens and how those responses are affected by predisposition;
- Antigen and pathogen features most likely to induce protective immunity, and the anticipated immune responses to those features;
- Emerging medical needs (via AI systems) such as infectious disease outbreaks, and the associated required investment in vaccination development and implementation.

Subtopic 2: CHIMs

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

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

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

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

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

- At least one in vitro model should be included for each of the following mucosas: gastro-intestinal, respiratory and urovaginal.

- Pathogens of interest include influenza, RSV, C. difficile, Bordetella pertussis, Moraxella catarrhalis, nontypeable Haemophilus influenzae, Chlamydia trachomatis, Neisseria gonorrhoeae, herpes simplex virus, norovirus, Pseudomonas aeruginosa, ExPEC (extra-intestinal pathogenic Escherichia coli) and cytomegalovirus.[1]

Subtopic 4: in silico biomanufacturing

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

- Vaccine-product stability (drug substance/product);

- The parameters to maintain process robustness for unit-operation scale up or scale down, and for process transfer.

This will also include:

- Defining the new approach to working which integrates these models in the biomanufacturing regime;

- Initiating a dialogue with relevant regulatory authorities, that paves the way for future use of predictive stability and process scale-up modelling in chemistry, manufacturing, and control (CMC) dossiers for new and improved vaccines.

Subtopics and the Call process

The Call process has two stages.

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

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

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

In the event that no short proposal is over the threshold for one or two subtopics, stage 2 of the Call will still be initiated by the merger of the remaining consortia and the industry consortium. The overall IMI2 JU maximum financial contribution and the EFPIA in-kind contributions will be adapted accordingly, based upon the allocation provided under the section ‘Indicative budget’.

If no short proposal is selected for Subtopic 3, activities related to the overall coordination and project management (proposed work package (WP) 1, as well as the overall communication and dissemination activities (proposed WP6), will be preferentially transferred to the Subtopic 2 leader,

[1]Pathogens not of interest include: fungi, parasites, syphilis, *Acinetobacter*, *Enterococcus*, *Klebsiella pneumoniae*, *Mycoplasma pneumoniae*, *legionella*, enteroviruses, coxsackieviruses, adenovirus, bocavirus, Chikungunya/Zika, hantavirus, hepatitis viruses C and E, HIV-1, human herpesvirus 6 (HHV-6), MERS/SARS, parvovirus B19, and West-Nile virus

together with the amount of the relevant financial contribution identified for these activities under the section ‘Indicative budget’.

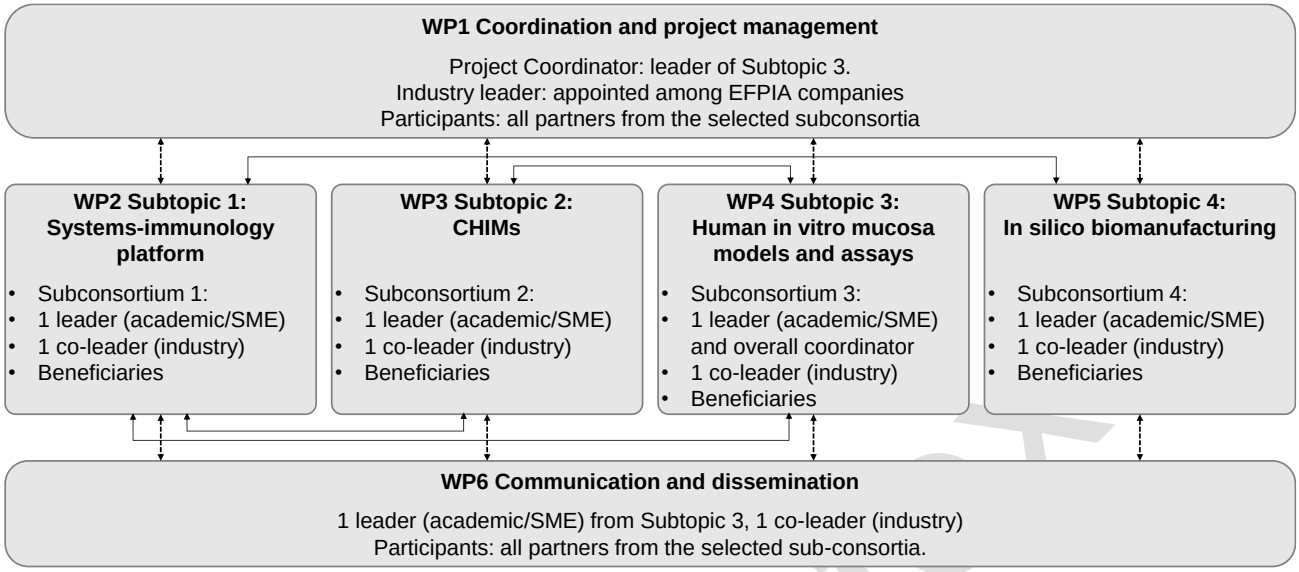

Figure 1: Consortia composition and interactions between suggested work packages (WPs), where each of the four subtopics will constitute distinct work packages.

Expected key deliverables

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

All subtopics (under the direction of the coordinator)

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

Subtopic 1

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

Subtopic 2

- New CHIMs that can accelerate the development of vaccines against, influenza, RSV and C. difficile;
  - Definition of clinical and laboratory (immunological and microbiological) endpoints for efficacy and/or safety, for use in larger field trials;
  - Improved or new comprehensive pre-screening methodologies that capture relevant predispositions;
  - Clear definitions of rescue therapy including appropriate infection control and contingency plans, and for using CHIMs in at-risk populations;
  - Identification of key parameters for CHIM standardisation, generalised adoption, and ultimately, regulatory acceptance.

Subtopic 3

- Prototype next-generation in vitro models (as defined above) and assays for clinically-relevant (surrogate) endpoints with guidelines for good-laboratory-practice (GLP) implementation including robust biostatistical plans for:
  - Evaluating the interactions between pathogens or their antigens with human gastro-intestinal, respiratory and urovaginal mucosas, ideally including interfaces with immune-system components such as innate-immune cells, antibodies or T cells;
  - Addressing immunological mechanisms during convalescence from naturally-acquired infection or disease;
  - Addressing heterogeneity within a particular human population;
  - Evaluating human samples from biobanks, including serum, stool, vomitus, or mucosal secretions from vaccine recipients or individuals infected with a relevant human pathogen.
- Scientific validation of selected prototype model(s) could be performed in a clinically-relevant setting, e.g. in parallel with a CHIM.

Subtopic 4

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

Expected impact

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

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

All subtopics

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

Subtopic 1

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

Subtopic 2

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

Subtopic 3

- The likelihood of the next-generation in vitro models and assays being incorporated into vaccine-development programmes on a wider scale, and how their potential versatilities and associated guidelines for use will support this incorporation;

- The potential for the next-generation in vitro models and assays to replace the use of animal testing in research, licensure and release of vaccines (with regulatory agency approval) in the future

Subtopic 4

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

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

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

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

- Manage research data including use of data standards;[2]
- Disseminate, exploit, and sustain the project results. This may involve engaging with suitable biological and medical sciences Research Infrastructures;[3]
- Communicate the project activities to relevant target audiences.

In addition, the following additional exploitation[4]/dissemination[5] obligations must be considered to maximise impact:

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

Potential synergies with existing Consortia

Synergies and complementarities should be considered with relevant national, European and non-European initiatives (including suitable biological and medical sciences research infrastructures**Error! Bookmark not defined.**) to incorporate, whenever possible, past achievements, available data and lessons learnt, thus avoiding unnecessary overlap, and duplication of efforts and funding.

Industry consortium

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

All subtopics:

- Expertise in vaccine development, manufacturing processes and global regulatory affairs;
- Industry leadership in IMI projects;

[2] Guidance on data management is available at http://ec.europa.eu/research/participants/docs/h2020-funding-guide/cross-cutting-issues/open-access-data-management/data-management_en.htm
[3] http://www.corbel-project.eu/about-corbel/research-infrastructures.html
[4] Article 28.1 (Additional exploitation obligations) of the IMI2 Grant Agreement will apply
[5] Article 29.1 (Additional dissemination obligations) of the IMI2 Grant Agreement will apply

- Establishing links with other major existing initiatives (e.g. Human Vaccines Project, HIC-Vac in the United Kingdom, IMI2-Periscope, IMI2-VITAL, IMI2-FLUCOP, IMI2-RESCEU, IMI2-iConsensus, etc.), and where possible, obtaining access to relevant databases or datasets.

Subtopic 1

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

Subtopic 2

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

Subtopic 3

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

- Contributions to sevices
  - Sanofi Pasteur intends to provide a contribution for investigating the use of next generation in vitro systems in evaluating vaccine safety.

Subtopic 4

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

Indicative duration of the action

The indicative duration of the action is 66 months.

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

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

Expertise and resources expected from applicants at stage 1

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

The stage 1 short proposals should include suggestions for creating a full-proposal architecture for the subtopic. It should also recognise potential inter-subtopic interactions within the project.

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

Subtopic 1

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

- Communication and dissemination skills;
- Business sustainability plans.

Subtopic 2

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

It may also require mobilising, as appropriate, the following resources: clinical infrastructures for inpatients, data on previous CHIM activities with specific pathogens, existing ethical and regulatory frameworks.

Subtopic 3

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

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

Subtopic 4

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

- Communication and dissemination skills;
- Business sustainability plans;
- The size of the consortium should be proportionate to the objectives of the topic while ensuring its manageability.

SMEs

- Suitable SMEs could be considered in the four subtopics for the following activities:
- Back-end and front-end IT infrastructure construction for in silico platforms;
- Manufacture (and associated optimisation) of challenge pathogens for CHIMs;
- Design/production of monitoring devices for biomanufacturing;
- Project management activities.

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

In their stage-1 proposals applicants should:

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

Suggested architecture

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

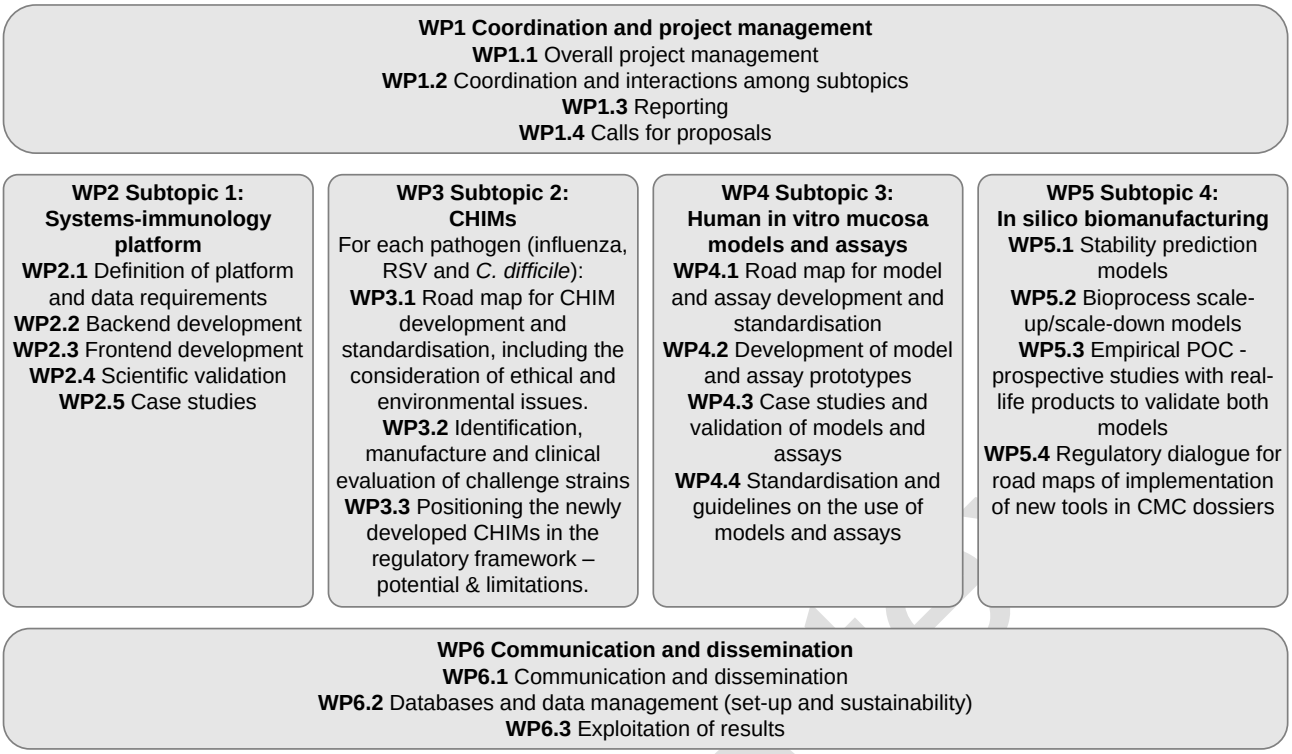

Figure 2: The project could be composed of two horizontal work packages (WPs) for project management and communication and four subtopics, each comprising several workstreams.

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

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

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

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

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

Data Management

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

Dissemination, exploitation and sustainability of results

In their stage 2 proposal, applicants must provide a draft plan for dissemination and the exploitation, including sustainability of results. A full plan as a distinct deliverable must be delivered within the first 6 months of the project[7], and updated during the project lifetime and could include identification of:

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

Sufficient resources should be foreseen for activities related to dissemination and exploitation, including the plan for the sustainability of the project results. This may involve engaging with suitable biological and medical sciences Research Infrastructures (RIs).[8]

Communication

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

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