

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

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 to boost drug development for rare diseases by enhancing patient access to clinical trials and trial preparedness of investigational sites, by increasing acceptability of new tools and methods, and by preventing research fragmentation across Europe.

It will have a direct impact not only on patients with rare and ultra-rare¹ 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” areas² and increased 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 (impact on the current 95% of underserved rare diseases).
- By fostering the use of alternative innovative clinical designs to randomized 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 EU³ (ACT EU) initiative, proactive delivery of patient-oriented medicines across populations including patients with rare/ultra-diseases. Europe becomes 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 and avoiding patients’ disadvantages/burden (e.g., travel etc.) and alignment amongst healthcare providers (Policy makers, Regulators and HTA bodies) referring companies for selected diseases to these networks.

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

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

² “White spot”: conditions for which there is no approved treatment option and where development is not currently commercially viable.

³ <https://www.ema.europa.eu/en/human-regulatory/research-development/clinical-trials/accelerating-clinical-trials-eu-act-eu>

use and dissemination of Playbooks⁴, which as a result will optimise the current situation⁵ and increase the number of new approved medicines targeting rare/ultra-rare diseases currently underserved.

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 and 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”⁶ 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 approaches⁷ to transform the way treatments are developed with a view of accelerating approval and access.
2. Pressure-test new clinical trial designs by using the playbooks co-created with all stakeholders through case studies and modelling, addressing up to 4 selected paediatric/rare diseases (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:

- **Playbooks⁸ for designing novel clinical trials (CT)** for rare diseases /clusters of diseases that also can 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 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 e.g., real world evidence (RWE), remote elements etc.
 - Guidance from expert advice to developers on specific aspects when designing CTs.

⁴ 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.

⁵ <https://www.nature.com/articles/d41573-022-00019-z> / <https://irdirc.org/resources-2/rd-metrics/>

⁶ White spots: conditions for which there is no approved treatment option and where development is not currently commercially viable

⁷ Framework defined as structured processes and methodologies

⁸ Refer to footnote 72 (playbook).

- **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.
- **Certified/qualified clinical trials sites** scientifically and operationally (especially in the areas of ATMPs) with readily available pools of patients ready to be recruited in CTs where appropriate; working to agreed site standards along comparable processes 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, such as 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 & 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 EU 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 in 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 deliver more medicines for patients with rare diseases. This topic, which contributes to the Rare Disease MOONSHOT Initiative⁹, 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 & innovation ecosystem.

The topic aims at unravelling roadblocks on the current clinical development pathways and delivering 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, the use and the implementation of innovative clinical trials design (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

⁹ <https://www.eurordis.org/rare-disease-moonshot/>

clusters of diseases, while also addressing scientific and statistical challenges with the generation and interpretation of small, incomplete and/or heterogeneous data sets to help support CT and product approval.

- Identify good practices to address knowledge gaps including collection of natural history data, development of relevant new endpoints and of patient reported outcomes (PROs) to be incorporated into the CT design.
- Benchmark new clinical trials 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 Playbooks 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 in CTs where appropriate.

To be successful and deliver according to the objectives, it will be 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 RD¹⁰) 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 ERNs¹¹ are being established under the Directive on patients' rights in cross-border healthcare, with their registries under the supervision of the Member States¹², and therefore any plan for collaboration between ERNs and industry should be compatible with the principles¹³ 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, ERNs' registries, etc.) in line with these principles.
- to utilise the Commission's infrastructure for the RD registry data & 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 Consortium¹⁴, IMI EU-PEARL¹⁵, EUnetHTA²¹¹⁶.
- to build upon the results of H2020 research projects such as ERICA and FP7 projects developing methodologies for clinical trials for small populations¹⁷, namely IDEAL¹⁸, InSPiRe¹⁹ or ASTERIX²⁰. It will be

¹⁰ EJP RD (European Joint Programme on Rare Diseases): <https://www.ejprarediseases.org/>

¹¹ https://health.ec.europa.eu/european-reference-networks/overview_en

¹² https://health.ec.europa.eu/european-reference-networks/board-member-states_en

¹³ https://health.ec.europa.eu/system/files/2020-03/statement_industry_conflictinterest_en_0.pdf

¹⁴ <https://ncats.nih.gov/programs/BGTC>

¹⁵ <https://eu-pearl.eu/>

¹⁶ <https://www.eunetha.eu/eunetha-21/>

¹⁷ <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>

¹⁸ IDEAL – Integrated DEsign and Analysis of clinical trials in small population groups (rwth-aachen.de): <https://www.ideal.rwth-aachen.de>

¹⁹ InSPiRe (Innovative methodology for small populations research): <https://cordis.europa.eu/project/id/602144>

²⁰ ASTERIX (Advances in Small Trials designs for Regulatory Innovation and eXcellence): <http://www.asterix-fp7.eu/>

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 Screen4Care²¹, IMI c4c²², Remedi4All²³, C-Path RDCA-DAP²⁴,
- to help overcome 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 4 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 the 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 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 Enterprises (SMEs), will be essential for this project. Similarly, patients’ involvement and connection with clinicians, health care providers and rare diseases networks will be essential as well as collaboration with regulators to ensure appropriate development and implementation of the playbooks.

Pre-identified industry consortium and contributing partner(s)

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 stage 2, 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

²¹ <https://screen4care.eu/>

²² <https://conect4children.org/>

²³ <https://remedi4all.org/>

²⁴ <https://portal.rdca.c-path.org/>

Indicative budget

The maximum financial contribution from IHI up to EUR 8 500 000. **NB: this amount is indicative and subject to change, pending approval by the IHI Governing Board.**

The indicative in-kind and financial contribution from industry partners is EUR 9 100 000. **NB: this amount is indicative and subject to change, pending approval by the IHI Governing Board.**

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 stage 2, the consortium selected at stage 1 and the predefined industry consortium will jointly agree on a different duration if needed, when submitting the full proposal.

Contribution of the pre-identified industry consortium

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

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

Applicant consortium

The stage 1 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.

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 European countries. For the development of the playbooks, input from other relevant stakeholders, in particular HTA bodies would be necessary.

At stage 2, the consortium selected at stage 1 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 stage 1.

To deliver successfully according to the objectives, it will be 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

[To be determined: The specific obligations described in the Conditions of the calls and calls management rules under “Specific conditions on availability, accessibility and affordability” [apply][do not apply]