innovative health initiative

IHI

4th Call for proposals

Two-stage call

COCIR efpia EuropaBio MedTech Europe from diagnosis to cure Vaccines Europe

Co-funded by the European Union

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Introduction

The Innovative Health Initiative Joint Undertaking (IHI JU) is a partnership between the European Union and industry associations representing the sectors involved in healthcare, namely COCIR (medical imaging, radiotherapy, health ICT and electromedical industries); EFPIA, including Vaccines Europe (pharmaceutical industry and vaccine industry); EuropaBio (biotechnology industry); and MedTech Europe (medical technology industry).

IHI JU aims to pioneer a new, more integrated approach to health research and builds on the experience gained from the Innovative Medicine Initiative 2 Joint Undertaking (IMI2 JU).

IHI JU aims to translate health research and innovation into real benefits for patients and society, and ensure that Europe remains at the cutting edge of interdisciplinary, sustainable, patient-centric health research. Health research and care increasingly involve diverse sectors. By supporting projects that bring these sectors together, IHI JU will pave the way for a more integrated approach to health care, covering prevention, diagnosis, treatment, and disease management.

As current health challenges and threats are global, IHI JU should be open to participation by international academic, industrial and regulatory actors, in order to benefit from wider access to data and expertise, to respond to emerging health threats and to achieve the necessary societal impact, in particular improved health outcomes for Union citizens.

Topics overview

HORIZON-JU-IHI-2023-04-01-two-stage **Expanding translational knowledge in minipigs: a path to reduce and replace non-human primates in non-clinical safety assessment**	The maximum financial contribution from IHI JU is up to EUR 8 500 000. The indicative in-kind contribution from industry partners is EUR 8 910 000. The indicative in-kind contribution and financial from IHI JU contributing partners is EUR 492 000. The indicative in-kind contribution from industry partners may include in-kind contributions to additional activities (IKAA).	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.
HORIZON-JU-IHI-2023-04-02-two-stage **Patient-centric blood sample collection to enable decentralised clinical trials and improve access to healthcare**	The maximum financial contribution from IHI JU is up to EUR 4 500 000. The indicative in-kind and financial contribution from industry partners is EUR 3 574 000. The indicative in-kind contribution from IHI JU contributing partners is EUR 300 000. The indicative in-kind contribution from industry partners may include in-kind contributions to additional activities (IKAA).	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

HORIZON-JU-IHI-2023-04-03-two-stage **Inclusive clinical studies for equitable access to clinical research in Europe**	The maximum financial contribution from IHI up to EUR 33 000 000. The indicative in-kind contribution from industry partners is EUR 33 600 000. The indicative in-kind and financial contribution from IHI JU contributing partner is EUR 250 000. The indicative in-kind contribution from industry partners may include in-kind contributions to additional activities (IKAA).	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
HORIZON-JU-IHI-2023-04-04-two-stage **Establishing novel approaches to improve clinical trials for rare and ultra-rare diseases**	The maximum financial contribution from IHI is up to EUR 8 500 000. The indicative in-kind and financial contribution from industry partners is EUR 9 100 000. The indicative in-kind contribution from industry partners may include in-kind contributions to additional activities.	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
HORIZON-JU-IHI-2023-04-05-two-stage **Safe & Sustainable by Design (SSbD) packaging and single use device solutions for healthcare products**	The maximum financial contribution from IHI is up to EUR 8 300 000. The indicative in-kind and financial contribution from industry partners can go to EUR 8 300 000. The indicative in-kind contribution from industry partners may include in-kind contributions to additional activities (IKAA).	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

HORIZON-JU-IHI-2023-04-06-two-stage **Sustainable circular development and manufacturing of healthcare products and their quantitative environmental impact assessment**	The maximum financial contribution from IHI is up to EUR 20 550 000. The indicative in-kind and financial contribution from industry partners is EUR 20 550 000. The indicative in-kind contribution from industry partners may include in-kind contributions to additional activities (IKAA).	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

Call conditions for single stage and two-stage calls

**For Call 4 please refer to the conditions relevant to the two-stage call*

The submission deadline for short proposals (SPs) will be 8 November 2023, and the deadline for full proposals (FPs) will be 23 April 2024.

Scientific evaluation of the SPs under the two-stage call will be completed by 2023. Grant Agreement Preparation (GAP) will be completed within 3 months from the notification to applicants of the evaluation results of the full proposal, and maximum eight months from the final date of submission of the FPs, in line with the applicable time to grant (TTG).

Conditions of the calls and call management rules

For call management, IHI JU will utilise the EC IT infrastructure available under Funding & Tender opportunities - Single Electronic Data Interchange Area (SEDIA).

The General Annexes of the Horizon Europe Work Programme 2023-2024 shall apply *mutatis mutandis* to the calls for proposals covered by this Work Programme. In accordance with Article 5(2)(a) of the Council Regulation (EU) 2021/2085, in duly justified cases, derogations related to the specificities for IHI JU may be introduced in the relevant Work Programme. Where necessary, this will be done when the topic texts are identified in this Work Programme.

To maximise the efficiency of the calls management, IHI JU will continuously explore and implement simplifications and improve its processes while maintaining the highest standards of the evaluation process, in line with the applicable Horizon Europe rules.

All proposals must conform to the conditions set out in Regulation (EU) 2021/695 of the European Parliament and of the Council of 28 April 2021 establishing Horizon Europe – the Framework Programme for Research and Innovation, laying down its rules for participation and dissemination.

Any specificity for IHI JU is highlighted in the below sections.

General conditions relating to the IHI JU calls

ADMISSIBILITY CONDITIONS	**THE CONDITIONS ARE DESCRIBED IN GENERAL ANNEX A.**
Eligibility conditions	The conditions are described in General Annex B.
Financial and operational capacity and exclusion	General Annex C.
Award criteria	The criteria are described in General Annex D.
Documents	The documents are described in General Annex E.
Procedure	The procedure is described in General Annex F.

Standard admissibility conditions, pages limits and supporting documents

General Annex A ('Admissibility') to the Horizon Europe Work Programme 2023-2024 shall apply *mutatis mutandis* for the calls for proposals covered by this Work Programme.

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

- for a single-stage call, the limit for RIA full proposals is 50 pages;
- at stage 1 of a two-stage call, the limit for RIA short proposals is 20 pages;
- at stage 2 of a two-stage call, the limit for RIA full proposals is 50 pages.

Standard eligibility conditions

General Annex B to the Horizon Europe Work Programme 2023-2024 shall apply *mutatis mutandis* for the calls for proposals covered by this Work Programme unless otherwise provided in this Work Programme.

Per the above and by way of derogation from General Annex B of the Horizon Europe Work Programme 2023-2024:

According to Article 119 of the Council Regulation (EU) 2021/2085, for indirect actions selected under calls for proposals covered by this Work Programme:

- applicant consortia must ensure that at least 45% of the action's eligible costs and costs for additional activities related to the action are provided by contributions (IKOP, FC, IKAA) from private members which are members of IHI JU, their constituent or affiliated entities, and contributing partners;

- While the constituent or affiliated entities of the members other than the union of IHI JU can contribute any of those contribution types, contributing partners can only contribute IKOP and FC, not IKAA;

- further to the above, the applicant consortium must submit a self-declaration that the required percentage of 45% contributions will be provided;

- the eligibility condition above and self-declaration requirement do not apply to the first stage of a two-stage application;

- at project level, the maximum amount of non-EU IKOP is set to:

    - one hundred percent (100%) for IHI JU Call 4

    - Thirty percent (30%) for IHI JU Call 5[1]

This is justified as a means to ensure the achievement of project objectives based on Article 119(5) of Council Regulation (EU) 2021/2085, and to ensure full openess to non-EU IKOP in these calls[2].

Entities eligible for funding

In relation to the single stage calls for proposals covered by this Work Programme, the relevant provisions of the General Annex B to the Horizon Europe Work Programme 2023-2024 shall apply *mutatis mutandis*.

By way of derogation, in relation to the two-stage calls for proposals covered by this Work Programme, the following provisions shall apply:

- Legal entities identified in the topic text of the call for proposals shall not be eligible for funding from IHI JU. Nevertheless:

- These entities will be entitled to provide contributions as IHI JU members other than Union or contributing partners.

- Legal entities participating in indirect actions selected under this type of calls for proposals shall not be eligible for funding where:

    a. they are for-profit legal entities with an annual turnover of EUR 500 million or more;

    b. they are under the direct or indirect control of a legal entity described in point (a), or under the same direct or indirect control as a legal entity described in point (a);

    c. they are directly or indirectly controlling a legal entity referred to in point (a).

In line with Article 5(2)(a) (additional conditions in duly justified cases) and Article 119(3) (private contributions to amount of at least 45 % of an indirect action's eligible costs and costs of its related

[1] Even if this threshold of 30% is not intended as an eligibility condition *per se*, proposals recommeded for funding that will feature a non-EU IKOP amount higher than the 30% of IKOP, will be requested to remove the exceeding part. If this case, this non-EU IKOP reduction exercise will need to comply with eligibility criteria whereby at least 45% of the action's eligible costs and costs for additional activities related to the action are provided by contributions (IKOP, FC, IKAA) from private members which are members of IHI JU, their constituent or affiliated entities, and contributing partners.

[2] It has to be noted that, pursuant Article 119(4) of Council Regulation (EU) 2021/2085, at the level of the IHI JU programme, non-EU IKOP must not exceed 20% of in-kind contributions to operational costs provided by private members which are IHI JU members, their constituent or affiliated entities, and contributing partners. furthermore, at the level of the IHI JU programme, IKAA shall not constitute more than 40% of in-kind contributions provided by private members which are IHI JU members.

additional activities) of the Council Regulation (EU) 2021/2085, under two-stage submission procedures, the following additional condition applies:

- The applicants which are IHI JU members other than the Union, or their constituent entities and affiliated entities, and contributing partners and that are pre-identified in the topics – under the section 'Industry consortium' – of a call for proposals shall not apply at the first stage of the call. The applicant consortium selected at the first stage shall, in preparation for the proposal submission at the second stage , merge with the pre-identified industry consortium.

In addition, in line with Articles 11 and 119(1) and (3) of the Council Regulation (EU) 2021/2085, legal entities providing in kind contributions as constituent entities or affiliated entities of IHI JU private members or as contributing partners that are:

- Not eligible for funding in two-stage calls for proposals; or

- Not established in a country generally eligible for funding in accordance with Part B of the General Annexes to the Horizon Europe Work Programme 2023 – 2024,

May exceptionally sign the grant agreement.

This is subject to the following conditions:

- Their participation is considered essential for implementing the action by the granting authority; and

- They participate without requesting any funding.

The essentiality of non-EU legal entities for implementing the action shall be ascertained by the granting authority.

List of countries and applicable rules for funding

With reference to Article 23 of the Council Regulation (EU) 2021/2085, the eligibility of participants in a proposal submitted to a call for proposals for any of the topics in this Work Programme will take into account any application of Art 22(5) of the Horizon Europe Regulation triggered for topics from other Horizon Europe Work Programmes for proposals with similar scope.

Types of Action: specific provisions and funding rates

General Annex B ('Eligibility') to the Horizon Europe Work Programme 2023-2024 shall apply *mutatis mutandis* for the calls for proposals covered by this Work Programme.

Technology Readiness Levels (Trl)[3]

TRL definitions included in General Annex B ('Eligibility') to Horizon Europe Work Programme 2023-2024 shall apply *mutatis mutandis* for the calls for proposals covered by this Work Programme.

Evaluation rules

General Annex D ('Award Criteria') to the Horizon Europe Work Programme 2023-2024 shall apply *mutatis mutandis* for the calls for proposals covered by this Work Programme with the following additions: The relevant calls for proposals launched under this Work Programme shall specify whether the call for proposals is a single-stage or two-stage call, and the predefined submission deadline.

[3] The TRL is not utilised for IHI calls 4 and 5, however, it might be used in future IHI JU calls

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 type of action, as follows:

For all evaluated proposals, each criterion will be scored out of 5. Half marks may be given.

For the evaluation of proposals under both single-stage and two-stage submission procedures:

- the threshold for individual criteria will be 3;
- the overall threshold, applying to the sum of the three individual scores, will be 10;
- proposals that pass individual thresholds and the overall threshold will be considered for funding, within the limits of the available budget. Proposals that do not pass these thresholds will be rejected.

Under the single-stage evaluation process, evaluated proposals will be ranked in one single list. The highest ranked proposals, within the framework of the available budget, will be invited to prepare a Grant Agreement.

Under the two-stage evaluation procedure, and on the basis of the outcome of the first stage evaluation, the applicant consortium of the highest ranked short proposal (first stage) for each topic will be invited to discuss with the relevant industry consortium the feasibility of jointly developing a full proposal (second stage).

If the first-ranked consortium and industry consortium decide that the preparation of a joint full proposal is not feasible, they must formally notify IHI JU 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 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.

If the preliminary discussions with the higher ranked proposal and the industry consortium fail, the applicant consortia of the second and third-ranked short proposals (stage 1) for each topic may be invited by IHI JU, in priority order, for preliminary discussions with the industry consortium. The decision to invite lower-ranked consortia to enter into discussions with the industry consortium will take into account the content of the report from the joint report from the first-ranked consortium and industry consortium.

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, IHI JU may organise hearings with the applicants to:

1. clarify the proposals and help the panel establish their final assessment and scores, and/or
2. improve the experts’ understanding of the information presented

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.

The IHI JU evaluation procedure is confidential.

The members of the applicant consortia shall avoid taking any actions that could jeopardise confidentiality.

Following each evaluation stage, applicants will receive an ESR evaluation summary report) regarding their proposal.

Indicative timetable for evaluation and grant agreement preparation

Information on the outcome of the evaluation (single-stage, or first stage of a two-stage):

- Single-stage: Maximum 5 months from the submission deadline at the single-stage.
- Two-stage: Maximum 5 months from the submission deadline at the first stage.

Information on the outcome of the evaluation (second stage of a two stage):

- Maximum 5 months from the submission deadline at the second stage.

Indicative date for the signing of grant agreement:

- Single-stage: Maximum 8 months from the submission deadline.
- Two-stage: Maximum 8 months from the submission deadline at the second stage.

General Annex G ('Legal and Financial setup of the Grant Agreements') to the Horizon Europe Work Programme 2023-2024 shall apply *mutatis mutandis* for the calls for proposals covered by this Work Programme.

Budget flexibility

General Annex F to the Horizon Europe Work Programme 2023-2024 shall apply *mutatis mutandis* to the calls for proposals covered by this Work Programme.

Submission tool

Proposals in response to a topic of an IHI 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.

Proposals including clinical studies[4]

Under the single-stage submission procedures and for stage 2 of the two-stage submission procedures: Applicants envisaging including clinical studies must provide details of their clinical studies in the dedicated annex using the template provided in the submission system[5].

[4] Clinical study covers clinical studies/trials/investigations/cohorts and means, for the purpose of this document, any systematic prospective or retrospective collection and analysis of health data obtained from individual patients or healthy persons in order to address scientific questions related to the understanding, prevention, diagnosis, monitoring or treatment of a disease, mental illness, or physical condition. It includes but it is not limited to clinical studies as defined by Regulation 536/2014 (on medicinal products), clinical investigation and clinical evaluation as defined by Regulation 2017/745 (on medical devices), performance study and performance evaluation as defined by Regulation 2017/746 (on in vitro diagnostic medical devices).

[5] Template for providing essential information in proposals involving clinical studies - https://ec.europa.eu/info/funding-tenders/opportunities/docs/2021-2027/horizon/temp-form/af/information-on-clinical-studies_he_en.docx

Specific conditions on availability, accessibility and affordability (3a)

When the specific topic condition so requires, the following conditions shall apply:

- The participants must, during the lifetime of the project and for a period of four years after project end, use their best efforts to ensure that those products or services that are developed by any of the participants and are totally or partly based on the results of clinical studies performed as part of the activities of the selected project, will be broadly[6] available and accessible, at fair and reasonable conditions.

- In particular, and always to the extent permitted by applicable competition law:

  a. At the proposal stage[7], and as part of the Plan for the Dissemination, Exploitation, and Communication Activities ('PDECA') which forms part of the proposal, the applicant consortium must identify potential and expected project results that may be subject to the 3A conditions and broadly outline their strategy to achieve the above objectives.[8]

  b. At the project interim review stage, if relevant[9], the PDECA should be updated with a revised 3A strategy. This update should be based on the progress of the clinical studies conducted or to be conducted as part of the project and include any pertinent action to be implemented both during the project and over the four years after project end.

  c. At the end of the project, the PDECA should be updated, to provide the expected planning for further product development and (if already scheduled) product launch, within the timeframe of four years after the project end and in order to meet those objectives laid out under point 1 above.[10]

  d. Within 12 months from the project end date, and on a yearly basis thereafter for a period of 3 years (totalling four years from project end), a confidential report[11] must be submitted to IHI JU by the owner of the project result describing the status of the development of the product and of any other exploitation actions, planned or undertaken, concerning the products/services.

[6] This covers EU Member States and countries that are associated to Horizon Europe at the time of call opening.
[7] As mentioned, for those 3A specific projects, the 3A content in the PDECA will be checked during the evaluation stage. Omission/inadequate treatment of 3A would be identified as a shortcoming . The content however, once considered adequate, will not be utilised for positive scoring and will not contribute towards any evaluation criteria.
[8] Suggested components would be 1) Identification of planned clinical studies that might generate results for which the provisions are relevant; 2) Confirmation that the consortium members are aware of the provisions and will consider them accordingly. 3)Tentatively identifying markets/areas where the product/service could be be made affordable, accessible, available. These points could be checked at the evaluation stage.
[9] As discussed, this interim point allows a realistic appraisal of the 3A possibilities during the proejct lifetime, particularly as to the viability of specific expected 3A results.
[10] Per the Model Grant Agreement ('MGA') Article 16, the beneficiaries must complete the Results Ownership List ('ROL') which identifies each result generated in the project and the owner thereof. The ROL should inform on the relevant results for which owners implement the 3A strategy in the PDECA for the four years following the project.
[11] Cognizant of IP sensitivities, confidential info, and commercial realties, the IHI JU suggests that the confidential report PDECA could, if needed, be composed of two parts:

1. **A high-level abstract**, to be made publicly available (not containing confidential information), comprising:
a) Broad summary of the result's development to this point, including a detailed description of the result and the potential product or service that could incorporate or partly incorporate the result;
b) Broad description of expected downstream actions (including product and service applications);
c) broad assessment of expected impact of the above downstream actions towards ensuring Affordability, Availability, and Accessibility.
2. **A Confidential Annex** in which:
a) The owning beneficiary explains if the result is a product or service (or is expected to become one within 4 years) or not, and if yes, further confirms:
   i. The planned measures to be taken to effect the 3A obligations;
   ii. That the owning beneficiary will undertake all necessary actions to adhere to the 3A provisions to the best of its capacity;
   iii. That the owing beneficiary will keep the IHI JU updated on a yearly basis on the progress.

JU right to object to transfer/exclusive licensing

According to the Horizon Europe rules, and in order to protect Union interests, the right for IHI JU to object to transfers of ownership of results or to grants of an exclusive licence regarding results should apply to participants. Therefore, the provisions set out in General Annex G to the Horizon Europe Work Programme 2023-2024 on the right to object apply generally. It should be noted that in accordance with the Council Regulation (EU) 2021/2085 and the Horizon Europe model Grant Agreement, the right to object applies also to participants that have not received funding from IHI JU and for the periods set therein. In choosing whether to exercise the right to object, IHI JU will, on a case-by-case basis, make a reasoned decision in compliance with the legal basis.

Country specific eligibility rules

Following the Horizon Europe Programme Guide, participation in IHI JU indirect actions will be open but eligibility for funding will be however limited to legal entities established in an EU Member State, Associated Country or Low- and Middle-Income Countries (please consult the list in the Horizon Europe Programme Guide[12]).

Given the invasion of Ukraine by Russia and the involvement of Belarus, legal entities established in Russia, Belarus or in any occupied territory of Ukraine are not eligible to participate in any capacity. Exceptions may be granted on a case-by-case basis for justified reasons, such as for humanitarian purposes, civil society support or people-to-people contacts.

[12] https://ec.europa.eu/info/funding-tenders/opportunities/docs/2021-2027/horizon/guidance/programme-guide_horizon_en.pdf

Topic 1: Expanding translational knowledge in minipigs: a path to reduce and replace non-human primates in non-clinical safety assessment

Expected impacts to be achieved by this topic

EU legislation[13] makes it a legal obligation to replace, reduce and refine the use of animals in research (the '3Rs' principle), including a specific focus on restricting the use of the non-human primates (NHPs) unless scientifically justified. The development of *in vitro* models for human safety assessment is still challenging due to complex biological responses in various organ systems following drug treatment. Therefore, laboratory animals will still be requested in the safety testing of new therapeutics and innovative medical technologies until non-animal approaches have reached the necessary level of maturity and validation to ensure that only safe treatments reach patients, and that patients get timely access to the most innovative therapeutics.

A substantial amount of work has already been conducted to increase the scientific knowledge and understanding of the role of minipigs in toxicity testing[14] and the pig is often used e.g., in the toxicological evaluation of small molecules. Replacing NHPs with minipigs in the safety testing of new therapeutic modalities has been, however, more difficult, due to the lack of translational knowledge, but will be an important ethical step towards minimising the use of NHPs. New drug modalities are often designed to engage human targets with high specificity, which is the rationale for selecting NHPs in the safety testing of this kind of drug candidates. By expanding the translational knowledge in minipigs versus NHPs and humans, the scientific justification for selecting pigs as an alternative to NHPs can be improved.

The project funded under this topic adheres to the principles of the 3Rs by: i) closing the current translational knowledge gaps regarding minipigs versus NHPs and humans, offering the opportunity to replace NHPs with pigs, improve the reproducibility of pig studies, and advance the underlying knowledge of biological processes to facilitate the development of non-animal alternatives (reduce, refine and replace); ii) creating scientific and technological opportunities in animal housing facilities to collect, digitalise and generate more reproducible data in freely moving, undisturbed animals with the potential to reduce the total number of animals, and improve animal welfare and data quality (reduce, refine).

Closing the translational knowledge gap regarding minipigs versus NHPs and humans will enable the development of new, refined, and digital research tools, which will contribute to:

- reducing and replacing the overall number of NHPs in research without compromising human safety.
- improving disease understanding that will open up new research pathways, and enhanced use of non-invasive digital technologies that can improve animal welfare (refinement), and furthermore, are potentially applicable to humans.
- improving the sustainability and quality of biomedical research and development (R&D) in areas of unmet medical need by ensuring access to well-characterised minipig models in R&D of new therapeutics and innovative medical technologies.
- optimising knowledge sharing between academia, regulators, and the health care industry to accelerate the generation of knowledge and medical innovation.

[13] DIRECTIVE 2010/63/EU OF THE EUROPEAN PARLIAMENT AND OF THE COUNCIL of 22 September 2010 on the protection of animals used for scientific purposes; https://eur-lex.europa.eu/legal-content/EN/TXT/?uri=celex%3A32010L0063
[14] The RETHINK project on minipigs in the toxicity testing of new medicines and chemicals: Conclusions and recommendations. https://doi.org/10.1016/j.vascn.2010.05.008

- fostering the development and validation of non-animal models and approaches by implementing translational data obtained in the future project, which could pave the way to such models.

Data generation will be based on early discussions with regulatory authorities and academic partners, thereby ensuring the contribution to the development and validation of non-animal approaches.

Expected outcomes

- Obtain and share biological knowledge of minipigs, thereby facilitating the development of innovative solutions by improving the translational understanding between minipigs *versus* NHPs and humans, including further understanding of the minipig immune system, with the overall aim to replace, reduce and refine the use of animals in non-clinical safety assessment.

- A regulatory pathway for nonclinical safety assessment of biologicals and other new therapeutic modalities in minipigs with the potential to impact regulatory strategies.

- Publicly available databases and software for physiological, genomic, transcriptomic, metabolomic, proteomic and epigenetic minipig data to understand underlying mechanisms of disease/toxicities and find new mode of actions for pharmaceutical interventions.

- Characterised and validated genetically modified minipig models:

  - genetically modified minipig models based on the CRISPR/Cas9 gene-editing technology.

  - minipigs with ‘humanised’ immune system components and effectors for testing biologicals.

  - small-sized micropig for efficacy/safety assessment to facilitate compound availability in pharmaceutical R&D.

- Assessment of the utility of the minipig as a relevant toxicology species for immuno-safety testing using therapeutics which have been tested preclinically and clinically. Assisting and synergising the already existing translational and regulatory efforts related to immunological safety evaluation. Developing validated antibodies and *in vitro* immunoassays to characterise the immune system and assess the immuno-safety of therapeutics in minipigs.

- Minipig-specific technology for automated study data: validated medical devices, biosensors, algorithms, software, and digital animal housing. Machine learning and artificial intelligence (AI)-based tools to monitor abnormalities in behaviour and physiological systems in undisturbed animals.

To ensure long-term sustainability, all the interdisciplinary science-based knowledge obtained and generated in the project arising from this topic will be shared, integrated, digitalised, and published in peer-reviewed journals, encouraging industry and academia to develop innovative medical science solutions and technologies, such as scientifically and ethically sound animal models, assays, biomarkers, monitoring devices, biosensors for normal physiological behaviour, and algorithms. Based on the close collaboration with regulatory bodies, the knowledge generated in the project is further expected to impact regulatory guideline strategies. All outputs will require long-term sustainability and maintenance to fulfil the scope of the project.

Scope

Challenges

- Increasing need to find alternatives to testing in NHPs in line with EU legislation.
- Almost no precedence in minipig use for safety testing of biologicals and new therapeutic modalities [e.g., oligonucleotides, small interfering RNAs (SiRNAs), crystallisable fragments (Fcs), antigen-binding fragments (Fabs), single-chain variable fragments (scFvs), monoclonal antibodies (mAbs), vaccines, gene-editing and cell-based therapies].
- Lack of scientific knowledge to scientifically justify a de-selection of NHPs in the non-clinical safety assessment of new therapeutics. Lack of public minipig reference 'omics' with good quality annotation: Full genome sequencing, in parallel with baseline transcriptomics, proteomics, metabolomics and epigenetic information.
- Lack of 'humanised' and genetically modified models available for efficacy/safety testing, including genetically modified smaller micropigs to address cases of limited substance supply.
- Significant knowledge gap on the minipig immune system and reduced number of laboratory tools and reagents when compared to other toxicology species (rodent and non-rodent).
- Lack of widespread use of biosensors, medical devices, 'intelligent' animal housing for automated data collection and analysis in minipig studies.

Objectives

The overall objective of this topic is to characterise the minipig for use in R&D of new therapeutics and innovative medical technologies. The knowledge generated in this proposal may facilitate innovative health solutions and improve disease understanding and human predictions. The goal is to advance biomedical R&D by generating background scientific data to evaluate if the minipigs could be a viable and feasible alternative to NHPs in key therapeutic areas, with a special focus on translatability from minipigs to humans.

Key activities

- Compile and publish existing historical safety data in minipig biomedical R&D and discuss data with regulators.
- Evaluate the translatability of minipigs in human risk assessment following treatment with biologicals and new therapeutic modalities, and discuss future perspectives of the minipigs with regulatory agencies, e.g., by requesting regulatory interactions with European Medicines Agency (EMA) such as scientific advice and/or novel methodology qualification advice to understand possible regulatory hurdles in using minipigs for safety assessment.
- Minipigs multi-omics and imaging: Generate omics reference data (genomics, transcriptomics, proteomics, metabolomics, and epigenetic information) to enable translational research in minipigs. To further characterise the minipig, imaging technologies such as magnetic resonance imaging (MRI), computed tomography (CT) scans and positron emission tomography (PET) scans are also of interest.
- Genetically modified pig models including the micro-pig: Characterise and validate humanised and genetically modified minipig models, including the micropig to generate translatable animal models in non-clinical safety assessment.

- iPig: Digital technologies, clinical data collection and AI: Create, validate, qualify, and benchmark digital solutions that can objectively measure clinically relevant and functional biomarkers in minipigs for use in preclinical toxicity studies in line with the regulatory agencies' requirements.

- Minipig immune system: validate reagents, assays, and biomarkers for immunological investigations: Conduct investigative studies in minipigs to support their translational significance in immuno-safety assessments and validate reagents/assays.

- Project management: Compile, digitalise, and publish existing and newly-produced data.

Why the expected outcomes can only be achieved by an IHI project

Generating and compiling comprehensive and complex biomedical datasets within various therapy areas, some of which will be for AI purposes, requires the involvement of multidisciplinary skills across several industry sectors (pharmaceuticals, medical technologies, biotech, vaccines, etc.) including small and medium-sized Enterprises. Previous examples of precompetitive public-private projects (SAFE-T and eTRANSAFE) within the Innovative Medicines Initiative (IMI) and private multi-company initiatives (such as BioCelerate) demonstrated the value of a neutral broker to facilitate precompetitive sharing of proprietary information. Expanding such collaborations beyond one sector to integrate tools, data and know-how from the technology and biotechnology sectors, and joining forces with academic partners from various sectors in unprecedented collaborations, requires exploring new precompetitive grounds and calls for this neutral brokerage to continue.

The involvement of regulatory authorities at all stages of the project generated by this topic is essential considering its objective to develop alternatives that can be used to generate data for regulatory purposes. Close collaboration will contribute to accelerating the development of new knowledge; align validation processes with regulatory requirements; and ultimately, lead to the implementation of new solutions in regulatory practice and their deployment in research practice.

Pre-identified industry consortium and contributing partner(s)

The pre-identified industry consortium that will contribute to this cross-sectoral IHI proposal is composed of the following industry partners:

Pharmaceutical/biotech/vaccine companies:

- Bayer
- Boehringer Ingelheim
- Bristol Myers Squibb
- Lundbeck
- Merck KGaA
- Novo Nordisk (Lead)
- Novartis
- Pfizer
- Roche
- Sanofi

Other companies:

- LabCorp
- Charles River

In addition, the following contributing partners will participate to the IHI project:

- VeriSim Life
- JDRF

In the spirit of partnership, and to reflect how IHI two-stage call topics are built upon identified scientific priorities agreed together with a number of proposing industrial beneficiaries, it is envisaged that IHI proposals and projects may allocate a leading role within the consortium to an industrial beneficiary. Within an applicant consortium discussing the full proposal to be submitted for the second stage, it is expected that one of the industrial beneficiaries may become the coordinator or the project leader. Therefore, to facilitate the formation of the final consortium, all beneficiaries are encouraged to discuss the weighting of responsibilities and priorities with regards to such leadership roles. Until such roles are formalised by execution of the Grant Agreement, one of the proposing industrial leaders shall facilitate as project leader an efficient drafting and negotiation of project content and required agreements.

Indicative budget

The maximum financial contribution from IHI is up to EUR 8 500 000.

The indicative in-kind contribution from industry partners is in total EUR 8 910 000.

The indicative in-kind and financial contribution from IHI JU contributing partners is EUR 492 000.

Due to the global nature of the participating industry partners, it is anticipated that some elements of the contributions will be in-kind contributions to operational activities from those countries that are not part of the EU nor associated to the Horizon Europe programme.

The indicative in-kind contribution from industry partners may include in-kind contributions to additional activities.

Indicative duration of the action

The indicative duration of the action is 60 months.

This duration is indicative only. At the second stage, the consortium selected at the first stage and the pre-identified industry consortium and contributing partners may jointly agree on a different duration when submitting the full proposal.

Phase 1: Evaluation of existing minipig data, develop databases, develop bio sensors and algorithms. Data will be published in peer reviewed journals. Knowledge gaps will be identified, and the development of minipig models will be initiated. Molecule selection and investigations for Phase 2 will be planned and slots for the studies will be booked.

Phase 2: Adolescent and adult male and female minipigs will be treated with modalities e.g., oligos, SiRNAs, Fcs, Fabs, scFvs, mAbs, vaccines, gene-editing, or cell-based therapies, as an alternative to the current precedence of safety testing in NHPs.

Phase 3: Biomaterial from the minipig studies in Phase 2 will be distributed to various work package members (iPig, multi-omics, immuno-safety) for further evaluation. Mechanisms and translational aspects will be explored.

Phase 4: Database scrutinisation, compile, discuss and distribute new knowledge, publication in peer reviewed journals, propose regulatory recommendations, and promote digital solutions.

Contribution of the pre-identified industry consortium and contributing partners

The pre-identified industry consortium and contributing partners expect to contribute to the IHI proposal by providing the following expertise and assets:

- Experimental settings: Pharmaceutical drug candidates, drug products, animals including genetically modified animals, animal units, experimental equipment, laboratories.
- Data: access to standard toxicology and clinical safety endpoints, historical data, gene expression, immunosafety biomarkers and assays.
- Expertise: nonclinical expertise, data science, regulatory expertise, immunosafety, 'omics' evaluation, disease models, devices.
- Technology: Standard for Exchange of Nonclinical (SEND) databases and SEND visualisation systems, implants, device software.

The allocation of the EUR 200 000 financial contribution will be decided by the full consortium at the second stage when preparing the full proposal.

Applicant consortium

Public partners:

- Database constructors: merging large databases from different sectors (various public and industry partners) containing complex biological datasets e.g., genomic, transcriptomic, metabolomic, proteomic and epigenetic data.
- Suppliers of genetically modified minipigs and tissue samples.
- Partners experienced with, and suppliers of, MRI, CT and PET scanning in pigs.
- Academic partners developing and validating biomarkers to ensure human translatability.
- Inventors of technologies for automated digital data collection in patients and pigs: validated medical devices and biosensors to measure normal physiological behaviour.
- Inventors of validated algorithmic tools for machine learning and artificial intelligence for automated digital animal housing and prediction of toxicities in minipig vs. human.
- Inventors of validated antibodies and *in vitro* immunoassays to characterise the immune system and assess immuno-safety of therapeutics in minipigs.
- Project administration with experience in public-private partnerships.

Regulatory authorities: Advisors.

Dissemination and exploitation obligations

The specific obligations described in the Conditions of the calls and call management rules under 'Specific conditions on availability, accessibility and affordability' do not apply.

Topic 2: Patient-centric blood sample collection to enable decentralised clinical trials and improve access to healthcare

Expected impacts to be achieved by this topic

Collecting venous blood samples for diagnostic purposes has been the cornerstone for informing patient care and a key element of clinical trials. Ordering a blood draw has become almost a reflex for clinicians and drug developers, however venipuncture is still the traditional way to collect blood. Venipuncture can be painful and requires individuals to see their healthcare provider or visit a clinic. This results in a burden on patients, doctors, healthcare systems, payers, and the pharmaceutical industry. A particularly high burden may be imposed on vulnerable populations such as children and elderly individuals, as it may lead to increased exposure to disease during a pandemic, or to anaemia (e.g. in oncology). Furthermore, the current procedure is too inflexible to allow for ongoing monitoring for treatment, progression, or intervention in decentralised clinical trials and clinical practice [1)]. There is a great need for the acceptance and implementation of patient-centric (as opposed to clinic-centric) sampling approaches.

The generation of an infrastructure and logistics for at-home collection of small-volume (less than 500 µl) blood samples ('microsampling') as an alternative to venipuncture for routine central lab analysis will contribute to the following impacts:

- It will deliver a much-improved experience to our patients by decreasing the burden on patients (in particular vulnerable populations) and optimising patient care in Europe.
- It will improve decentralised clinical trials, trials at home, and inclusion trials.
- It will facilitate monitoring for prevention, treatment, and surveillance.

Expected outcomes

The results of the project generated by this topic will enable innovations in healthcare delivery and research by generating the infrastructure and logistics for blood collection at home, that is simple, minimally invasive, less painful, convenient, and feasible.

Importantly, the project will also provide new insights and enrich information related to the research questions by creating an unprecedented data set that will enable multiple secondary research options for years to come. Notably:

- It will create insights into the public acceptability for microsampling home: are patients comfortable with a new kind of medical technology? What training is necessary?
- Are we able to advance the transition of care from the hospital to the home? Does the care quality improve?
- How do we utilise the higher frequency of data, including its integration with electronic medical records and using advanced analytics methodology?
- Do doctors' practices and decisions change with the increased frequency of biomarker data, and does it lead to better outcomes for the patient?

While integrating existing components for microsample collection and central lab analysis, quality standards for the new infrastructure and logistics will be rigorously and transparently validated and established in Europe and harmonised with parallel ongoing efforts in the USA. The harmonisation will critically enhance the implementation of microsampling in global clinical trials of new therapeutics. The

validation and establishment of microsampling at home by patients and/or their caregivers will be undertaken in ways that are acceptable for patients and their caregivers, health care professionals, regulatory agencies, policy makers, Health Technology Assessment (HTA) experts, payers, and advocacy groups.

Scope

The overall aim of the project generated from this topic is to create and validate the infrastructure and logistics for blood collection by the patient and/or caregiver at home as a healthcare tool and an alternative to the current gold standard venous blood for routine clinical assays. This project will employ only commercially available CE-marked microsampling devices, according to their intended use.
The development of new devices for blood sampling or of new clinical assays / analytes is not the focus of this project, and no new clinical assays will be evaluated. Similarly, given their current maturity, home sample analysis is out of scope.

Training materials, customised for patients and caregivers as well as for medical personnel will be developed, ensuring the acceptability of the new approach to these groups. Interactions with regulatory authorities, the European Medicines Agency (EMA), local European agencies as well as regulatory agencies from non-EU European countries and the US Food and Drug Administration (FDA) will be sought to advance the regulatory acceptability of the logistics model and harmonisation across the EU, other non-EU European countries and the US. Further, key stakeholders (e.g. policy makers, HTA experts, payers, patient advocacy groups) will be encouraged to implement the infrastructure and logistics throughout Europe. Lastly, the best ways to integrate, transmit, and analyse (including AI) the data generated will be explored. Results will be shared broadly through peer-reviewed publications or other mechanisms.

To be noted – home blood microsampling has been used in geographically restricted pilot projects [2)]. With the project generated from this topic, it is expected to generalise them, and leverage the learnings from the pilot projects, to enable broad adoption. Importantly, it is known that patients greatly appreciated this experience compared to the traditional blood sampling methods currently in use.

Applicants should in their proposal address the following:

Demonstration of concordance between patient-centric microsampling techniques and venipuncture

This requires delivery of a framework across Europe for establishing concordance between capillary blood as collected by microsampling devices outside of traditional collection setting by the patient and/or caregiver, versus the gold standard venous blood, for routine clinical assays.

- To generate an umbrella / master protocol that is acceptable for regulatory authorities in EU and non EU-European countries, and can be easily adopted for future applications (e.g. in additional patient populations, countries, by any vendor or organisation). To assure patient-centricity, feedback on the umbrella protocol by patient representatives and caregivers will be sought.

The umbrella / master protocol should include:

- sites in at least 3 EU Member States,
- and may include additional sites in (with at least one in Eastern Europe[15]):

[15] Armenia, Azerbaijan, Belarus, Georgia, the Republic of Moldova and Ukraine are European countries but not part of the EU (https://www.eeas.europa.eu/eeas/eastern-europe_en).

    - third countries associated to Horizon Europe
    - third countries not associated to Horizon Europe
  - at least two different types (e.g., finger stick, upper arm capillary) of commercially available CE-marked microsampling devices; for clarity, at least one device should perform liquid blood sampling, the additional devices may collect dried blood;
  - routine clinical assays: i.e. blood chemistry, liver and lipid panels;
  - collection of at least 50% of microsamples by the patient and/or the caretaker; the other 50% may be taken by hospital or nursing personnel (including remote nurses, e.g., in general practices, or traveling nurses);
  - collection of least 50% of microsamples at home; the project may include collections in other locations (e.g. hospitals, general practitioners, specialists' offices) for concordance testing and establishing microsampling of capillary blood versus venous blood for routine assays.
- To design, adapt, and translate patient-facing materials, obtain ethics board approvals, obtain competent/regulatory authority approvals, recruit healthy human volunteers and expand to a patient population which should be agreed upon in a project committee, collect biological samples and conduct bioanalysis according to the study protocol.
- To investigate potential errors related to the mishandling of samples and design ways to mitigate them, as well as the potentially harmful downstream effects for the individual.
- To conduct concordance analyses according to existing regulatory guidance for routine clinical assays [3)], and define sample quality criteria (if applicable).

Validation of the logistics of sample collection and shipping, standardising central lab analysis.

This requires identification of an optimum workflow for device ordering, fulfilment, shipping, at-home collection and return to central labs and a seamless integration of microsampling into current central lab processes, accessioning, analysis and reporting.

- To select at least two different types of CE-marked microsampling devices and identify and audit device vendors with ordering (portal) and fulfilment capabilities; to work with device vendors on ordering devices.
- To define appropriate shippers/processing/temperature based on the devices and assay requirements, and confirm requisition requirements.
- To identify strategic partners in terms of logistical expertise, e.g. global couriers.
- To identify countries to test devices in and confirm regulatory requirements for self-collections or collections by caretaker and shipping of devices.
- To define the support need for the use of devices and training participants on devices; to identify telehealth partners e.g. for identification verification.

Due to the ongoing conflict in Ukraine, the participation of legal entities from Russia or Belarus in Horizon Europe and IHI JU projects is prohibited. https://research-and-innovation.ec.europa.eu/strategy/strategy-2020-2024/europe-world/international-cooperation/russia_en#:~:text=Russian%20researchers%20and%20organisations%20are,various%20EU%20and%20Russian%20funding

- To identify the best ways to integrate the new data with existing electronic medical records and medical decision frameworks.

- To investigate the 'green dimension' of logistics: microsampling has the potential to reduce the green footprint of office visits and transportation required (fuel, costs, carbon emissions).

- To confirm the accessioning process needed, reporting requirements, and data management model.

- If possible, to assess the cost savings obtained with microsampling methods as compared to gathering blood in the hospital.

Education and medical & patient acceptability

- To deliver training materials for patients, caregivers and clinical trial sites, taking into account the variety of patients' and caregivers' ages, abilities, etc., and ensuring smooth behind-the-scenes shipment logistics and support.
- To develop guidelines for compiling training materials to meet expectations from different training recipients, such as clinical sites, patients, caregivers, telehealth and home health providers, leveraging previous feedback collected from users (patients, caregivers, principal investigators (PIs) and medical personnel), including to develop training by telehealth.
- To develop a plan to collect patient, caregiver and medical personnel (site staff, PIs, trial coordinator) experience and feedback:

    - to develop a well-designed questionnaire that will be used either electronically or in paper format, develop tool(s) to collect feedback and store the information, pilot the use, refine the questionnaire and data base as needed;

    - to implement the questionnaire to collect feedback from different groups (patients and caregivers, medical personnel, regulators, device manufactures);

    - to maintain a database of information collected and perform data analysis to obtain patient acceptability scores;

    - to get insights into research questions related to the implementation of microsampling which are described in 'Expected outcomes' (see above).

- To publish survey results to validate the training and feedback with other patient advocacy groups.

Regulatory acceptability and implementation in clinical practice in the EU, other non-EU European countries and the US

- To prepare an overview of the regulatory landscape of microsampling at home per country in the EU, third countries associated to Horizon Europe, and other European countries, and to conduct an in-depth exploration in those countries that might be suitable for the microsampling logistics modelling.

- To establish an early and continuous dialogue with the European Medicine Agency (EMA) Innovation Task Force, in addition to local regulatory agencies of the EU, and relevant authorities of other non-EU European countries and the FDA:

    - to assess acceptability with regulators and seek prospective input on the umbrella / master protocol, choice of countries and approach to validating the logistics;

    - to discuss the best strategy/timing for qualification and/or integration of project outputs into regulatory practices, prepare relevant documents (e.g. briefing books, guidance document) to share project results, request scientific and qualification advice, and seek a harmonisation with the regulatory agencies from other non-EU European countries and the FDA, which is key to global clinical trials of new therapeutics.

- To interact with policy makers, HTA experts, payers, and advocacy groups to facilitate the implementation of project results in clinical practice throughout the EU, and other non-EU European countries and the US.

Why the expected outcomes can only be achieved by an IHI project

A joint concerted initiative is required to create a practical implementation path in Europe for patient-centric blood samples in decentralised clinical trials, trials at home, and inclusion trials.

It is essential that industry partners from different sectors, e.g. the pharmaceutical industry, medical device manufactures, *in vitro* diagnostic companies, exchange knowledge and experience and contribute complementary infrastructures. Moreover, collaboration is required with clinical centres that are experienced in conducting decentralised trials, and with academia and SMEs that are experienced in methods and devices for microsampling and data collection and analysis. The engagement of patients, caregivers, and health care professionals is required to ensure the incorporation of the user experience into the novel infrastructure and logistics for patient-centric blood microsample collection at home. Lastly, the involvement of regulators, policy makers, payers, and HTA experts will facilitate the acceptance of the microsampling logistics model.

It is crucially important to develop a harmonised approach that is both acceptable and accessible to all stakeholders in the healthcare systems to ensure implementation across Europe, and this can be best assured under a public-private partnership.

Pre-identified industry consortium and contributing partners

The pre-identified industry consortium that will contribute to this cross-sectoral IHI project is composed of the following pharmaceutical and medical technology industry partners:

- Astra Zeneca
- Bayer
- Becton Dickinson
- Eli Lilly (Lead)
- Gilead
- GlaxoSmithKline
- Labcorp
- MSD
- Novartis
- Pfizer
- Q2labs solutions
- Roche
- Servier
- Janssen

In addition, the following contributing partners will participate to the IHI project:

- JLL
- Miebach Consulting

In the spirit of partnership, and to reflect how IHI Two-Stage call topics are built upon identified scientific priorities agreed together with a number of proposing industrial beneficiaries, it is envisaged that IHI proposals and projects may allocate a leading role within the consortium to an industrial beneficiary. Within an applicant consortium discussing the full proposal to be submitted for Second Stage, it is expected that one of the industrial beneficiaries may become the coordinator or the project leader. Therefore, to facilitate the formation of the final consortium, all beneficiaries are encouraged to discuss the weighting of responsibilities and priorities with regard to such leadership roles. Until such roles are formalised by execution of the Grant Agreement, one of the proposing industrial leaders shall facilitate as project leader an efficient drafting and negotiation of project content and required agreements.

Indicative budget

The maximum financial contribution from IHI is up to EUR 4 500 000.

The indicative in-kind and financial contribution from industry partners is EUR 3 574 000.

The indicative in-kind contribution from IHI JU contributing partners is EUR 300 000.

Due to the global nature of the participating industry partners, it is anticipated that some elements of the contributions will be in kind contributions to operational activities from those countries that are neither part of the EU nor associated to the Horizon Europe programme.

The indicative in-kind contribution from industry partners may include in-kind contributions to additional activities.

Indicative duration of the action

The indicative duration of the action is 42 months.

This duration is indicative only. At Second Stage, the consortium selected at First Stage and the predefined industry consortium and contributing partners may jointly agree on a different duration when submitting the full proposal.

Contribution of the pre-identified industry consortium and contributing partners

The industry consortium and contributing partners expect to contribute to the IHI project by providing the following expertise and assets:

Grant administration:

- To provide legal support for project related tasks.

Clinical trial and medical expertise:

- To design the protocol of the umbrella / master study.

Technologies:

- Analytical techniques and sample analysis.
- Microsampling techniques and provision of 1 device for the collection of capillary blood of the finger stick; for clarity, at least one device should perform liquid blood sampling, the additional devices may collect dried blood.

- Relevant samples might be provided.

Logistics:

- To identify and audit device vendors, logistics and telehealth partners.
- To define acceptable sample quality, collection compliance tests, and shipment requirements ensuring appropriate sample bioanalysis given collection (including at-home collection) and shipment.
- To confirm accessioning processes needed, reporting requirements, and the data management model.

Training materials:

- Expertise in defining needed support for use of devices, providing guidance in feedback collection and guiding principles for developing training materials for patients, caregivers and healthcare professionals.
- To facilitate user group, technical and compliance Key Opinion Leader (KOL) panel discussions.

Integration of requirements of regulatory authorities, HTA, payers, policy makers, and advocacy groups:

- To prepare an overview of the regulatory landscape of microsampling at home in Europe.
- To interact with regulatory authorities, HTA, payers, policy makers and advocacy groups to facilitate acceptability of the microsampling logistics modelling and its implementation throughout the EU and harmonization with efforts in other non EU-European countries and the USA.

Furthermore, the industry consortium will help with data flow, data management, operational support for clinical sites, project management, data and knowledge management, and the communication and dissemination of results. It will also provide contributions to joint meetings and steering committees, networking, exploitation and sustainability.

Applicant consortium

The First Stage applicant consortium is expected, in the submitted short proposal, to address the scope and deliver on the expected outcomes of the topic, taking into account the expected contribution from the pre-identified industry consortium and contributing partners.

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. The focus of this project is not on development of novel devices or assays, but on integration of existing innovative technologies to establish the infrastructure and logistics for patient-centric blood microsample collection at home in Europe.

Applicant consortia should bring together partners with relevant expertise such as patients and patient representatives, patient-centric organisations, healthcare professionals, clinical trial centres with experience in decentralised trials, research organisations, and health technology developers. SMEs are encouraged to join the consortium, in particular those with expertise in various methods and devices that enable microsampling. Moreover, the participation is encouraged of SMEs which have expertise in interaction with patient groups, collecting user experience data and prioritising patient care needs, and the development of training materials for patients, caregivers and healthcare professionals. For facilitating acceptability and implementation of the microsampling logistics model across Europe, input from other

relevant stakeholders, in particular regulatory agencies, payers, HTA bodies and advocacy groups would be necessary.

Applicants should clearly outline their approach for data capture, storage and sharing within the consortium as well as sharing results through peer-reviewed publications or other mechanisms. They must ensure that the relevant results and data repositories will be sustainable after the end of the project and made public.

This will require mobilising the following expertise and/or resources:

Grant administration:

- To provide financial administration, submission of deliverables, periodic reports etc.

Project management:

- To coordinate internal communication and meetings, general oversight and management of communication, exploitation and dissemination activities, risk management.
- To provide and maintain an IT infrastructure, to develop and implement an efficient data governance and management strategy of the joint consortium according to adequate standards and deliver the “Data Management Plan”.
- To coordinate networking, joint activities and synergies with other European initiatives, or other relevant groups (e.g. patient-centric organisations, advocacy groups).
- To develop a strategy for the exploitation and sustainability of project results and outcomes and deliver the “Exploitation and Sustainability Plan”.

Umbrella / master study:

- To obtain the necessary authority approvals, develop participant / patient facing materials, provide recruitment of participants / patients and conduct the umbrella / master study including the collection of biological samples.

Technologies:

- To analyse samples according to the protocol.
- To perform statistical evaluations of concordance according to existing regulatory guidance for routine clinical assays.
- To provide microsampling techniques and at least 1 device for the collection of capillary blood of the upper arm.

Logistics:

- To develop logistical capability around implementing new technologies for microsampling, work with device vendors on ordering devices, develop protocols for the testing of microsampling devices, act as investigative sites to test devices including Institutional Review Boards (IRB), consents etc., and train participants on devices.

Training materials:

- To engage and activate patients, caregivers, clinicians, and hospitals and obtain feedback on the support needed, develop questionnaires to collect their experience, perform data analysis, assess acceptability and concerns, and develop and refine training materials for different recipients.

Interactions with regulatory authorities, HTA bodies, payers, policy makers, and advocacy groups:

- To contribute to the regulatory landscape for microsampling at home in the EU and in other non-EU European countries.

- In conjunction with industry, to discuss with regulatory authorities, HTA bodies, payers, policy makers, and advocacy groups the acceptability and implementation of the microsampling logistics modelling in the EU and harmonisation with efforts in other non-EU European countries and the US.

- To prepare relevant documents of the approach and the results being generated by the project (e.g. briefing books, EMA guidance document).

At Second Stage, the consortium selected at First Stage and the predefined industry consortium and contributing partners will form the full consortium. The full consortium will develop in partnership the full proposal, including the overall structure of the work plan and the work packages, based upon the selected short proposal at First Stage.

Dissemination and exploitation obligations

The specific obligations described in the Conditions of the calls and calls management rules under “Specific conditions on availability, accessibility and affordability” do not apply.

References

1) Fantana AL, Cella GM, Benson CT, Kvedar JC, The Future of Drug Trials Is Better Data and Continuous Monitoring, Harvard Business Review, 2019 https://hbr.org/2019/05/the-future-of-drug-trials-is-better-data-and-continuous-monitoring

2) Wickremsinhe ER, Fantana AL, et al. Standard Venipuncture Versus a Capillary Blood Collection Device for the Prospective Determination of Abnormal Liver Chemistry. JALM 2022 (accepted for publication).

3) CLSI. Measurement Procedure Comparison and Bias Estimation Using Patient Samples. CLSI guideline EP09c, Wayne, PA: Clinical and Laboratory Standards Institute; 2018.

Topic 3: Inclusive clinical studies for equitable access to clinical research in Europe

Expected impacts to be achieved by this topic

The following impacts are expected:

- Awareness and understanding of what diversity, under-represented and underserved communities look like in geographies across Europe, including barriers and gaps to recruitment and retention in different types of clinical research, such as clinical studies[16] on medical products, clinical investigations for medical devices, and performance studies in in vitro diagnostics (IVDs), cohorts, and registries.

- Enhanced representativeness of underserved populations in clinical studies across Europe, through the building of a patient-centric, sustainable infrastructure that improves the recruitment and retention of these patients.

- Increased study data reliability and genetic diversity by including different demographic groups, thereby enhancing patient trust in the evidence generated. More patients benefit from increased access to improved innovative health technologies including medicinal products and medical devices that meet the specific needs and profiles of all patient populations.

- Promoting the implementation of new tools, solutions, approaches, or process models that will reduce the burden of clinical studies and facilitate and increase diverse patient populations' access to clinical studies.

- Contribution to the Accelerating Clinical Trials in the EU[17] (ACT-EU) objectives to proactively deliver inclusive patient-oriented medicines development and delivery across populations.

Expected outcomes

The research and innovation (R&I) action (project) to be supported under this topic should aim to deliver results that contribute to all of the following expected outcomes.

- Researchers, including industry stakeholders, clinical investigators and healthcare providers, strengthen the understanding, through use cases, of the impact of study design/protocols and study conduct on patient recruitment/retention that will help future clinical studies. These stakeholders will also benefit from gaining clarity on what clinical study diversity means in Europe, especially considering the emerging guidance from the US Food and Drug Administration (FDA) on clinical trial diversity in the US.

- Patients will benefit from a sustainable, easy-to-use digital platform, built with input from patients and/or patient support organisations, enabling more underserved patients to identify clinical studies that they are eligible for. Investigators/sites would be able to locate patients for ongoing clinical

[16] Clinical study EC definition as per Horizon Europe information on clinical studies template: Clinical study covers clinical studies/trials/investigations/cohorts and means, any systematic prospective or retrospective collection and analysis of health data obtained from individual patients or healthy persons in order to address scientific questions related to the understanding, prevention, diagnosis, monitoring or treatment of a disease, mental illness, or physical condition. It includes but it is not limited to clinical studies as defined by Regulation 536/2014 (on medicinal products), clinical investigation and clinical evaluation as defined by Regulation 2017/745 (on medical devices), performance study and performance evaluation as defined by Regulation 2017/746 (on in vitro diagnostic medical devices).

[17] https://www.ema.europa.eu/en/documents/regulatory-procedural-guideline/accelerating-clinical-trials-eu-act-eu-delivering-eu-clinical-trials-transformation-initiative_en.pdf

studies. This will benefit both recruitment and retention of underserved patients as it will act as a match-making portal that will be accessible to all sponsors (including academics/investigator-initiated trials, industry, etc.), and provide patient support to enable patients to allay their concerns in a timely manner, increasing their knowledge/education and building trust toward clinical research

- Researchers, including industry stakeholders, sponsors, clinical investigators, clinical research organisations, healthcare providers and patients/caregivers benefit from a toolbox of new approaches, tools, solutions and best practice approaches to facilitate and increase patient recruitment and retention, to better design and conduct clinical studies including adaptive designs, registry studies and decentralised studies with a particular focus on under-represented and underserved patient populations in Europe. Taking account of regulatory requirements, this will lead to more effective clinical studies with an increased recruitment/retention of diverse patient populations that is supported by a community-informed approach.

- Increasing population representativeness also better reflects real-world patients and helps the generalisability of the study findings, leading to better innovations. This is a positive outcome for all patients (not just underserved patients). Targeted under-represented and underserved patient populations have increased trust in clinical studies, which helps to overcome recruitment, participation, and retention challenges through educational programmes, public outreach, and community outreach/engagement.

- Clinical investigators, clinical sites and existing clinical networks benefit from cultural competency and educational training to better engage with diverse populations. New investigators from underserved communities will benefit from inclusion in clinical studies.

- The pool of clinical sites with access to diverse clinical research staff that can facilitate the education, recruitment, and retention of diverse populations in clinical studies is broadened.

- Community-based sites and organisations are better engaged to provide input on the conduct of clinical studies and to promote diversity in patient populations through inclusive enrolment practices.

- Regulators, health technology assessment bodies and payers benefit from better information on heath technologies including medicinal products, medical devices benefit-risk profile across the patient populations for use in clinical practices.

- Data standards established in agreement with regulators. Standardisation of data standards for demographic descriptors across sponsors such as race, ethnicity, gender, sex, and other selected diverse factors for the defined underserved and under-represented populations are essential for consistent reporting and valid demographic measurement.

Scope

Patient recruitment and retention remains a leading challenge in the efficient completion of clinical studies, including studies on medicinal products, medical devices, or IVDs. Furthermore, despite advancement of enrolment practices designed to better reflect the population most likely to use the health technologies in clinical practice, there is still only limited diversity within recruited patient populations. The under-representation of diverse populations (due for instance to their race and ethnicity, gender, age, socio-economic status, geographical location) creates knowledge gaps about the risks and benefits of health technologies for these specific populations.

This topic aims to develop a multi-faceted, intersectional approach to overcome the multifactorial barriers associated with the recruitment and retention of underserved patient populations in clinical studies and to contribute to transforming the way clinical studies are conducted in Europe.

To fulfil this aim, the following activities around the defined themes should be addressed.

Landscape

- Agree a definition of “underserved” populations in Europe with regulators, that includes populations facing socio-economic, systemic, or cultural barriers that prevent equitable access to clinical studies. This may be broader than populations currently defined in the demographics that sponsors collect, such as age, sex, gender, race, and ethnicity. This could include rural populations, refugees, homeless, illiterate, disabled people, and those belonging to minority populations.

- Estimate the current participation of diverse study populations in clinical studies differentiated by success in recruitment and retention; identify and evaluate the factors that contribute to and limit existing initiatives to increase diversity of recruitment and retention in clinical studies.

- Define and develop country-, social- and culture- specific understanding of factors driving under-representation and underserved populations in Europe. Shape the development of guidance on how to reach and retain underserved populations in clinical studies in different settings and countries, and how to collect data in a GDPR[18]-compliant fashion across Europe.

- Establish a sustainable patient-centric digital platform (open to all sponsors) connecting the patients, patient support organisations, sponsors, and investigators at different sites (including in community settings, hospitals, primary physicians, etc). To ensure patient engagement, the platform should use lay language and make use of existing resources such as ClinicalTrials.gov information; patient support information developed by patient organisations, or Clinical Trials Information System (CTIS). This is important to ensure that the patient/community engagement activities undertaken lead to patients being directed to use the platform, leading to an improvement in participation of diverse patients. The needs of underserved populations with access barriers to digital platforms or language barriers should be considered.

- Define the governance structure and maintenance/ownership of the platform. The active involvement of underserved patients / patient representatives is expected in the planning and development of the platform, as well as governance activities.

- Understand the interface between international, regional, and local approaches from a patient-centricity perspective (while the strategies may need to be developed and implemented locally, they will be part of multi-regional/multi-country clinical studies conducted by sponsors).

Protocol design and clinical operations

- Establish criteria for measuring ‘representativeness’, i.e. patients enrolled in the trial represent the prevalence of the disease in different sub-populations. For example:

    - Representation: age, sex, gender, race, ethnicity (measured against prevalence).

    - Inclusion: socioeconomic status, rural vs. urban access, sexual orientation, disability, payer status (private vs public), pregnancy/lactation status, etc.

[18] General Data Protection Regulation

- Identify and assess existing tools and solutions for patient recruitment and retention that could be used for recruitment and retention of a diverse population from a European perspective. Develop a set of suitable tools, solutions, and strategies applicable for different types of clinical studies, including studies with medicinal products, medical devices, or IVDs.

- Identify and review aspects of study design such as narrow eligibility criteria, methodological approaches, logistical and other patient-related factors that could limit broader patient and communities' engagement, taking account of regulatory requirements; define recommendations for best practices.

- Explore and validate approaches that improve access, participation, recruitment, and retention of diverse patient populations, including innovative technology solutions, clinical research methodologies (e.g., adaptive, home based/hybrid), leveraging real world data sources etc.

Community engagement

- Raise awareness, develop educational activities and inclusive toolkits to increase knowledge and trust of target populations towards clinical studies to overcome recruitment, participation, retention challenges and to enable early patient engagement.

- Develop targeted activities to foster community engagement and build trust with patients.

- Establish connections between different stakeholders in the community e.g. researchers, industry stakeholders, patients, caregivers, investigators, and healthcare providers.

Investigators / clinical sites

- Build new site capabilities and develop training activities to increase the number of community-based sites and expand the pool of investigators, including investigators from under-represented communities and naïve investigators, to set them up in geographies where the infrastructure is missing.

- Create the necessary support mechanisms and define specialised training e.g. cultural competency training, naïve investigator training, etc. through existing clinical networks, medical institutions, patient organisations and community-based organisations. Existing resources such as Clinical Trials Transformation Initiative (CTTI), or other projects such as IMI (Innovative Medicines Initiative) projects conect4children (c4c) and EUPATI can be leveraged.

To ensure the applicability of the solutions/tools/recommendations, the applicants should test them in pilot use cases, which will be determined during the project based on the availability of cases from sponsor companies and in discussion with the consortium, in one or more disease areas of choice. The proposed disease areas should constitute an unmet public health need and a significant burden to patients, healthcare systems and society (e.g. breast cancer, prostate cancer, hypertension, lupus etc). Furthermore, the proposed areas should be representative to allow broad implementation across diverse disease areas, different cultural and geographical distributions, types of clinical research such as clinical studies on medical products, clinical investigations for medical devices, performance studies for IVDs, and studies testing non-pharmacological and rehabilitation interventions.

The purpose of the pilot use cases is to test tools and solutions for patient recruitment and retention, assess the functionality of the digital platform, and test the improvements brought by the digital platform on patient recruitment and retention. The focus will be on testing the robustness of the infrastructure to ensure the solutions put in place are "fit for purpose". The testing could establish the viability of the solutions, for example:

- number of new sites added to the platform;
- number of under-represented investigators trained through this initiative;
- number of investigators that serve underserved patient populations;
- effectiveness of community engagement activities as judged by patient support organisations;
- effectiveness of recruitment and retention activities via the platform, as experienced by investigators and patients;
- analysis of number of users of the platform and the type of content accessed by users.

Applicants are expected to consider the potential regulatory impact of the results and as relevant develop a strategy/plan for generating appropriate evidence, and to engage with regulators in a timely manner (e.g., through the EMA Innovation Task Force, qualification advice).

In their proposals, applicants should leverage and build on existing tools & solutions and best practice experiences that have already been developed at national European and/or international level, including tools developed in IMI/IHI projects.

Why the expected outcomes can only be achieved by an IHI project

To achieve the transformation outlined above, a broad cross-sectoral collaboration is needed including healthcare professionals to give insights on their experience with the current technology utilisation and act as champions for the new developments, academic researchers, health economists, hospital management, public procurers, technology developers and vendors and patients, who will benefit from the solutions. Integrating data from multiple origins/sources requires the cooperation of data holders, both public and private, in a non-competitive, neutral setting like an IHI project. Improving clinical studies that address patients' needs is of paramount importance for the private and public sector. Recruitment, retention, and the insufficient participation of underserved patient populations in clinical studies are a challenge that the entire health industry faces, including large and small and medium-sized pharmaceutical and medical technology companies. Efforts to tackle those are riddled with complexities such as the geographical complexity (a solution appropriate in one country may be less appropriate in another). In addition, the multitude of healthcare partners in the health ecosystem hinders scalability of initiatives that can be put in place. Cultural barriers also exist that may result in the mistrust of under-represented and underserved patients towards clinical research.

An important paradigm change is needed to succeed in better including under-represented populations, requiring collaboration among stakeholders: patients, caregivers, academia, healthcare practitioners, clinical investigators, industry, sponsors, contract research organisations, regulators, health technology assessment bodies. payers, social scientists, and ethicists, etc. A cross-sectoral and multidisciplinary public-private approach is the only way to harness the insights from key stakeholders, consider all perspectives, and adjust the trajectory in real time. Increasing the recruitment and retention of underserved patient populations is a multistakeholder effort and the IHI provides the framework to bring together all sectors, and all involved in clinical research, including patients and caregivers to succeed in promoting more inclusive clinical studies.

Pre-identified industry consortium

The pre-identified industry consortium that will contribute to this cross-sectoral IHI project is composed of the following pharmaceutical and medical technology industry partners:

- Abbvie
- AstraZeneca
- Bristol Myers Squibb

- Eli Lilly
- GlaxoSmithKline
- Janssen
- Novartis (Lead)
- Novo Nordisk
- Pfizer
- Roche
- Sanofi
- Takeda

In addition, the following contributing partner will participate in the IHI project:

- JDRF

In the spirit of partnership, and to reflect how IHI two-stage call topics are built upon identified scientific priorities agreed together with a number of proposing industrial beneficiaries, it is envisaged that IHI proposals and projects may allocate a leading role within the consortium to an industrial beneficiary. Within an applicant consortium discussing the full proposal to be submitted for the second stage, it is expected that one of the industrial beneficiaries may become the coordinator or the project leader. Therefore, to facilitate the formation of the final consortium, all beneficiaries are encouraged to discuss the weighting of responsibilities and priorities with regard to such leadership roles. Until such roles are formalised by execution of the Grant Agreement, one of the proposing industrial leaders shall facilitate as project leader an efficient drafting and negotiation of project content and required agreements.

Indicative budget

The maximum financial contribution from IHI up to EUR 33 000 000.

The indicative in-kind contribution from industry partners is EUR 33 600 000.

The indicative in-kind and financial contribution from IHI JU contributing partner is EUR 250 000.

Due to the global nature of the participating industry partners, it is anticipated that some elements of the contributions will be in-kind contributions to operational activities from those countries that are neither part of the EU nor associated to the Horizon Europe programme.

The indicative in-kind contribution from industry partners may include in-kind contributions to additional activities (IKAA).

Indicative duration of the action

The indicative duration of the action is 72 months.

This duration is indicative only. At the second stage, the consortium selected at the first stage, the pre-identified industry consortium and the contributing partner may jointly agree on a different duration when submitting the full proposal.

Contribution of the pre-identified industry consortium

The pre-identified industry consortium and contributing partner expect to contribute to the IHI project by providing the following expertise and assets:

- Expertise in legal, ethics and compliance, regulatory, diversity, equity and inclusion (DEI) in clinical research and clinical study design both at a local and regional level.

- At a minimum, three use cases (in selected disease areas) are expected to be used as “pilots” to test the infrastructure that will be established during the project. There could be additional comparator use cases depending on testing criteria. Industry contributions will be based on the ‘disease/indication’ and total number of participants interacting with the solutions/platform put in place through this project. The contributions could extend to costs incurred to recruit and retain included patients (in Europe) in the pilots, such as investigator fees, site coordinator fees, digital recruitment/social media costs, reimbursement of patient costs (transportation, etc), community engagement activities, patient retention activities, etc. Costs that do not relate to recruitment and retention activities will be excluded such as costs linked to safety and efficacy assessments, therapeutic ingredients, and supply chain costs.

- Contribution to the elaboration of educational programme and training materials building on existing materials. Sharing potential expertise or technologies that are beneficial for the broader community to help reduce the burden of participating in clinical research.

- Leverage synergies with existing IMI/IHI initiatives and TransCelerate collaborations across industry.

- Capability to enable the platform to be used widely (and adopted as a single solution) by a variety of stakeholders that are currently funded by the pharmaceutical industry to run clinical studies, e.g. contract research organisations (CROs), sites, patient support and advocacy organisations.

- The allocation of the EUR 200 000 financial contribution will be decided by the full consortium at the second stage when preparing the full proposal.

Applicant consortium

The first stage applicant consortium is expected, in the submitted short proposal, to address the scope and deliver on the expected outcomes of the topic, considering the expected contribution from the pre-identified industry consortium and the contributing partner.

This may require mobilising the following expertise and/or resources.

- Knowledge of the existing clinical studies and site databases in Europe.

- Project management expertise in running cross-sectorial projects.

- Partners with expertise in building a patient-centric digital platform that connects various health ecosystem stakeholders, for e.g. patients, patient support organisations, sites, CROs, sponsors, registries.

- Expertise in gathering patient insights for clinical studies – such as input to protocol design, user acceptance testing of the platform, etc.

- Partners who have strong relationships with patient representatives / patient organisations to ensure patient-centricity at all levels of the project.

- Partners with relevant expertise like healthcare professionals, community organisations, sites, CROs.

- Public health experts, social scientists, behavioural scientists, to help change behaviours and mindsets. Communication expertise to reach underserved communities. Patient advocacy experts that in particular work across multiple disease areas and countries in Europe.

- Knowledge on the regulatory aspects (including good clinical practice of drug and medical device development).

- Experience with consumer-directed communications and/or interactions and/or patient advocacy (social media reach and expertise in health sector communications preferred).
- Experience with localised epidemiology data (i.e. incidence/prevalence) overlayed by demographics and/or local ethnopharmacology.
- Expertise in delivering capability-building activities and cultural competency training to the sites.
- Experience in onboarding naïve investigator sites.

At the second stage, the consortium selected at the first stage, the pre-identified industry consortium and the contributing partner will form the full consortium. The full consortium will develop in partnership the full proposal, including the overall structure of the work plan and the work packages, based upon the selected short proposal at the first stage.

Dissemination and exploitation obligations

The specific obligations described in the conditions of the calls and call management rules under “Specific conditions on availability, accessibility and affordability” do not apply.

Topic 4: Establishing novel approaches to improve clinical trials for rare and ultra-rare diseases

Expected impacts to be achieved by this topic

The research and innovation (R&I) action (project) to be funded under this topic is expected to transform the clinical research landscape and boost drug development for rare diseases by enhancing patient access to clinical trials and trial preparedness of investigational sites, increasing acceptability of new tools and methods, and preventing research fragmentation across Europe.

It will have a direct impact not only on patients with rare and ultra-rare[19] diseases but also on all stakeholders involved in drug development. More specifically, the expected impact will include the following:

- New pathways co-created by all interested parties and new rules / best practices for early engagement will facilitate clinical development in 'white spot' areas[20] and increase the likelihood that pharmaceutical and biotech companies will test drugs originally intended for common diseases in rare/ultra-rare disease populations with a plausible disease-modifying mechanism of action (MOA).

- Patients with rare/ultra-rare diseases will benefit from cutting-edge clinical development of new health innovations in Europe (impacting the current situation of 95% of underserved rare diseases).

- By fostering the use of alternative innovative designs for randomised clinical trials, patients will have a higher probability of being assigned to active treatment, whether in Phase 2 and/or in Phase 3 registrational trials (especially critical for rare paediatric genetic diseases where the window of therapeutic intervention may be relatively narrow).

- Continuum of evidence generation accelerates authorisation and patient access / treatment / deployment.

- In line with the Accelerating Clinical Trials in EU[21] (ACT-EU) initiative, proactive delivery of patient-oriented medicines across populations including patients with rare/ultra-rare diseases will be increased. Europe is becoming more attractive for the clinical development of medicines for rare/ultra-rare diseases thanks to the uptake of innovative methodological approaches for conducting successful clinical trials for rare/ultra-rare diseases.

- Optimised and predictable referral of patients (physically and virtually) to expert centres, facilitated through incentives, while avoiding patients' disadvantages/burdens (e.g., travel etc.) and inconsistency between healthcare providers would help sponsors in their clinical development where appropriate.

Overall, the success of the project should be determined by measuring an increase in the use of innovative trials, including complex trials, designed to target selected populations with rare/ultra-rare diseases, and in the use and dissemination of playbooks[22], which will optimise the current situation[23] and increase the number of new approved medicines targeting rare/ultra-rare diseases that are currently underserved.

[19] Ultra-rare diseases: diseases with a prevalence <1 per 50000 persons (https://err.ersjournals.com/content/29/156/200195)

[20] 'White spot': conditions for which there is no approved treatment option and where development is not currently commercially viable.

[21] https://www.ema.europa.eu/en/human-regulatory/research-development/clinical-trials/accelerating-clinical-trials-eu-act-eu

[22] Playbook: a book/guide including comprehensive guide on a technical topics, describing both overarching strategy and tactical approaches, and including all information relevant to the design, conduct, implementation and analyses of innovative CTs.

[23] https://www.nature.com/articles/d41573-022-00019-z / https://irdirc.org/resources-2/rd-metrics/

Expected outcomes

The project generated from the topic should not only develop capacities and capabilities to execute innovative trial designs, but also plan to identify solutions to address scientific gaps as well as technical and operational challenges, and to collaborate / find synergies with relevant existing initiatives to establish a new, dedicated, rare disease specific and sustainable infrastructure. The project is expected to support innovation and optimise drug development for rare diseases with high unmet medical needs by focusing on clinical trials conducted for small populations and clusters of diseases with commonalities.

With a focus on addressing 'white spots[24]' in a subset of the 95% of underserved rare diseases, the R&I action to be supported under this topic should:

1. Deliver novel rare/ultra-rare disease-specific methodological approaches[25] to transform the way treatments are developed with a view towards accelerating approval and access.

2. Pressure-test new clinical trial designs by using the playbooks co-created with stakeholders through case studies and modelling, addressing up to four selected paediatric / rare disease (or clusters of ultra-rare diseases with commonalities) case studies, and different types of interventions (at least one for advanced therapy medicinal products (ATMP)).

In more detail, all the following outcomes are expected to be delivered:

- **Playbooks[26] for designing novel clinical trials (CT)** for rare diseases / clusters of diseases that can also be used for education and training. Jointly created with and validated by regulators, health technology assessment (HTA) bodies, these playbooks should include:
  - good practice recommendations for multinational innovative studies, electronic health records (EHRs) driven registries and longitudinal natural history studies;
  - standardised processes across all disease areas, countries and sites for fast and reliable feasibility processes, allowing – for example – for early feasibility assessment to support the design of feasible development programmes. Effectiveness assessment of optimised CT designs as compared to the 'gold-standard' CT design for rare diseases;
  - study protocols co-created by expert network(s) with regulators, HTA bodies, patients, and industry;
  - agreement on a minimum set of data variables to be included in every registry / newly designed real-world data (RWD) source (baseline patient characteristics, disease-related information, etc.) to ensure usability for regulatory decision-making and study planning;
  - information to support clinical research network set-up for conducting innovative trials including, for example, real world evidence (RWE), remote elements etc;
  - guidance from expert advice to developers on specific aspects when designing CTs.
- **Alignment and complementarity with the European Partnership on Rare Diseases** (in particular the 'Clinical Research Network') co-funded by Horizon Europe and Member States and Associated countries, to create synergies and avoid overlaps.

[24] 'White spots' - conditions for which there is no approved treatment option and where development is not currently commercially viable
[25] Framework defined as structured processes and methodologies
[26] Refer to footnote 67 (playbook).

- **Certified/qualified clinical trial sites** scientifically and operationally (especially in the areas of ATMPs) with readily available pools of patients ready to be recruited into CTs where appropriate; working to agreed site standards along comparable process and quality standards.

- **Structured and predictable system for referral of patient** (physically and virtually) to expert centres, facilitated through incentives and avoiding patient disadvantages (travel etc.) and incongruity amongst healthcare providers.

Scope

Developing medicines for rare diseases involves complexities and challenges beyond those typically seen for common conditions, in particular:

- for most rare diseases, disease aetiology, biology and natural history are insufficiently understood, while there are often no established endpoints for use in clinical trials;

- enrolling, engaging and retaining patients, including patients who may be far apart geographically;

- designing and evaluating clinical trials, including using/identifying relevant outcome measures;

- ensuring the quality of patient data, and enabling re-use of data (e.g. registries);

- underdeveloped and fragmented clinical trial infrastructure for the conduct of clinical studies, including those using ATMPs and for cell and gene therapies;

- an evolving and internationally fragmented global regulatory and landscape.

The evaluation of the regulations on Orphan Medicinal Products and Paediatric Medicines by the European Commission has concluded that those regulations have boosted the development of new therapies for rare diseases but have not yet adequately managed to direct research and innovation towards the areas of greatest unmet medical need. There is clearly a need for holistic and inclusive solutions to address the persisting root causes of these unmet medical needs and to deliver more medicines for patients with rare diseases. This topic, which contributes to the Rare Disease MOONSHOT Initiative[27], is expected to be an important catalyst for innovation for patients affected by some of the 95% of rare diseases without treatment options. Importantly, the project selected under this call would also align with the identified strategic priorities of the Horizon Europe co-funded Partnership on Rare Diseases that is expected to start in mid-2024 and to consolidate the Rare Disease (RD) research and innovation ecosystem.

The topic aims to unravel roadblocks on the current clinical development pathways and deliver methodological solutions for innovative clinical trial designs and analyses, including regulatory considerations**.**

To fulfil this aim, the proposal should:

- identify good practices for the design, use and implementation of innovative clinical trial (e.g., basket trials, platform trials, in silico trials) and of tools/methods (e.g., RWD, digital health technologies, quantitative approaches, trial with remote elements) developed for small populations and clusters of diseases, while also addressing scientific and statistical challenges with the generation and interpretation of small, incomplete and/or heterogenous data sets to help support CT and product approval;

[27] https://www.eurordis.org/rare-disease-moonshot/

- identify good practices to address knowledge gaps including the collection of natural history data, the development of relevant new endpoints and patient reported outcomes (PROs) which should be incorporated into the CT design;

- benchmark new clinical trial designs (i.e. basket, platform CTs, shared control arm trials between different sponsors…) that should be assessed and compared to the existing 'gold standard' CT model for rare diseases (i.e. single arm);

- focus on paediatric and adult rare diseases ('white spots');

- develop appropriate capacity and capability for innovative clinical trials as well as education and training programmes based on lessons learnt from existing initiatives and developers' experience so that best practices to optimise drug development in rare diseases can be shared and disseminated, and playbooks deployed;

- develop a virtual platform for knowledge and tool sharing, which could be also used for playbook deployment;

- identify clinical trial sites which are certified/qualified scientifically and operationally (especially in the areas of ATMPs) with readily available pools of patients ready to be recruited into CTs where appropriate. Taking into account the cohort size of such clinical trials it will be quite important to ensure the cultural and geographical distribution of the CT at EU level;

To be successful and deliver according to the objectives, it is important:

- to capitalise on past public investments and collaborate with relevant stakeholders, e.g. with the European Reference Networks (ERNs) and their registries, the European Joint Programme on Rare Diseases (EJP RD[28]) and the future European partnership on rare diseases (RDP) to foster a more cost-effective pathway for the development of treatments for patients with rare diseases in Europe. The ERNs[29] are being established under the Directive on patients' rights in cross-border healthcare, with their registries under the supervision of the Member States[30], and therefore any plan for collaboration between ERNs and industry should be compatible with the principles[31] set up by the ERN Board of Member States and the Commission services. Hence the need to identify solutions to unlock industry collaboration with ERNs (e.g., leveraging on ERNs' clinical expertise, ERN registries, etc.) should be in line with these principles;

- to utilise the European Commission's infrastructure for the RD registry data and clinical cohorts ecosystem, namely the European Platform on Rare Disease Registration (EU RD Platform) for clinical data management;

- to leverage key learnings from existing ongoing initiatives, e.g., the Bespoke Gene Therapy Consortium[32], IMI EU-PEARL[33], EUnetHTA21[34], or of the IRDIRC "Orphan Drug Development Guidebook" project[35] which aims at creating a simple guidebook for academic and industrial drug developers describing the available tools and initiatives specific for rare disease development and how best to use them;

[28] EJP RD (European Joint Programme on Rare Diseases): https://www.ejprarediseases.org/
[29] https://health.ec.europa.eu/european-reference-networks/overview_en
[30] https://health.ec.europa.eu/european-reference-networks/board-member-states_en
[31] https://health.ec.europa.eu/system/files/2020-03/statement_industry_conflictofinterest_en_0.pdf
[32] https://ncats.nih.gov/programs/BGTC
[33] https://eu-pearl.eu/
[34] https://www.eunethta.eu/eunethta-21/
[35] https://irdirc.org/activities/task-forces/orphan-drug-development-guidebook-task-force/

- to build upon the results of Horizon 2020 (H2020) research projects such as the European Rare disease research Coordination and support Action (ERICA) and FP7 projects developing methodologies for clinical trials for small populations[36], namely IDEAL[37], InSPiRe[38] or ASTERIX[39]. It will be crucial to optimise their findings (if necessary) based on new scientific/technological progress and find synergies with other existing projects, whether completed or ongoing;

- to build synergies with the new cluster of Horizon Europe projects on developing new effective therapies for RD with no approved options (expected to start in Q3 2023) and to partner with existing projects/initiatives, e.g., IMI (Innovative Medicines Initiative) Screen4Care[40], IMI conect4children (c4c)[41], Remedi4All[42], C-Path RDCA-DAP[43];

- to help overcome the fragmentation of the clinical trial environment across Europe;

- to identify solutions to overcome hurdles in the implementation of cross-border patient participation in clinical trials;

- to develop best practices to support the development of innovative and 'regulatory-grade' clinical trials and generate the appropriate evidence for regulatory and HTA decision-making.

Once developed and established, the playbooks and related infrastructures will be pressure-tested through case studies and modelling, using up to four selected paediatric/rare diseases (with at least one ultra-rare disease or clusters of diseases) and different types of interventions (at least one being an ATMP).

Why the expected outcomes can only be achieved by an IHI project

To tackle the challenges, and in line with the IHI objectives, a multidisciplinary public-private partnership driving innovative and solution-driven science and technology is the only way to harness expertise from all the relevant stakeholders (i.e., patients, academia, regulators, health industry representatives, etc.) and to consider all relevant perspectives and adjust the trajectory in real time. IHI provides frameworks for a structured dialogue among stakeholders including regulatory, HTA bodies and healthcare authorities, and succeeds in creating clinical trials / research initiatives reflective of global populations.

There is a need to break down existing silos and bring together the expert ecosystem and stakeholders. This should help in optimising and streamlining the development of assets relevant for paediatric / rare diseases by removing key technical bottlenecks and identifying best practices. Therefore, collaboration and synergies between the experts from industry, academia, patients' organisations, not-for-profit organisations, biotech, research institutions, clinics, and small and medium-sized enterprises (SMEs), will be essential for this project. Similarly, patients' involvement and connection with clinicians, health care providers and rare disease networks will be essential as well as collaboration with regulators to ensure appropriate development and implementation of the playbooks.

[36] https://cordis.europa.eu/search?q=contenttype%3D%27project%27%20AND%20programme%2Fcode%3D%27HEALTH.2013.4.2-3%27&p=1&num=10&srt=/project/contentUpdateDate:decreasing
[37] IDEAL – Integrated DEsign and AnaLysis of clinical trials in small population groups (rwth-aachen.de): https://www.ideal.rwth-aachen.de https://cordis.europa.eu/project/id/602552
[38] InSPiRe (Innovative methodology for small populations research): https://cordis.europa.eu/project/id/602144
[39] ASTERIX (Advances in Small Trials designs for Regulatory Innovation and eXcellence): http://www.asterix-fp7.eu/
[40] https://screen4care.eu/
[41] https://conect4children.org/
[42] https://remedi4all.org/
[43] https://portal.rdca.c-path.org/

Pre-identified industry consortium

The pre-identified industry consortium that will contribute to this cross-sectoral IHI project is composed of the following pharmaceutical and medical technology industry partners:

- AstraZeneca (Lead)
- Bayer
- Boehringer-Ingelheim
- Ipsen
- Janssen
- Novartis
- Roche
- Sanofi
- Servier
- UCB

In the spirit of partnership, and to reflect how IHI two-stage call topics are built upon identified scientific priorities agreed together with a number of proposing industrial beneficiaries, it is envisaged that IHI proposals and projects may allocate a leading role within the consortium to an industrial beneficiary. Within an applicant consortium discussing the full proposal to be submitted for the second stage, it is expected that one of the industrial beneficiaries may become the coordinator or the project leader. Therefore, to facilitate the formation of the final consortium, all beneficiaries are encouraged to discuss the weighting of responsibilities and priorities with regards to such leadership roles. Until such roles are formalised by execution of the Grant Agreement, one of the proposing industrial leaders shall facilitate as project leader an efficient drafting and negotiation of project content and required agreements.

Indicative budget

The maximum financial contribution from IHI is up to EUR 8 500 000.

The indicative in-kind and financial contribution from industry partners is EUR 9 100 000.

Due to the global nature of the participating industry partners, it is anticipated that some elements of the contributions will be in-kind contributions to operational activities from those countries that are neither part of the EU nor associated to the Horizon Europe programme.

The indicative in-kind contribution from industry partners may include in-kind contributions to additional activities.

Indicative duration of the action

The indicative duration of the action is 60 months.

This duration is indicative only. At the second stage, the consortium selected at the first stage and the pre-identified industry consortium will jointly agree on a different duration if needed, when submitting the full proposal.

Contribution of the pre-identified industry consortium

The pre-identified industry consortium expects to contribute to this IHI project by providing the following expertise and resources to:

- build solution components that are sustainable and scalable;
- generate site standards and quality processes to support the build-up and training of research network hubs and expert sites;
- engage and raise awareness amongst patient groups;
- provide regulatory expertise, to help with other experts to build playbooks;
- provide anonymised data that could be used as control arms;
- support virtual trial platform providers, directly or indirectly;
- support sustainability of existing trial networks and/or data sources, directly or indirectly;
- aid centres in building referral networks;
- provide support for the conduct of natural history studies for ultra-rare diseases, identification of standard of care – patient flow, and development of patient registries;
- seek expert input/advice for ultra-rare diseases.

The allocation of the EUR 575 000 financial contribution will be decided by the full consortium at the second stage when preparing the full proposal.

Applicant consortium

The first stage applicant consortium is expected, in the submitted short proposal, to address the scope and deliver on the expected outcomes of the topic, considering the expected contribution from the pre-identified industry consortium.

This will require mobilising the following expertise and/or resources among others:

- for the development of new endpoints, biomarkers in rare/ultra-rare and paediatric diseases;
- for epidemiology and natural history diseases;
- for translational science;
- for data management and standards;
- for devices, digital health and registries;
- for clinical operations, and in engagement with patient representatives and other interest organisations within the area of public health;
- for education and training;
- for European Research Networks;

- for project management expertise in running cross-sectorial projects.

Applicant consortia should bring together partners with relevant expertise such as regulators, healthcare professionals, patient representatives / organisations, health technology developers, research organisations, academia, biostatisticians, legal experts, ethicists. Participation of SMEs with expertise in clinical development in small populations and/or in the use of digital health technologies is encouraged. The composition of the consortium should also ensure a broad geographical representation of EU member states. For the development of the playbooks, input from other relevant stakeholders, in particular HTA bodies, would be necessary.

At the second stage, the consortium selected at the first stage and the pre-identified industry consortium and contributing partners will form the full consortium. The full consortium will develop in partnership the full proposal, including the overall structure of the work plan and the work packages, based upon the selected short proposal at the first stage.

To successfully deliver according to the objectives, it is important to engage with stakeholders within the health (research) ecosystem such as health authorities, health technology assessment (HTA) bodies and regulatory bodies, starting with the European Medicines Agency (EMA).

Dissemination and exploitation obligations

The specific obligations described in the conditions of the calls and call management rules under ‘Specific conditions on availability, accessibility and affordability’ do not apply.

Topic 5: Safe & Sustainable by Design (SSbD) packaging and single use device solutions for healthcare products

Expected impacts to be achieved by this topic

The project is expected to strengthen and make more competitive the European healthcare industry by positioning it at the forefront of the development of medical technologies, products, and services of the future - those that generate less waste, require less waste treatment, have reduced carbon footprints, increased circularity, and other approaches that reduce the environmental impact of healthcare.

It aims to promote the development of new health products by integrating the principles of the safe & sustainable by design (SSbD) framework[44], from the earliest design stages, and notably for packaging and device design including the end-of-life of a product. In the context of this call, packaging includes primary packaging in direct contact with products (e.g. drugs, medical devices, *in vitro* diagnostic reagents, etc.) and secondary packaging made of plastic polymer materials – excluding secondary and tertiary cardboard packaging. Medical devices refer to single-use plastic pharmaceutical and medical devices used for the administration of medicines such as pens used for insulin injection or devices used for surgeries such as trocars and staplers. They may contain additional components such as metals and electronic components as is the case of smart staplers, for example.

The project should as a minimum have all of the following impacts:

- Developers of health products (e.g. drugs, medical devices, in vitro diagnostic reagents, combination devices, etc.) are able to draw general lessons and best practices for their current research, and integrate research results on packaging and devices that generate less waste, make more efficient use of materials, and minimise the use of single-use components.
- Alignment with the European Green Deal objectives for healthcare systems, especially in the field of waste management and CO2 reduction, as well as an improved competitive position for healthcare companies.
- Improving the recyclability of medical devices, independent of whether the material of construction (e.g. plastic, metals) is classified as non-hazardous or infectious waste.[45]
- Reduced carbon footprint of health products in alignment with the Paris Agreement on climate change and the European Green Deal (55 % by 2030, NetZero by 2050).
- Propose new solutions that are holistic in nature, and which do not create additional adverse ESG (environment, social & governance) issues.
- New solutions should facilitate circularity even if the end points are not a closed loop back into the healthcare sector and instead are used for other applications.
- Identify a range of physical, mechanical, chemical and/or composting recycling infrastructures such that packaging materials and single-use medical devices (e.g. pens used for insulin injection, surgical trocars) can be recycled.

[44] https://publications.jrc.ec.europa.eu/repository/handle/JRC128591
[45] https://www.who.int/news-room/fact-sheets/detail/health-care-waste

Expected outcomes

The project should contribute to the following outcomes:

3. Paradigm shifts in standard materials to shape products of the future (e.g. reduced material usage by pushing the boundaries on material specifications such as down gauging foils/films, blending virgin and recycled polymers, inclusion of more sustainable materials as newly proposed from material suppliers, etc.).

4. Development of new and effective technologies, products and innovations that generate minimal waste from packaging and enable the recycling of used devices (including devices which have been in contact with human tissues, i.e. infectious waste[46]) throughout their lifetime of use in healthcare systems, by applying the principles of the safe & sustainable by design (SSbD) framework.

5. Alignment with the European Packaging and Packaging Waste[47] and Ecodesign of Sustainable Products[48] Directive proposals.

6. Such innovations – i.e. packaging materials & single-use medical devices (e.g., pens used for insulin injection, surgical trocars) are easily accessible in sufficient quantities to healthcare providers (e.g., hospitals, medical analysis laboratories, caregivers, and patient associations/organisations).

7. Environmentally-friendly packaging and device materials are designed from sustainable raw components and manufacturing processes with minimal carbon footprint.

8. Selective sorting procedures, implementable by healthcare providers.

9. The creation of short circuits for recycling packaging and device waste from healthcare providers' locations.

Healthcare systems more widely adopt a lifecycle assessment approach, enabling healthcare to become a more sustainable industry with closer and more circular recycling loops for packaging as well as single-use devices, including those which may have been contaminated (i.e. infectious waste).

Solutions should include a holistic approach such as:

1. adoption of biomass balanced materials that reduce environmental impacts, and

2. inclusion of advanced recycling technologies such as various chemical recycling technologies (hydrolysis, pyrolysis, solvolysis, etc.) if improvements to environmental impacts can be properly documented.

Patient outcomes and the safety/performance of medical products should not be compromised by the environmentally-friendly packaging and device solutions to be developed by the project.

Notably, these packaging solutions should be compliant with existing standards (e.g. primary packaging with sterile barrier: ISO 11607) to guarantee the safe use of medical products, i.e. maintenance of the safety and performance levels that are claimed throughout their intended shelf life.

- Depending on the use cases selected by the project, they must provide a sterile barrier, maintain controlled humidity, protect against light, etc. throughout their shelf life, including shipment from manufacturing site to end users.

[46] https://www.who.int/news-room/fact-sheets/detail/health-care-waste
[47] https://environment.ec.europa.eu/publications/proposal-packaging-and-packaging-waste_en
[48] https://environment.ec.europa.eu/publications/proposal-ecodesign-sustainable-products-regulation_en

- When used as a sterile barrier, they should be compatible with common sterilisation processes (e.g. steam, gas sterilisation such as hydrogen peroxide; radiation treatments such as e-beam, gamma irradiation, X-rays, etc.).

- When used as medical products for use in humans, existing safety & biocompatibility standards are met such as European Pharmacopeia (EP) compendia, ISO 10993, etc. (e.g. not generating extractible and leachable harmful products during the full shelf life of the products).

- The chemical and physical properties of the new material formulations should also guarantee the intended shelf life of the medical products (e.g. up to 5 years).

- Work with regulators (e.g. European Chemicals Agency (ECHA), European Directorate for the Quality of. Medicines & HealthCare (EDQM), European Pharmacopeia (EP), US Pharmacopeia (USP), American Chemical Society (ACS), etc.) to create new or revised standards/monographs for new materials that are used in health products. By extension, this engagement should contribute to the generation of future product eco-design labels / green claims.

- For example, the use of packaging composed of biodegradable, recyclable and/or environmentally benign ingredients is favoured if the claimed performance and safety of the medical products are maintained.

- Improved and simplified protocols for the management, collection, and recycling of medical device waste (packaging and devices) to reduce waste management costs for healthcare providers and minimise the environmental impact of the medical waste generated by medical devices.

- Protocols for the collection of single-use devices and their packaging to drive circularity should be easily implementable by healthcare providers. Their adoption must be possible for the greatest number of healthcare providers, regardless of their location. They may potentially include the decontamination of products if they have been in contact with human tissues to allow their sorting and recycling under the safest conditions.

- Improved and simplified protocols for supply chains and logistics for sorting of packaging waste of health products for healthcare providers with a minimised carbon footprint.

The outcomes must be as cost-effective as possible so as not to burden health systems with prohibitive additional costs.

Overall, the project is expected to yield strong results from the use cases. The results should be taken as evidence to collaboratively shape European legislation on packaging and packaging waste and the eco-design of sustainable products for health technology industries.

Scope

Product development

The project should accelerate the implementation of alternative eco-packaging and device materials through collaborative work by including policy makers, regulators, and standards bodies. It should identify, characterise, and test new replacement materials according to specifications and in compliance with existing standards (e.g. primary packaging with sterile barrier: ISO 11607).

The project should examine the European landscape of materials, whether commercially available or under development, which may be acceptable as components of sustainable packaging and appliance solutions, from different perspectives, regulations, possibility to recycle with current and future waste management processes, and sustainability of industrial supply. Such a review can benefit from and

partner with the European Partnership for the Assessment of Risks from Chemicals (PARC) and with the successor partnership of the M.ERA-NET III and the AMI2030 initiative. In addition, synergies with projects funded in the Horizon Europe Cluster 4 addressing SSbD could be envisaged (HORIZON-CL4-2023-RESILIENCE-01-21: Innovative methods for safety and sustainability assessments of chemicals and materials (RIA); HORIZON-CL4-2023-RESILIENCE-01-22: Integrated approach for impact assessment of safe and sustainable chemicals and materials (RIA); HORIZON-CL4-2023-RESILIENCE-01-23: Computational models for the development of safe and sustainable by design chemicals and materials (RIA)).

Health tech companies are expected to design and develop new packaging and devices (e.g. insulin pens, staplers) by starting from solutions that already exist or are at an advanced stage of development (e.g. available paper-based covers / packaging seals reinforced with polyolefins, or mixtures of virgin and chemically recycled polymers for the manufacture of blisters), and/or by selecting fully compostable or recyclable materials (for example, biomass balanced polymers as currently proposed and under development by chemical companies) to generate innovative packaging and device solutions. The polymers or materials to be selected must not only be recyclable/compostable, but also manufactured with a minimal environmental footprint.

The design and development of the new packaging and devices should apply and adapt circular economy principles and be guided by the SSbD framework. It should be done in close partnership with all players of the value chain from the manufacturers of the raw materials to the end users, the healthcare providers. The packaging and device use cases of the project are highly expected to improve and enrich the current SSbD framework, through concrete feedback to the European Commission and lessons learned. It is envisioned that this will necessitate regular interactions between the project and the developers of the SSbD framework at the European Commission.

Recycling

The project should promote the management of waste from packaging and single-use devices (including complex devices) by end users, the healthcare providers, considered as key partners of the project. This should lead to the effective implementation of the sorting and recycling of waste through collaborative work, including technical, organisational, and regulatory aspects (e.g. allowing the reuse of plastics etc. after industrial disinfection and/or decontamination of infectious waste, development of new recycling processes, setting up composting units etc.). Preferably, healthcare providers should include not only hospitals, but also other end users such as nursing homes. Healthcare providers should preferably be from several EU Member States or associated countries (e.g. minimum 3 EU Member States or associated countries), given the great disparity of practices from one country to another, in terms of legislation and implementation of waste sorting and recycling.

Importantly, the project should extend existing life cycle assessment (LCA) based metrics systems to packaging and devices, by considering the life cycle of the packaging materials, from their manufacturing to their recycling / composting. The LCA study must be carried out by an independent institution. Key performance indicators are expected to come from comparing LCA metrics with the implementation of the SSbD framework, which should lead to better packaging and device recyclability and more favourable life cycle outcomes.

Another key element of the project is expected to come from an active partnership with European non-profit packaging associations, single-use plastic, and waste management associations and, possibly, standards bodies and approval bodies responsible for marketing authorisations. These institutions should work with European policy makers to support evidence-based policy making based on the findings of the different use cases of the project. The development and implementation of recyclable packaging and device solutions should also be articulated by the health tech trade associations, at the European (i.e. EFPIA, COCIR, MedTech Europe, EuropaBio and Vaccines Europe) or national levels, in particular with their working groups on sustainability and the circular economy.

General lessons / best practices and results will be shared as far as possible (e.g. peer-reviewed articles, white papers, press releases, web media, report deliverables, etc.). Communicating project results is essential to collaboratively shaping the acceptability, adoptability, and implementation of European legislation on packaging and packaging waste and the eco-design of sustainable products for health technology industries.

Besides this topic, another topic in this IHI call entitled “Sustainable circular development and manufacturing of healthcare products and their quantitative environmental impact assessment” will aim to improve the manufacturing efficiency of drug substances of chemical/biological origin (covering all chemical drug substances, proteins, oligonucleotides, vaccines or polypeptides etc.) by developing new manufacturing technologies, saving natural resources like water and fossil or fossil-based raw materials, and reducing waste in accordance with circularity principles (reduce, reuse, refine, recycle).

To jointly develop new strategies to ensure a greener healthcare industry along the whole value chain, and to avoid overlaps, a close collaboration between the two topics is essential and should be reflected by providing dedicated resources in both projects to align on common life cycle assessment (LCA) methodologies and LCA data.

Why the expected outcomes can only be achieved by an IHI project

To fully develop and foster the adoption of recyclable packaging and device recycling solutions to drive a circular economy for healthcare products, it is essential that different industry sectors come together and exchange knowledge and best practices to find optimal solutions. Combining expertise from various industrial and research sectors is critical to the success of this project.

It is essential that health tech industry partners from different sectors, e.g. the pharmaceutical industry, medical device manufacturers, *in vitro* diagnostic, biotech & vaccine companies, etc. exchange knowledge and experience and provide complementary use cases.

Healthcare providers (HCPs) are identified as key stakeholders as end users of healthcare products. Packaging and device management goes through HCPs with the implementation of selective sorting solutions to integrate them into appropriate recycling channels. HCPs should be from different European Union countries, preferably a minimum of three countries of different sizes.

This cross-sectorial collaboration is expected to include circular economy specialists, notably for life cycle assessment (LCA), European not-for-profit packaging, single use plastics and waste recycling associations, and, possibly, standardisation bodies. Such institutions and all partners of the project are committed to working with European policy makers to support evidence-based policy making.

Beyond classical health tech industries, the project may be even more impactful by including as partners other industry players of the value chain, notably from the materials and packaging industries.

This will ensure optimal implementation of the technical and scientific innovations expected to stem from this topic. IHI JU offers a unique opportunity to break down existing silos along the packaging and device

value chain for a measurable impact on adopting recyclable packaging and device materials and reducing waste from packaging & device materials.

Pre-identified industry consortium

The pre-identified industry consortium that will contribute to this cross-sectoral IHI project is composed of the following pharmaceutical and medical technology industry partners:

- Boehringer Ingelheim
- Eli Lilly
- Fresenius Medical Care
- J&J
- Medtronic (Lead)
- Novo Nordisk
- Pfizer
- Takeda

In the spirit of partnership, and to reflect how IHI two-stage call topics are built upon identified scientific priorities agreed together with several proposing industrial beneficiaries, it is envisaged that IHI proposals and projects may allocate a leading role within the consortium to an industrial beneficiary. Within an applicant consortium discussing the full proposal to be submitted for the second stage, it is expected that one of the industrial beneficiaries may become the coordinator or the project leader. Therefore, to facilitate the formation of the final consortium, all beneficiaries are encouraged to discuss the weighting of responsibilities and priorities regarding such leadership roles. Until such roles are formalised by execution of the Grant Agreement, one of the proposing industrial leaders shall facilitate as project leader an efficient drafting and negotiation of project content and required agreements.

Indicative budget

The maximum financial contribution from IHI is up to EUR 8 300 000.

The indicative in-kind and financial contribution from industry partners can go to EUR 8 300 000.

Due to the global nature of the participating industry partners, it is anticipated that some elements of the contributions will be in kind contributions to operational activities from those countries that are neither part of the EU nor associated to the Horizon Europe programme.

The indicative in-kind contribution from industry partners may include in-kind contributions to additional activities (IKAA).

Indicative duration of the action

The indicative duration of the action is 48 months.

This duration is indicative only. At the second stage, the consortium selected at the first stage and the pre-identified industry consortium may jointly agree on a different duration when submitting the full proposal.

Contribution of the pre-identified industry consortium

The industry consortium is not limited to health tech companies (i.e. pharmaceutical, medical devices, *in vitro* diagnostic & imaging companies, etc.).

The industry consortium expects to contribute to the IHI project by providing the following expertise and assets.

- Grant administration & project management
  - To provide legal support for project-related tasks.
  - To support project management.
- Packaging & single-use pharmaceutical and medical device use cases
  - To design and develop safe & sustainable packaging solutions and to apply the safe & sustainable by design (SSbD) framework. For example, such activities should consider from project start, i) recycling routes; and ii) if relevant, second life of packaging and devices.
  - To implement and execute flagship projects guided by the SSbD framework by including recyclable materials as components of sustainable packaging and appliance solutions.
  - To identify materials not yet marketed and/or under development, but compatible with the regulatory and normative requirements of the industrial manufacture of health products.
  - If the design and development stages are successful, industrialisation activities are expected to lead to the implementation of new pilot and/or industrial manufacturing lines.
  - To be inspired by and learn from other industries by possibly exploiting synergies, with the food industry for example.
  - To look for cost-effectiveness: new and innovative sustainable solutions should be reasonably cost-efficient compared to existing solutions.
  - To identify implementable sustainable solutions: New and innovative sustainable solutions should be still acceptable and adoptable by end-users (e.g. patients, nurses / caregivers, healthcare providers [HCPs], etc.), or even better compared to existing solutions.
  - To compare the performance of the sustainable packaging & device solutions with existing solutions and determine if they are suitable to be used with current products, according to specifications and standard requirements. It is essential that the sustainable packaging and device solutions do not compromise the safety and performance of the medical products.
- Recycling
  - To contribute to the definition of “recyclable” vs. “recycle-ready” with all partners of the project. Recycling activities may be preceded by decontamination procedures in case of contact with human tissues.
  - As a first intent, “recyclable” means that a product is likely to be recycled and the infrastructure exists such that the “recycle-ready” product can be recycled.
  - Physical, mechanical, and chemical recycling and composting are recycling solutions that are considered in scope.
  - Burning and landfill solutions should be avoided as much as possible.

- Recyclable “at all” is good enough, but it does not have to be a closed loop in the health tech industry. Raw materials can also be re-used in other industries. The primary goal is re-use of recycled packaging and device materials.

- To understand drug-product interactions and biological contamination as potential limitations to recycling and propose solutions to overcome them.

- From waste management audits of HCPs, the industry and the public consortia will work together to make recommendations to improve the sorting and recycling of packaging and single-use devices.

The allocation of the EUR 400 000 financial contribution will be decided by the full consortium at second stage, when preparing the full proposal.

Applicant consortium

The first-stage applicant consortium is expected, in the submitted short proposal, to address the scope and deliver on the expected outcomes of the topic, considering the expected contribution from the pre-identified industry consortium.

Beyond grant administration and project management, 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. It should include any relevant public and private organisations.

Grant administration

- To provide financial administration, submission of deliverables, periodic reports etc.

Project management

- To coordinate internal communication and meetings, general oversight and management of communication, exploitation and dissemination activities, risk management.

- To provide and maintain an IT infrastructure, to develop and implement an efficient data governance and management strategy of the joint consortium according to adequate standards and deliver the “data management plan”.

- To coordinate networking, joint activities and synergies with other European initiatives, or other relevant groups (e.g. Horizon Europe and IHI projects, etc.).

- To develop a strategy for the exploitation and sustainability of project results and outcomes and deliver the “exploitation and sustainability plan”.

- To prepare relevant documents / reports of the results being generated by the project (e.g. briefing books, guidance documents, etc.) to be shared with any stakeholders committed to the development, evaluation and regulation of packaging and single-use solutions including European regulators, policymakers and standards organisations.

Project activities

- Consortium to review, evaluate and recommend materials (already existing or under development at the pilot scale) which can be selected as safe and sustainable packaging and single-use devices, according to the regulatory landscape and current specifications / standards for packaging and single-use devices.

- Consortium to review and evaluate the waste management process solutions of the recommended list of materials with a focus on existing recycling schemes, at the industrial level or at a pilot scale, which can be leveraged by healthcare providers. The review should provide a European landscape assessment and highlight any regional disparities. It should also integrate the national and European regulations and incentives of waste management and recycling.

- The consortium should be acquainted with planned activities under the European Partnership for the Assessment of Risks from Chemicals (PARC) and take advantage of the partnership as a facilitator for open data and methodology sharing with risk assessors and their scientific networks.

- Healthcare providers (HCP) including hospitals, medical analysis laboratories, caregivers, and patient associations to contribute to the identification, evaluation and implementation of sorting and waste management solutions of packaging and single use devices. HCPs are also expected to generate audit reports on the waste they generate by categories (non-hazardous & hazardous) and by materials (e.g. plastic, metal, paper). The report should also include quantitative data on waste volumes / costs per category, identification of waste minimisation, opportunities / potential cost savings, facility walk through / stream analysis of waste, application of waste reduction principles (e.g. 10 R's rule[49]), improvement plans for compliance with regulation and waste minimisation goals set at the national level (e.g. see the Dutch example of Green Deal Sustainable Care 2.0[50]) or European level.

- From the waste management audit reports, recommendations to optimise waste management should be made by all actors of the value chain, including HCPs and health tech industries.

- HCPs with their external waste management partners are expected to run pilot studies of waste management from the use cases provided by the healthcare industries.

- Policy makers, health tech trade associations, notified bodies (for medical devices and in vitro diagnostic products), European Medicines Agency (EMA) and/or organisations working with EMA, environmental health, and sustainability (EHS) institutions, advocacy groups, standards organisations as partners or members of the advisory board, to work in partnership with all partners of the project on the acceptability, applicability and implementation of regulations on safe and sustainable packaging and single use devices.

- European non-profit packaging, single-use plastics & waste recycling societies or associations as partners to work with the industry consortium, policy makers and standards organisations to support evidence-based policy making from the findings of the project. These societies or associations are also expected to provide data and insight on trends of eco-design and waste management of health tech products, but also of products from other industries when possibly benefiting the health tech industries.

- Small and medium-sized packaging companies will co-develop innovative, safe and sustainable solutions with the industry consortium.

- Small and medium-sized health tech companies including vaccines and biotech players are also invited to develop their own packaging and / or device solutions.

- Consortium – public and/or private entities – to assist the physical, chemical characterisation of new safe and sustainable solutions for packaging and single use devices, including compliance with the regulatory packaging and device requirements.

[49] https://www.sciencedirect.com/science/article/pii/S0921344919304598
[50] https://www.government.nl/topics/sustainable-healthcare/more-sustainability-in-the-care-sector

- Consortium – public and/or private entities – to evaluate the biocompatibility and toxicity of the new packaging and single-use devices according to regulatory and standard requirements (e.g. analysis of extractables and leachable compounds).

- To contribute to the regulatory landscape for life cycle assessment (LCA) standards in the EU and in other non-EU European countries.

- In conjunction with industry, to discuss with regulatory authorities, standards organisations, and advocacy groups the acceptability and implementation of the LCA metrics and in the EU and harmonisation with efforts in other non-EU European countries and the US.

- Evaluate the life-cycle assessment, including the costs in a comparative way (sustainable vs. current solutions).

- To evaluate the environmental impact of the new packaging and single-use device solutions with a holistic view, by including:

    - environmental toxicity of the end products;

    - environmental impact of the manufacturing process of the starting materials and their transformation into packaging and single-use devices.

- Standards bodies to adapt, revise, change current standards to accommodate the use of the sustainable solutions from the evidence generated by the use cases of the project and, possibly, other findings, notably captured by the different European non-profit packaging, single-use plastics and waste societies or associations.

- Subject to the rules of the IHI Horizon Europe Model Grant Agreement applicable to IHI, all major findings of the project – except for confidential information, notably pertaining to generated intellectual property – should be publicly disseminated and communicated. They should provide strong evidence to shape the acceptability, adoptability and the implementation of the future European regulations on packaging and single use devices.

- The project may include the question of certification or green claims of the materials used for the packaging and device solutions and also of the packaging and device solutions themselves.

Dissemination and exploitation obligations

The specific obligations described in the Conditions of the calls and calls management rules under “Specific conditions on availability, accessibility and affordability” do not apply.

Topic 6: Sustainable circular development and manufacturing of healthcare products and their quantitative environmental impact assessment

Expected impacts to be achieved by this topic

This project will pave the way for European healthcare industries to collaborate cross-sectorially to improve the manufacturing efficiency of drug substances of chemical/biological origin (covering all chemical drug substances, proteins, oligonucleotides, vaccines or polypeptides etc.) by saving natural resources like water and fossil or fossil-based raw materials and consumables, in addition to reducing waste in accordance with circularity principles (reduce, reuse, refine, recycle).

Healthcare industries in the Organization for Economic Cooperation and Development (OECD) countries are responsible for 3-8% of natural carbon dioxide emissions[51]. The invention of new and creative technology in the field of chemistry and biotechnology will make Europe the central driver of innovation for the supply of drugs made of renewable resources. The ultimate goal of the project is to significantly reduce the environmental impact of the manufacture of medicines.

Based on life cycle assessment, most of the environmental impact of a typical medicine is generated during manufacturing operations. This project will address gradual changes in the reduction of virgin resource consumption, greenhouse gas emissions (GHG), waste generation and water consumption and minimise contaminating effluents from industry. This would be achieved by the development/introduction of shorter manufacturing routes, lower energy processes, reductions in solvent and chemical use, the introduction of biorenewable materials, and the replacement of substances of concern (e.g. PFAS = poly- and perfluorinated alkyl substances, chlorinated organic solvents) with more benign alternatives (which may be commercially available or under development) like aqueous-based reagents.

Establishing diversified sustainable supply chains of raw materials that are independent of volatile market situations will promote the security of medicines as finished products by the European healthcare industry and contribute to the health of European citizens by safeguarding the continuous availability of drugs for patients. The new chemical technologies developed will provide access to newly discovered fine chemicals and pharma building blocks. This will allow industries to become independent of fossil-based raw materials like crude oil and strengthen the European science and technology community.

The harmonisation of environmental sustainability assessment methodologies across the whole healthcare sector will influence European environmental regulations to make life cycle assessments (LCA) comparable between different pharmaceutical manufacturing processes and will contribute to establishing a novel European LCA guideline, aligned with the EU Product Environmental Footprint[52] methodology and its underlying relevant methods and standards.

The project will provide a recognised contribution from the life science sector to the Green Deal[53] and Chemicals Strategy for Sustainability[54] of the European Union, in line with the Pharmaceutical Strategy for Europe[55].

[51] Environmental considerations in the selection of medical staplers: A comparative life cycle assessment, Journal of Cleaner Production, 371, 2022, 133490.
[52] https://eplca.jrc.ec.europa.eu/permalink/PEF_method.pdf
[53] https://ec.europa.eu/info/strategy/priorities-2019-2024/european-green-deal_en
[54] https://environment.ec.europa.eu/strategy/chemicals-strategy/implementation_en
[55] https://eur-lex.europa.eu/legal-content/EN/TXT/?uri=CELEX:52020DC0761

Expected outcomes

We expect all of the following outcomes to be generated from the topic.

1. Generation of novel, process-intensified manufacturing methods and unit operations according to safe and sustainable by design (SSbD) principles with the following goals.

    a. Reducing solvent volumes in chemical synthesis and cleaning operations: Large volumes of pure and high-quality organic solvents are required for pharmaceutical manufacturing without ever being reused or recovered. The goal is to identify ways to either eliminate solvents, by increasing the usage of water-based reactions; reuse solvents; or more preferably avoid entirely the use of high solvent volumes. Innovative methods (e.g. surface functionalisation) of cleaning and rinsing techniques (equipment, medical devices) need to be developed to minimise solvent waste.

    b. Replacement of substances of concern:

        i. by either replacing reagents with less toxic chemicals, e.g. replacements of chlorinated solvents, toxic reagents, heavy metal based homogeneous catalysts;

        ii. by identifying alternative routes to target the chemical transformation, e.g. through catalytic or biocatalytic rather than stoichiometric chemical transformations, or by reducing the overall number of steps (e.g. through cascade reactions) with a significant impact on the use of solvents and chemicals.

    c. Reducing total water volumes in fermentation processes (both upstream and downstream) by innovative fermentation designs, e.g. continuous manufacturing, perfusion technology and reusable downstream processing aids, or preferably by reducing or recycling the purified water (PW), and particularly high quality water (e.g. sterile water for injection (WFI)) volumes.

    d. New fermentation/cultivation and purification technologies (e.g. alternatives to chromatography or innovative chromatography technologies, buffers and resins) with reduced water and energy demands.

    e. Reducing energy consumption in chemical or biotechnological processes: Heating, cooling and sterilisation / cleaning in place (CIP/SIP) operations are energy intensive. Use of alternative chemical transformation steps or sterilisation techniques should help to reduce energy consumption.

    f. Harvesting new sources of raw materials other than fossil sources to have reliable access to readily-available starting materials, solvents, reagents, homogeneous catalysts (where possible transition metal based or, if necessary, rare earth metal based) or biocatalysts (enzymes for catalytic chemical transformations).

    g. Changing biomanufacturing[56]: Many biotechnological manufacturing processes rely on single-use equipment, consumables and materials, and this contributes to an increase in solid waste generation, especially plastics. Novel single-use materials will be developed from renewable sources with the possibility of recovering valuable materials like transition metals/rare earth metals from electronic components of single-use equipment (single-use reactors, electrodes, probes etc.) or using single-use equipment manufactured from renewable resources.

[56] The term “biomanufacturing” describes all manufacturing methods that utilize procaryotic or eucaryotic cell systems to produce biomolecules for use in medicines (e.g. therapeutic proteins, monoclonal antibodies (mABs), mRNA for vaccines) or chemical synthesis (e.g. enzymes).

2. According to the World Economic Forum 2022 report, the pharmaceutical industry is fuelling the climate crisis where the sector is responsible for 4.4% of global emissions and its CO_2 footprint is forecast to triple by 2050[57]. Reducing the generation of greenhouse gases (mainly CO_2, methane, nitrous oxide) is a key element to preventing climate change. Any attempt to improve the efficiency and environmental compatibility of a manufacturing process under development is expected to reduce the generation of GHGs everywhere on the planet. A thorough assessment of the origins and the life cycles of all chemicals, reagents, solvents and API (active pharmaceutical ingredient) drug substances procured must be performed to have a complete cradle-to-gate analysis of the GHG generation to be measured as GHG footprint per mass/dose/treatment. All changes in manufacturing processes should include considerations of the economic impacts. This includes the development of thresholds for the recovery and reuse of solvents.

3. All aspects of process designs should be quantified in standardised assessment systems comprising as many influence factors as possible to describe the full environmental impact of a single drug product on everybody's environment. Artificial intelligence (AI) / machine learning (ML) driven technology should help to sharpen the full picture of the environmental impacts from material supplies via manufacturing to the consumer and waste (= cradle-to-gate analysis). A publicly accessible digital toolbox will be developed that guides development chemists, biotechnologists and engineers to create the best possible manufacturing processes that produce safe and high-quality products with the minimum environmental impact possible.

4. The harmonisation of assessment systems[58] across the healthcare industry is expected to be incorporated into European environmental guidelines, and standards aligned with existing standards outside the scope of the EC.

Scope

Many programmes launched on green chemistry and green pharmaceuticals (e.g. Innovative Medicines Initiative [IMI] projects like CHEM21 and iCONSENSUS, or HORIZON-HLTH-2021-IND-07-01 projects) aim to demonstrate the technical feasibility of applying new methods to improve the overall efficiency and robustness of single manufacturing steps and how to assess their impact on the environment.

The scope of this topic is as follows.

- To transfer approaches from green chemistry and technology into biomanufacturing by developing new types of upstream and downstream processing methods with increased efficiency, more balanced energy consumption and less waste (stainless steel vs. single-use equipment), continuous manufacturing (perfusion cell cultures vs. fed-batch), and the production of enzymes as process reagents in the manufacture of pharmaceutical products.

- To apply innovative technology to the chemical synthesis of e.g. small molecules, oligonucleotides, peptides and vaccines, by removal of hazardous chemicals, and streamline manufacturing processes and energy consumption, mainly by introducing new production and analytical technologies using "greener" solvents, smaller solvent volumes (e.g. mechanochemistry, alternatives to chromatography), continuous manufacturing processes (e.g. flow-chemistry) and emphasising catalysis and enzymatic chemistry. More sustainable sterilisation processes as alternative to ethylene oxide sterilisation for devices.

[57] https://www.weforum.org/agenda/2022/11/pharmaceutical-industry-reduce-climate-impact
[58] Assessment System means a set of measures that collects and analyses data of raw materials, consumables, equipment performance, and unit operations to evaluate and improve the performance of inputs, the unit, and its output.

- To identify, characterise and test novel replacement materials for single-use equipment and process aids (tubing, bags, PVCs (polyvinyl chlorides)) based on materials from renewable sources, e.g. BioPET (biorenewable polyethylene therephthalate).

- To create new life cycle assessments (LCA) of drug substances and drug products of all (including new) modalities[59] to gain a holistic view of the end-to-end environmental impact of all materials, energies, chemicals and wastes involved in the production of medicines, with the ultimate goal of achieving comparability of diverse manufacturing processes, technologies and products, e.g. chemical entities (tablets / liquid formulations) or biologics (lyophilised / liquid formulations).

- To promote diversified value/supply chains resulting in a shift away from dependencies on specific suppliers and ingredients, thereby promoting the security and resilience of the European pharmaceutical and healthcare industry and the health of European citizens.

- To harmonise and standardise the definitions, manufacturing ontologies, methodologies and frameworks for environmental impact assessment (e.g. LCA standards) of healthcare, including pharmaceutical products, across the European healthcare sector, and align with industries outside the EU (north America, Asia, UK etc.).

- To evaluate the applicability and relevance of the proposed solutions, existing impact assessments (e. g. life cycle assessments, based on existing industry standards, e.g. the standard developed by the Sustainable Markets Initiative, SMI) should be performed to show superiority in comparison to existing approaches.

Previous and current projects (cf. HORIZON-HLTH-2021-IND-07-01 projects IMPACTIVE, ENVIROMED, ETERNAL, SusPHARMA and TransPharm) have a strong focus on the environmental impact of current and new manufacturing technologies at low technology readiness level (TRL) using life cycle assessments. In this project, the industrialisation of new technology is pursued more intensively and on a larger scale at higher TRL by all partners. In this project, the standardisation of environmental impact assessment methodologies (e.g. LCA) of industrial processes is prioritised rather than the individual assessment of new technologies.

Continuous alignment and exchange with the relevant projects from the existing Horizon Europe and IMI programmes will avoid duplication of the work and allow for the harmonisation of scientific efforts.

Resources and learnings from previous and ongoing initiatives (e.g. projects funded under IMI1 / IMI2[60] or other Horizon 2020, Horizon Europe, NextGenEU and EU4Health projects) should also be taken into consideration.

Current projects like IMI project PREMIER[61] demonstrate the impact of drug substances, by bioaccumulation, in living organisms and mobility across the environment. In contrast, the aim of this project is to avoid the accumulation or distribution of any substances of concern in nature and therefore identify new transformations that can replace stoichiometric or catalytic use of toxic reagents or catalysts, respectively.

[59] The term “modality” includes biologically active macromolecules like proteins, oligopeptides, oligonucleotides/mRNA, vaccines, and protein conjugates.
[60] Findings from the IMI-funded projects CHEM21 and iCONSENSUS may be relevant. The CHEM21 project aimed to identify reactions and methodologies that addressed bottlenecks in the sustainability of processes applied to the synthesis of active pharmaceutical ingredients (APIs). The iCONSENSUS project aims to develop innovative analytical, hardware, software and high-throughput tools for the development, monitoring and control of mammalian cell cultivation processes for the production of biopharmaceuticals.
[61] https://imi-premier.eu/

Most fine chemicals originate from fossil sources. Creative utilisation of new sources is the key to directing our future manufacturing efforts into a more sustainable production of second-generation fine chemicals and drugs. Developing new skills and technologies by exploring renewable sources for the bulk production of chemical starting materials of high quality based on European research networks promotes and facilitates Europe's independence from raw material sources outside Europe and diversifies global supply chains. This will make sensitive supply chains more stable and guarantee reliable patient care in Europe.

The compilation of life cycle assessment data is a time-consuming and cost intensive process, requiring the collection of a large amount of data on raw materials, consumables, transport, manufacturing utilities, devices and other materials needed during the use phase and waste treatment of pharmaceutical products. Therefore, LCAs are created when the asset has already reached a mature development state. Early involvement of product environmental data can help guide development scientists in a more sustainable and overall impactful direction of manufacturing processes and technologies. While ongoing projects such as TransPharm[62] focus on developing new impact assessment methodologies for assessing the sustainability of pharmaceuticals, the project in this call will be complementary by applying harmonised standards for LCA. A harmonised set of standard data will be applied in close collaboration with SMI (Sustainable Markets Initiative) in this project based on a common set of product category rules (PCR), which will be fed into a shared database and digital planning tool that enables a non-expert user to investigate the environmental impact of new process designs, or later process or product changes. EU PEF / PEFCR (= product environmental footprint / product environmental footprint category rules) will be a key reference and over-arching starting point for a medicine-specific Product Environmental Footprint standard.

This project will therefore focus on the standardisation and harmonisation of assessing and scoring the environmental performance of systems across industry: healthcare and API manufacturing by chemical and biotech companies. They have developed a strong commitment to sustainability by design approaches over the past years with individually developed life cycle assessment methodologies to evaluate the environmental impact of their respective process developments and improvements. All methodologies lack a common framework of metrics and quantitative sets of descriptors to allow comparability of identical unit operations with different assessment systems.

The Chemicals Strategy for Sustainability has as its objective the transition towards safer and more sustainable chemicals in line with the SSbD principles. It will require that industry minimises, substitutes as far as possible, and phases out the most harmful chemicals in healthcare products whilst at the same time ensuring the sustainability / availability, safety, quality and efficacy of these products.

The early involvement of European regulatory authorities, both related to environmental footprinting requirements and from a medicine manufacturing perspective, are essential for the harmonisation of standards with existing European directives.

Besides this topic, another topic in this IHI call entitled "Safe & sustainable by design (SSbD) packaging and single use device solutions for healthcare products" will cover the reduction of waste, the recyclability and circularity as well as renewable feedstock of packaging materials. The impact of innovative packaging and device materials on the life cycle assessment (LCA) of the healthcare products will be investigated in this SSbD project. In order to jointly develop new strategies to ensure a greener healthcare industry along the whole value chain, and to avoid overlaps, a close collaboration between the two topics is essential and should be reflected by providing dedicated resources in both projects to align on common LCA methodologies and LCA data.

[62] https://transforming-pharma.eu/

Why the expected outcomes can only be achieved by an IHI project

Public partners/ small and medium-sized enterprises (SMEs): European science and technology is extremely powerful at collaborating on very basic research in order to create new manufacturing technologies and identifying alternatives to substances of concern (reagents/chemicals) used for manufacturing or as components of materials with direct contact to drug substances (e.g. primary packaging, process aids etc). The development of innovative and truly sustainable manufacturing technology and chemistry requires a highly skilled and modern academic research and innovation network that comprises university research groups, publicly funded research institutes and SMEs. The transformation of industrial manufacturing processes can only start with new knowledge developed and learnings shared from within independent research laboratories in science, engineering and novel therapeutic technologies. The wide scientific and industrial network of the partners in this consortium should serve as a starting point for an exchange with external partners in order to be able to implement the innovations more efficiently.

SMEs with unique platform technologies will feed new aspects into well-established material supply chains and manufacturing.

A project management office will provide administrative support to run the project.

Fine chemical and API manufacturers are the link between pharmaceutical or biotechnological industries and raw material suppliers. They play a key role in the overall life cycle of drug substance manufacturing as providers of chemical building blocks, bulk reagents, solvents and process materials.

Industrial partners will transfer research outcomes into industrial manufacturing practice and demonstrate the scalability of processes and validate the usability of new materials. Industry partners will assess any new ideas for their transferability into a commercial and scalable process to maintain the quality and safety of products and guarantee the safety and efficiency of a novel manufacturing process.

All partners, in combination with regulators, will eventually establish a cross-sectoral, harmonised standard life cycle assessment tool to quantify the environmental impact of different manufacturing routes in development that allows decisions to be made based on data rather than the experience of scientists. This tool should have the capacity to quantitatively support the selection of the most efficient and environmentally benign process by using real world data and innovative digital capabilities such as AI and ML.

Pre-identified industry consortium

The pre-identified industry consortium that will contribute to this cross-sectoral IHI project is composed of the following pharmaceutical and medical technology industry partners:

- AstraZeneca
- Abbvie
- Boehringer Ingelheim
- GlaxoSmithKline
- Janssen
- Medtronic
- Merck KGgA
- Novo Nordisk
- Olon
- Pfizer
- Sanofi (Lead)
- Servier

- SwiftPharma

In the spirit of partnership, and to reflect how IHI two-stage call topics are built upon identified scientific priorities agreed together with a number of proposing industrial beneficiaries, it is envisaged that IHI proposals and projects may allocate a leading role within the consortium to an industrial beneficiary. Within an applicant consortium discussing the full proposal to be submitted for the second stage, it is expected that one of the industrial beneficiaries may become the coordinator or the project leader.

Therefore, to facilitate the formation of the final consortium, all beneficiaries are encouraged to discuss the weighting of responsibilities and priorities with regard to such leadership roles. Until such roles are formalised by execution of the Grant Agreement, one of the proposing industrial leaders shall facilitate as project leader an efficient drafting and negotiation of project content and required agreements.

Indicative budget

The maximum financial contribution from IHI is up to EUR 20 550 000.

The indicative in-kind and financial contribution from industry partners is EUR 20 550 000.

Due to the global nature of the participating industry partners, it is anticipated that some elements of the contributions will be in kind contributions to operational activities from those countries that are neither part of the EU nor associated to the Horizon Europe programme.

The indicative in-kind contribution from industry partners may include in-kind contributions to additional activities (IKAA).

Indicative duration of the action

The indicative duration of the action is 60-72 months.

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

Contribution of the pre-identified industry consortium

The industry consortium expects to contribute to the IHI project by providing the following expertise and assets:

- Expertise in the development of drug substance and product manufacturing processes, aspects of environmental and occupational safety, cost efficiency, procurement of materials, energies and manufacturing equipment (e.g. supply chains, transportation, energy supply).
- Manufacturing equipment to scale up innovative technologies into the pilot plant scale and run test batches.
- Chemistry, manufacturing and controls (CMC) expertise in the development of new chemical entities or new modalities in terms of quality, patient safety, patient drug delivery systems and economy.
- Provide specifications on product categories and product data to feed the harmonised LCA methodology.
- Provide user requirements, delivery of manufacturing data to generate and feed the LCA tool.

- Provide user requirements to lead the development of new planning tools for safe and sustainable by design (SSbD) tools.

- The overall split of efforts should be 70%-80% investigation of new technologies, and 20%-30% creation of new standards/LCA tools in this project.

- Collaboration with other initiatives, e.g. SMI (Sustainable Markets Initiative), the ACS GCI Pharmaceutical Round Table, the British Standards Institute (BSI) and PEG (Pharmaceutical Environment Group) to harmonise efforts to define new standards of PCR (product category rules) and LCA.

Applicant consortium

The first stage applicant consortium is expected, in the submitted short proposal, to address the entire scope and deliver on the expected outcomes of the topic, taking into account the expected contribution from the pre-identified industry consortium.

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.

A project management office is expected to be member of the applicant consortium to provide the administrative support to run the project.

Applicants should clearly outline their approach for data capture, storage and sharing within the consortium as well as sharing results through peer-reviewed publications or other mechanisms. They must ensure that the relevant results and data repositories will be sustainable after the end of the project and made public.

Applicant consortia shall in addition provide the following expertise or resources.

Grant administration

- To provide financial administration, submission of deliverables, periodic reports etc.

Project management

- To coordinate internal communication and meetings, general oversight and management of communication, exploitation and dissemination activities, risk management.

- To provide and maintain an IT infrastructure, to develop and implement an efficient data governance and management strategy of the joint consortium according to adequate standards and deliver the “data management plan”.

- To coordinate networking, joint activities and synergies with other European initiatives, or other relevant groups (e.g. Horizon Europe and IHI projects).

- To develop a strategy for the exploitation and sustainability of project results and outcomes and deliver the “exploitation and sustainability plan”.

Interactions with regulatory authorities, health technology assessment (HTA) bodies, payers, policy makers, and advocacy groups

- To contribute to the regulatory landscape for life cycle assessment standards in the EU and in other non-EU European countries.
- In conjunction with industry, to discuss with regulatory authorities, standards bodies, and advocacy groups the acceptability and implementation of the LCA metrics in the EU and harmonisation with efforts in other non-EU European countries and the US.
- To prepare relevant documents regarding the approach used and the results generated by the project (e.g. briefing books, European Medicines Agency [EMA] guidance documents).

Technology

- Continuous manufacturing technology (flow chemistry, perfusion cell culture) in combination with online monitoring and in-process control.
- Innovative technology in manufacturing new chemical entities (NCE):
  - demonstrated expertise in pharmaceutically relevant chemical chemistry;
  - compulsory expertise: chemo catalysis and biocatalysis;
  - optional expertise: photochemistry, mechanochemistry, cell-based chemical transformations (oxidations, functionalisations).
- Innovative technology in manufacturing new biological entities (NBE):
  - new fermentation/cultivation technology with low volumes/low energy;
  - demonstrated expertise in pharmaceutically relevant expression systems;
  - innovative chromatography technologies, alternative purification technologies or other purification technologies replacing chromatography;
  - low energy utility preparation (e.g. WFI, steam);
  - ontologies in biomanufacturing.
- Innovative technology in manufacturing new medical devices (MD):
  - cleaning technology avoiding the use of solvents and detergents;
  - sustainable sterilisation processes (e.g. irradiation, supercritical CO2);
  - analytical methods to track chemical residues in medical devices;
  - checking the safety of new cleaning and/or sterilisation processes according to ISO10993 requirements;
  - cleaning & sterilisation process design based on SSbD framework principles.
- Innovative chromatography.

- Low energy, low solvent volume processes including reactions in/on water and recycling technologies.
- Utilisation and supply of raw materials, fine chemicals, consumables and solvents from renewable sources.
- Reuse technology of organic and aqueous solvents and catalysts to address waste reduction.
- Replacement of substances of concern to avoid regrettable substitutions.
- Expertise in conducting life cycle assessments of pharmaceutical products.
- Knowledge about existing LCA standards, tools and data for chemical and (bio)pharmaceutical products.
- AI/ML supported process design based on SSbD principles.
- Network with healthcare providers and regulatory stakeholders.

At the second stage, the consortium selected at the first stage and the pre-identified industry consortium will form the full consortium. The full consortium will develop in partnership the full proposal, including the overall structure of the work plan and the work packages, based upon the selected short proposal at the first stage.

Dissemination and exploitation obligations

The specific obligations described in the conditions of the calls and call management rules under “Specific conditions on availability, accessibility and affordability” do not apply.