**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: Patient-centred clinical-study endpoints derived using digital health technologies

### Expected outcomes

The action under this topic must contribute to all of the following outcomes:

- organisations and institutions involved in the development of therapies for the treatment and management of chronic disease have access to a unifying framework and consensus-based recommendations for:
  - using a combination of patient preference information (PPI), clinical outcome assessments (COAs), and digital health technology (DHT)-derived measures to demonstrate the importance to patients of what is being measured by DHT-derived clinical-study endpoints;
  - determining, from the patient perspective, what constitutes a minimal clinically important difference (MCID) in a patient-centred, DHT-derived clinical-study endpoint.
- new methods for analysing PPI and COA data collected using DHT and for combining data from PPI, COA, and DHT-derived measures are available to researchers;
- a consistent framework for engagement regarding the development and use of patient-centred, DHT-derived clinical-study endpoints is available to industry and stakeholders;
- acceptance of the use of PPI, COAs, and patient-centred DHT-derived measures in addition to or in combination with traditional clinical-study endpoints to provide a robust view of the benefits of a therapy to patients;
- acceptance of the use of patient-centred DHT-derived measures for clinical-study endpoints as reliable evidence for the evaluation of the clinical and economic benefit of therapeutic medicinal products and medical technologies among stakeholders including, but not limited to, patient groups, regulatory bodies, and health technology assessment (HTA) bodies (including the EU Member State Coordination Group on HTA), indicated by a qualification opinion, endorsement, adoption or other approval by each relevant stakeholder group;
- patient-centred, DHT-derived endpoints are implemented along with traditional clinical-study endpoints in clinical studies of therapies to treat chronic diseases, and data from DHT-derived clinical-study endpoints are used in regulatory and reimbursement decision-making.

### Scope

Three types of patient-centred information related to how a patient feels and functions contribute to the evaluation of outcomes of a therapy:

- patient preference information (PPI)
- clinical outcome assessments (COAs) (including patient-reported outcome (PRO) measures)
- digital health technology-derived (DHT-derived) measures

Each of these types of measures can be used to understand patient-centred benefits of therapies (i.e., meaningful improvements in how a patient feels or functions).

DHT-derived measures can capture patient-centred information about disease symptoms, physical, cognitive, and emotional functions, and experience with therapy. They can measure the status of a patient's health in ways that may be related to, but often differ from, COAs. For example, DHTs may measure activity intensity but not specific activities. Likewise, DHT-derived measures may detect changes in patient-centred outcomes - such as function - earlier than a patient may notice such a change. For patient-centred DHT-derived measures (i.e., DHT-derived measures that capture how a patient feels and functions) to be useful as endpoints in clinical studies, they must not only be technically validated, but also demonstrate that they measure functions, activities, symptoms, and other impacts of disease and treatment that are important to patients and measure changes in these outcomes that are meaningful to patients.

PPI, COAs, and DHT-derived measures are different, but complementary, types of patient-centred data. Because these measures are complementary, using these measures in combination will provide a more robust view of the benefits of therapies measured using DHT-derived endpoints from the patient perspective. Combining these complementary measures is necessary to demonstrate the utility of using DHT-derived measures as clinical study endpoints that reflect the value of treatment benefits to patients. Specifically, using these measures in combination may contribute to determining what constitutes a minimal clinically important difference (MCID) in patient-centred DHT-derived endpoints from the patient perspective in clinical studies of therapies to treat chronic diseases. For the purpose of this project, a chronic disease is defined as a long-term health condition that may not have a cure.

However, despite recent increases in the use of PPI, COAs, and patient-centred DHT-derived measures, there is no unifying framework for understanding the relationships among these measures, nor how they can be used in combination to demonstrate meaningful, patient-centred benefits of therapies for chronic diseases in clinical studies.

Therefore, uncertainties exist regarding the utility of these measures either alone or in tandem, and the meaningfulness to patients of patient-centred DHT-derived measures when used as clinical study endpoints in the development of therapeutic products (including, but not limited to, pharmaceutical products, combination products, and therapeutic devices) for the treatment of chronic diseases.

The topic aims to develop a unified framework and consensus-based recommendations for using multiple types of patient-centred information to support the use of DHT-derived endpoints to demonstrate therapeutic benefit. This will ensure that therapies addressing patients' needs are approved for use and reimbursed at levels that reflect the value of the therapies to patients.

To fulfil this aim, the action funded under this topic must:

- develop a framework for using PPI, COAs, and DHT-derived measures in combination for the development, acceptance and implementation of patient-centred DHT-derived clinical-study endpoints in clinical studies of potential treatments for chronic diseases.

  The framework will be designed to ensure that PPI, COAs, and patient-centred DHT-derived measures used in combination will be accepted as reliable evidence to support the use of DHT-derived clinical study endpoints in the evaluation of the clinical and economic benefit of therapeutic drugs and technologies.

  The framework must:

  o include recommendations for using the three types of patient-centred data in addition to or in combination with traditional clinical-study endpoints to provide evidence of the patient-centred benefits of therapeutic drugs and technologies;

- o describe the potential relationships among COAs, patient-centred DHT-derived endpoints and other common types of clinical study endpoints;
  - o identify and address issues related to how and under which circumstances data from PPI and COAs can be used to determine what constitutes a MCID in a patient-centred DHT-derived clinical-study endpoint from the patient perspective;
  - o identify and address issues related to whether and how data from PPI, COAs, and patient-centred DHT-derived measures can be pooled, including the need for new techniques (including, but not limited to, artificial intelligence, machine learning, and large language models) to jointly analyse pooled data from the different types of measures;
  - o address issues related to diversity in patient populations (e.g., disease type, disease stage, health literacy, cultural factors, etc.) on the use and results of PPI, COAs, and DHT-derived measures and the ethical and equity implications of patient diversity on the interpretation and utility of patient-centred measures of therapeutic benefit.

- develop recommendations for:

  - o using quantitative PPI to better understand COA data by demonstrating the relative importance of domains, items, and scores (and changes therein) within a COA instrument and relative to other commonly used endpoints (including endpoints included in relevant core outcomes sets) in clinical studies within the same therapeutic area;
  - o understanding the relationships between COA data and patient-centred DHT-derived endpoints in diverse therapeutic areas;
  - o using DHTs (e.g., apps, smart personal devices, smart drug-delivery devices, therapeutic medical technologies, etc.) to collect PPI and COA data;
  - o using quantitative PPI, COAs, and patient-centred DHT-derived measures in combination to demonstrate the importance to patients of what is being measured by DHTs and determining what constitutes a MCID in a patient-centred, DHT-derived clinical-study endpoint.

- conduct at least four use cases to provide evidence to support the framework and recommendations.

  Each use case should address one or more recommendations and all recommendations should be supported by one or more case studies. Applicants should specify the methodology to be applied in each use case and identify how each use case will inform the framework and recommendations. The set of use cases should:

  - o include a range of digital measurement domains (e.g., physical activity, sleep, cognition, fatigue, or others) and address differences between passive and interactive DHTs.
  - o include a range of patient ages (e.g., paediatric, adolescent, younger adults, and older adults).
  - o address issues related to diversity in patient populations (e.g., disease type, disease stage, health literacy, cultural factors, underserved patient populations, etc.)
  - o address issues related to combining and/or jointly analysing PPI, COA, and/or DHT-derived data using new techniques (including, but not limited to, artificial intelligence, machine learning, and large language models).
  - o be conducted in partnership with academic medical centres and focus on all of the following areas:
    - − paediatric radiation oncology
    - − lung cancer
    - − non-motor and motor symptoms in Parkinson's disease

- obesity

All use cases must be conducted in a way that is consistent with generally accepted international treatment guidelines in the relevant disease area.

The precise scope of the use cases will be developed by the full consortium during the preparation of the full proposal at the second stage. Case studies should not involve the *de novo* development of novel COAs, DHTs, or DHT-derived measures.

- include robust input from relevant stakeholders. Applicants are expected to specify how relevant stakeholders will be engaged and identify the type of stakeholder required and their expected role in the project. Accordingly, applicants are expected to:

  o engage patients, parents or carers of juvenile patients, and patient organisations as active partners in all aspects of the project to ensure that interaction between patients and research is active, meaningful, and collaborative across all stages of the research process. In this way, research decision making is guided by patients' contributions as partners, recognising their specific experiences, values, and expertise.

  o develop the framework and recommendations in consultation with stakeholders, including patient organisations, regulators, health technology assessment (HTA) bodies, and medical organisations to ensure consensus about what is required to demonstrate the patient-centred benefits of a therapy.

  o develop a regulatory strategy and interaction plan for evidence generation to support the regulatory qualification of the framework and recommendations and engage with regulators in a timely manner (e.g., national competent authorities, EMA Innovation Task Force, qualification advice).

- Complement and coordinate with other initiatives including:

  o ongoing and completed European projects (and their successor organisations), and initiatives related to patient engagement and use of digital measurement technologies. Such projects may include, but are not limited to, IMI/IHI projects PRO-active, H2O, PREFER and the PREFER Expert Network, SISAQOL-IMI, IDEA-FAST, MOBILISE-D, IMPROVE, PaLaDin as well as EUnetHTA 21;

  o existing frameworks and guidance documents related to patient-focused drug development such as those from FDA and EMA;

  o existing frameworks and guidance documents related to the development and deployment of digital clinical measures such as those from the Digital Medicine Society.

## Expected impacts

The action under this topic is expected to achieve the following impacts:

- greater benefit to patients from improved health care by ensuring that DHT-derived measures of how a patient feels and functions are accepted as patient-centred clinical-study endpoints;

- patients having improved access to innovations that meet their needs through the development of new and improved evidence-based methodologies for a more comprehensive assessment of the added value of innovative therapeutic drugs and technologies;

- better informed decision-making at all levels of the health care system (authorities, organisations) to facilitate cost-effective allocation of health resources, continuing innovation, and better health outcomes;

- greater understanding of the relationship between multiple patient-centred measurements including PPI, COAs, and DHT-derived measures and how these measures, when considered together, can provide greater insight into the patient perspective;

- reduced uncertainty regarding the PPI and COA data required to demonstrate the patient-relevance of DHT-derived clinical-study endpoints, and that needed to determine what constitutes a MCID in a patient-centred DHT-derived clinical-study endpoint for use in the development of pharmaceutical products, diagnostics, combination products, and therapeutic devices;

- improved and more efficient engagement between industry and stakeholders in the evaluation of technologies developed using patient-centred DHT-derived endpoints in clinical studies;

- increased speed and efficiency in the development and evaluation of innovative therapeutic technologies.

## Why the expected outcomes can only be achieved by an IHI JU action

A unifying framework for understanding the relationships among PPI, COAs, and DHT-derived measures and how these can be used in combination to demonstrate patient-centred benefits of therapeutic drugs and technologies is novel and requires input from multiple disciplines, each with their own practices and guidelines. In addition, stakeholders with an interest in the use of these measures in clinical development are numerous, varied and include multiple patient groups, regulatory authorities, and HTA bodies among others. As DHT-derived measurement and other patient-centred data are being used more often in clinical development, there is a need for consensus among pharmaceutical and therapeutic medical technology manufacturers, DHT developers, and other stakeholders to define the evidence needs surrounding the use of patient-centred, DHT-derived endpoints in the approval, economic assessment, reimbursement, and adoption of medical technologies. Such a consensus from a wide range of interested parties requires collaboration among multiple research disciplines and stakeholders to ensure that the information needs of decision makers related to this information are addressed consistently.

To achieve the outcomes outlined above, a cross-sectoral collaboration is needed with a particular involvement of and focus on patients to give insights into their experience with current technology utilisation and to contribute as partners in the development of patient-centred digital measures and digital measurement technologies. The collaboration must include patients and patient advocacy groups, academic researchers, patient preference researchers, COA experts, health economists, healthcare professionals, data analysts, regulatory and HTA stakeholders, and health technology and therapy developers. Integrating data from different origins/sources requires the cooperation of multiple data holders in a non-competitive, neutral setting like an IHI project.

Therefore, a precompetitive public-private project is the only way to harness the required expertise and incorporate the perspectives of all the relevant stakeholders in the recommendations.

## Pre-identified industry consortium and contributing partners

The pre-identified industry consortium that will contribute to this cross-sectoral IHI JU project is composed of the following pharmaceutical and medical technology industry beneficiaries ('constituent or affiliated entities of private members'):

- AbbVie
- AstraZeneca
- F. Hoffman-La Roche
- IQVIA

- Johnson & Johnson
- Molnlycke
- Novartis
- Novo Nordisk
- Pfizer (Lead)
- Siemens Healthineers/Varian
- UCB

In addition, the following contributing partners will participate in the IHI JU action:

- GENAIZ
- John Snow Labs

In the spirit of partnership, and to reflect how IHI JU two-stage call topics are built upon identified scientific priorities agreed together with a number of proposing industry beneficiaries (i.e. beneficiaries who are constituent or affiliated entities of a private member of IHI JU), it is envisaged that IHI JU proposals and actions may allocate a leading role within the consortium to an industry beneficiary. Within an applicant consortium discussing the full proposal to be submitted for stage 2, it is expected that one of the industry beneficiaries may become the project leader. Therefore, to facilitate the formation of the final consortium, all beneficiaries, affiliated entities, and associated partners are encouraged to discuss the weighting of responsibilities and priorities with regard to such leadership roles. Until the role is formalised by execution of the Grant Agreement, one of the proposing industry beneficiaries shall, as project leader, facilitate an efficient drafting and negotiation of project content and required agreements.

## Indicative budget

- The maximum financial contribution from the IHI JU is up to EUR 12 600 000.
- The indicative in-kind contribution from industry beneficiaries is EUR 9 434 420.
- The indicative in-kind contribution from IHI JU contributing partner(s) is EUR 3 867 000.

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

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

## 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 predefined industry consortium and contributing partner(s) may jointly agree on a different duration when submitting the full proposal.

## Contribution of the pre-identified industry consortium and contributing partners

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

- results and insights from existing pilots and studies*;

- real-world evidence (RWE) and clinical trial data*;

- expertise in medicine; clinical development of therapies; digital measurement technologies; patient reported outcome measures and clinical outcome assessments; patient preference information; clinical and real-world data collection and analysis;

- expertise in regulatory strategy, policy, and decision making; health technology assessment and reimbursement; and publication support;

- data platforms, digital tools, apps, remote monitoring technology, healthcare-specific Natural Language Processing (NLP), Artificial Intelligence (AI).

\* Contributions to this project may include historical data generated outside of the project timelines. In this case, it will be considered as background provided to the project but with no value assigned and will therefore not constitute part of the in-kind contribution from the pre-defined industry consortium.

## Applicant consortium

The first stage applicant consortium is expected, in the 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.

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

- demonstrated experience in managing multi-stakeholder, cross-sectoral projects

- demonstrated experience interacting with regulatory authorities, HTA bodies, citizens and/or patient representatives

- expertise in PPI, COAs, and DHT-derived measures

- expertise in clinical study design

- expertise in health technology assessment and economic evaluation of therapies

- expertise in the public health impacts of therapeutic technologies

- expertise in advanced data management and data analytics techniques including, but not limited to, large-language models and artificial intelligence

- academic medical centres that can manage clinical case studies

- DHT partners that can contribute to the clinical case studies within the chosen clinical areas.

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

## Glossary

| Acronym | Meaning |
|---------|---------|
| AI | Artificial Intelligence |
| COAs | clinical outcome assessments |
| DHT | digital health technology |
| EMA | European Medicine Agency |
| FDA | Food and Drug Administration |
| HTA | health technology assessment |
| IHI | Innovative Health Initiative Joint Undertaking |
| IKAA | in-kind contributions to additional activities |
| IMI | Innovative Medicines Initiative |
| MCID | minimal clinically important difference |
| NLP | Natural Language Processing |
| PPI | Patient preference information |
| PRO | patient-reported outcome |