innovative health initiative

IHI

8th Call for proposals

Two-stage call

COCIR efpia EuropaBio MedTech Europe from diagnosis to cure Vaccines Europe

Co-funded by the European Union

TABLE OF CONTENTS

Introduction....3

Call conditions for single stage and two-stage calls 4

Topics Overview....11

Topic 1 : A city-based approach to reducing cardiovascular mortality in Europe....13

Topic 2 : Novel endpoints for osteoarthritis (OA) by applying big data analytics 20

Topic 3 : Modelling regulatory sandbox mechanisms and enabling their deployment to support breakthrough innovation 29

Topic 4: Patient-centred clinical-study endpoints derived using digital health technologies....35

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.

Call conditions for single stage and two-stage calls

For Call 8 please refer to the conditions relevant to the two-stage call

The submission deadline for short proposals (SPs) will be 10/10/2024, and the deadline for full proposals (FPs) will be 23/04/2025.

Scientific evaluation of the SPs under the two-stage call will be completed by 2024 and FPs in Q2 2025. 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 2023-2025 shall apply *mutatis mutandis* to the calls for proposals covered by this Work Programme, including the "Restrictions for the protection of European communication networks" under General Annex B. 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.

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	The conditions are described in 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.
Legal and financial set-up of the grant agreements	The conditions are described in General Annex G.

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

STANDARD ADMISSIBILITY CONDITIONS, PAGE LIMITS AND SUPPORTING DOCUMENTS

General Annex A ('Admissibility') to the Horizon Europe Work Programme 2023-2025 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 the first stage of a two-stage call, the limit for RIA short proposals is 20 pages;
- at the second stage 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 2023-2025 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 2023-2025:

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 the 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 6
  - Twenty percent (20%) for IHI JU Call 7[1]
  - One hundred percent (100%) for IHI JU Call 8

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 openness 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 2023-2025 shall apply *mutatis mutandis*.

[1] Even if this threshold of 20% is not intended as an eligibility condition *per se*, proposals recommended for funding that will feature a non-EU IKOP amount higher than the 20% of IKOP, will be requested to remove the exceeding part. If this is the 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 to 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.

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 or as constituent or affiliated entities of either.

- 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 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 – 2025,

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 as well as Union legislation and guidance relevant for its application 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 2023-2025 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 2023-2025 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.

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:

	Excellence Aspects to be taken into account:	**Impact** Aspects to be taken into account:	**Quality and efficiency of the implementation** Aspects to be taken into account:
First stage evaluation of two-stage procedure	-Clarity and pertinence of the project's objectives, and the extent to which the proposed work is ambitious, and goes beyond the state of the art. -Soundness of the overall methodology.	-Credibility of the pathways to achieve the expected outcomes and impacts specified in the work programme, and the likely scale and significance of the contributions due to the project.	-Quality and effectiveness of the outline of the work plan. -Capacity of each participant, and extent to which the consortium as a whole brings together the necessary expertise.
Single-stage and second stage of two-stage procedure	-Clarity and pertinence of the project's objectives, and the extent to which the proposed work is ambitious, and goes beyond the state of the art. -Soundness of the proposed methodology, including the underlying concepts, models, assumptions, interdisciplinary approaches, appropriate consideration of the gender dimension in research and innovation content, and the quality of open science practices, including sharing and management of research outputs and engagement of citizens, civil society and end users where appropriate.	-Credibility of the pathways to achieve the expected outcomes and impacts specified in the work programme, and the likely scale and significance of the contributions due to the project. -Suitability and quality of the measures to maximise expected outcomes and impacts, as set out in the dissemination and exploitation plan, including communication activities.	-Quality and effectiveness of the work plan, assessment of risks, and appropriateness of the effort assigned to work packages, and the resources overall. -Capacity and role of each participant, and extent to which the consortium as a whole brings together the necessary expertise. -Clearly defined and effective integration of in-kind and financial contributions, including those of IHI JU private members, their constituent or affiliated entities to enable a successful public-private partnership.

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 second stage proposal. This notification must be accompanied by a joint report clearly stating the reasons why a second stage 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 second stage 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 (first stage) 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[3].

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 2023-2025 shall apply *mutatis mutandis* for the calls for proposals covered by this Work Programme.

[3] Failure to observe this restriction may result in IHI JU rejecting either the breaching participant or the full proposal per Article 141 point 1, letter (c) of the REGULATION (EU, Euratom) 2018/1046 of the European Parliament and of the Council of 18 July 2018 on the financial rules applicable to the general budget of the Union, amending Regulations (EU) No 1296/2013, (EU) No 1301/2013, (EU) No 1303/2013, (EU) No 1304/2013, (EU) No 1309/2013, (EU) No 1316/2013, (EU) No 223/2014, (EU) No 283/2014, and Decision.

BUDGET FLEXIBILITY

General Annex F to the Horizon Europe Work Programme 2023-2025 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 the second stage 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].

SPECIFIC CONDITIONS ON AVAILABILITY, ACCESSIBILITY AND AFFORDABILITY (3A)[6]

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[7] 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[8], 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.[9]

  b) At the project interim review stage, if relevant[10], 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

[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 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

[6] Article 125(3) of the Council Regulation (EU) 2021/2085.

[7] This covers EU Member States and countries that are associated to Horizon Europe at the time of call opening.

[8] 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.

[9] 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 made affordable, accessible, available. These points could be checked at the evaluation stage.

[10] As discussed, this interim point allows a realistic appraisal of the 3A possibilities during the project lifetime, particularly as to the viability of specific expected 3A results.

four years after the project end and in order to meet those objectives laid out under point 1 above.[11]

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[12] 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.

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 2023-2025 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.

FINANCIAL SUPPORT TO THIRD PARTIES

Financial support for third parties in IHI projects is allowed for call 8. The additional conditions contained in General Annex B to the Horizon Europe Work Programme 2023-2025 for Financial Support to Third Parties shall apply *mutatis mutandis.*

[11] 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.

[12] Cognisant 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.

Topics Overview

HORIZON-JU-IHI-2024-08-01 **A city-based approach to reducing cardiovascular mortality in Europe**	The maximum financial contribution from IHI JU is up to EUR 15 750 000. The indicative in-kind contribution from industry partners is EUR 15 750 000. 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-2024-08-02 **Novel endpoints for osteoarthritis (OA) by applying big data analytics**	The maximum financial contribution from IHI JU is up to EUR 14 000 000. The indicative in-kind contribution from industry partners is EUR 11 416 000. The indicative in-kind contribution from IHI JU contributing partners is EUR 4 260 000. 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-2024-08-03 **Modelling regulatory sandbox mechanisms and enabling their deployment to support breakthrough innovation**	The maximum financial contribution from IHI JU is up to EUR 5 200 000. The indicative in-kind and financial contribution from industry partners is EUR 4 261 096. 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-2024-08-04 **Patient-centred clinical-study endpoints derived using digital health technologies**	The maximum financial contribution from IHI JU is up to EUR 12 600 000. The indicative in-kind contribution from industry partners is EUR 9 434 420. The indicative in-kind contribution from IHI JU	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.

	contributing partners is EUR 3 867 000. The indicative in-kind contribution from industry partners may include in-kind contributions to additional activities.	

Topic 1 : A city-based approach to reducing cardiovascular mortality in Europe

Expected outcomes

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

- **patients and citizens** will benefit from better preventive measures, earlier detection and diagnosis, better outcomes for disease management, and access to innovative and effective treatments for cardiovascular disease (CVD), as needed;
- **healthcare providers** will benefit from updated, evidence-based guidelines on CVD management and more efficient clinical pathways. They will also gain clarity on best practice examples in health management and CVD prevention means in European cities;
- **healthcare system decision-makers** will have better evidence and tools to implement appropriate CVD prevention strategies, including digital therapies, allowing for their introduction into clinical practice and adoption by all segments of society;
- **health technology assessment bodies, payers and regulators** will benefit from better information on the real-life use of cardiovascular medicinal products, the benefit-risk profile of medical devices and the value of CVD prevention in cities / urban areas (note: a city / urban area is expected to have a population of at least 50 000 in its urban centre, in line with the OECD-EC (Organisation for Economic Co-operation and Development – European Commission) definition of a city[13],[14]);
- **researchers, including industry stakeholders, and clinical investigators** will benefit from models and findings that will help future programme implementation in other cities in Europe and beyond.

Scope

Cardiovascular diseases (CVD), the world's leading cause of mortality, are responsible for over 18 million deaths annually with a staggering cost of EUR 282 billion in 2021 [1]. The CVD risk has been acknowledged by WHO's Sustainable Development Goal (SDG) 3.4 which aims to reduce heart disease rates by one-third by 2030[15]. Trends in the EU27 and the UK from 1961 to 2018 show a decline in the share of the total population living in rural areas, while towns and cities experienced a smooth and constant population increase. Europe's level of urbanisation was 75% in 2022[16] and is expected to increase to approximately 83.7% in 2050**Error! Bookmark not defined.**. In cities, CVD risks are amplified by factors like pollution, scarcity of green spaces and stressful lifestyles. The trend towards urbanisation often leads to significant healthcare disparities and worsening of CVD outcomes especially among underserved and disadvantaged communities. Thus, an improvement of the management of CVD in cities would be of significant benefit for the great majority of the European citizens living in an urban context.

The focus of this topic is on identifying and creating scalable models, interventions, and practices to enhance the overall efficiency and effectiveness of CVD management based on existing (e.g. Cardio4Cities) [2] or new pilots in up to 5 cities, to build evidence for replication across Europe in different socio-economic conditions. These pilots should propose a good coverage of different locations and contexts in Europe and deliver scalable solutions that can be applied to other cities.

[13] OECD-EC, "Cities in Europe: The new OECD-EC definition." January 2012.

[14] European Commission, "Urbanisation in Europe." last updated July 2020.

[15] WHO, "Noncommunicable diseases (who.int)." September 2023.

[16] https://data.worldbank.org/

The action funded under this topic will consider primary and secondary prevention strategies, early detection, timely diagnosis and treatment (healthcare delivery), lifestyle changes (personal responsibility), and living environment (community responsibility).

Against this objective, the future action is expected to deliver:

- predictive models (developed and validated) that integrate various data sources – including electronic health records, environmental data, and lifestyle factors – to forecast cardiovascular risk at the individual and population levels in urban settings;
- models and/or good practices (including governance structure, funding/financing models, etc.) and roadmaps on cost-effective approaches to improve cardiovascular (CV) health management that can be replicated across Europe;
- recommendations for updating European guidelines and standards on CVD management (including primary and secondary prevention, and treatment);
- a stronger definition and improved selection of performance indicators on CV mortality, patient outcomes and economic impact of interventions;
- harmonised data standards for measurement of performance and impact (including PROMs[17], PREMs[18], patient preference, clinical outcome assessments etc.).
- an easy-to-use digital platform (ideally based on existing solutions to ensure interoperability) and high-quality data that enable a data-driven approach to CVD risk management, using standardised data reporting to facilitate comparison across cities;
- new solutions: digital and telehealth for early detection and monitoring of CVD patients, leveraging technologies for monitoring by incorporating wearables and apps to continuously monitor the population's adherence to cardiovascular medications and the occurrence of potential side effects. Moreover, this will enhance predictive models with more granular data leading to more precise risk assessments;
- recommendations on enhancing patient use of and access to technology and digital interventions (telemedicine, wearables, clinical mobile apps…); targeted prevention strategies, urban planning recommendations, and public health policies to mitigate these risks;
- a platform, network, or another support mechanism for exchange of good practice, learnings, and experience, to support further deployment of successful approaches across Europe and beyond;
- recommendations on improving living conditions to support the goal of decreasing impact of cardiovascular diseases.

To address this challenge, the action funded under this topic should:

- select up to five cities to serve as pilot use cases. These cities should be representative of the European context (in particular in relation to size and population) to allow broader implementation across regions/countries, different cultural and/or economic distributions, considering different health care structures (private/public) in different countries. Indicatively, each pilot city (or another urban administrative entity) is expected to have a population of at least 50 000 in its urban centre, in line with the OECD-EC definition of a city;
- conduct a gap analysis of existing cardiovascular disease screening and diagnostics, clinical pathways and public health policies to guide the development of scalable models and best practices to fill these gaps, also considering broader European application (for example, set targets, define

[17] PROM: Patient Reported Outcome Measurements

[18] PREM: Patient Reported Experience Measurements

actions, strengthen enablers). In this analysis, due attention should be given to high-stress lifestyles (nutrition, physical activity) and socio-economic disparities. The identified solutions for improvement should be based on data-driven insights to identify multi-sectorial interventions that improve the management of CVD risk factors (such as hypertension, diabetes, low-density lipoprotein cholesterol) and prevent these risks from developing. They should also consider the entire continuum of care (detect, treat, control). The work on performance indicators including harmonisation is key to set a baseline from which improvements can be made. Applicants are expected to consider all applicable legislative and regulatory constraints (national, regional, local) and their possible impact on the implementation and results of the project. End-users (including citizens, patients, healthcare professionals and providers, health technology developers among others) should be included from the start in the co-creation process to ensure future buy-in and implementation.

- collaborate with patients and citizens to develop strategies and guidance for effective CV health awareness campaigns;
- collaborate with healthcare professionals to review and adapt guidance on CVD prevention and management, identifying opportunities to maintain and optimise healthcare workforce resources and engagement;
- set up sustainable platforms and other support mechanisms for deployment of the models (sharing best practice between pilot cities and across regions);
- pilot novel and/or improved early detection and diagnostic solutions, patient management strategies, (including improved patient support, remote patient management, patient flows), and initiatives to maintain workforce engagement;
- explore potential funding tools to complement healthcare systems funding for managing cardiovascular health (including bonds, insurance, crowdsourcing, etc.) which could be used to implement the models;
- leverage existing and newly created sources of multimodal data (contemplating opportunities provided by EHDS) for decision making and management of CVD (collecting, connecting, standardising, processing and analysing);
- design and deploy communication and awareness-raising campaigns, including training and capacity-building for health workers to effectively address various population groups affected by CVD.

Applicants should consider synergies with relevant initiatives at national level and with other European health initiatives such as the European Innovation Partnership on Active and Healthy Ageing[19], Reference Site Collaboration Network[20], Urban Health Cluster[21], the Cities and Cancer Missions[22] and the Joint Action on Cardiovascular Diseases and Diabetes (JACARDI) funded by the EU4Health programme, to maximise the potential for creating models that can be applied in various urban settings to improve cardiovascular health. This collaborative approach underscores the potential for cross-applicability of health solutions in addressing chronic diseases.

The action should also consider learnings and synergies with other IMI and IHI initiatives such as H2O, EHDEN, BigData@Heart, iCARE4CVD, among others.

[19] European Commission, "The European Innovation Partnership on Active and Healthy Ageing (EIP on AHA)." Accessed March 2024.

[20] Reference Site Collaboration Network, "Home - RSCN." Accessed March 2024.

[21] Urban Health Cluster, "Urban Health Cluster | The first European Cluster to improve and safeguard health and well-being of citizens, leaving none behind." Accessed March 2024.

[22] European Commission, "EU Missions in Horizon Europe." Accessed May 2024.

Applicants are expected to consider the potential regulatory impact of the results and – as relevant – develop a regulatory strategy and interaction plan for generating appropriate evidence as well as engaging with regulators in a timely manner (e.g. national competent authorities, EMA Innovation Task Force, qualification advice).

Expected impacts

The action under this topic is expected to achieve all the following impacts and contribute to the following EU policies/initiatives:

- decrease the CVD burden in European cities by the reduction of CV events, disability, and mortality;
- enable future clinical pathways leading to improved patient outcomes;
- reduce the pressure of patient flow in the healthcare system via innovative diagnostic/detection solutions;
- strengthen the definition, standardisation and selection of performance indicators on CVD mortality, patient outcomes and economic impact of interventions, and thus improve future clinical pathways and intervention implementation studies;
- optimise healthcare expenditure to tackle the financial strain of CVD, amounting to €282 billion annually in the EU [3]. The emphasis is on prioritising spending for maximum efficiency and value, balancing the costs of advanced interventions with their long-term benefits;
- strengthen public awareness initiatives and incorporate improved diagnostic methods to enhance early detection and treatment of CVD, to reduce premature CVD deaths and support preventive healthcare measures;
- strengthen patient and citizen input to treatment pathways, disease monitoring and scientific guideline enhancement;
- contribute to the European policy on Active and Healthy Aging , and to the implementation of the European Commission's proposal for the European Health Data Space (EHDS) by providing FAIR data that are aligned with the EHDS requirements;
- start building a system for continual impact assessment and provide early evidence on the impact and effectiveness of the applied recommendations.

These impacts are in alignment with specific objectives 3 and 2 of IHI JU[23].

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

This action requires collaboration among multiple public and private sectors and stakeholders due to the multifaceted nature of urban CVD challenges. Economic viability is also a key consideration and will require multiple parties to come together for economy of scale. To achieve economic viability, actors must work together collaboratively in a consortium and not in a fragmented manner, for solutions to be adoptable by, and beneficial for, European health systems.

Pharmaceutical companies, biotech firms, medical device manufacturers, and health ICT sectors must join forces and collaborate to create an integrated approach to CVD management. Collaboration between private (industry) and public partners (city management, academia, healthcare practitioners, community, patients, payers) is key to ensure that the developed solutions are comprehensive, evidence-based, and aligned with public health needs and future expectations.

[23] https://www.ihi.europa.eu/sites/default/files/flmngr/IHI_Strategic_Research_and_Innovation_Agenda_3.pdf

The public-private partnership model ensures that industry innovations are effectively translated into practical health solutions, considering regulatory standards and real-world applicability.

Pre-identified industry consortium

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'):

- Daiichi Sankyo
- Huawei
- Menarini
- Novartis (Lead)
- Novo Nordisk
- Servier
- Siemens Healthineers

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 15 750 000.
- The indicative in-kind contribution from industry beneficiaries is EUR 15 750 000.

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 (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 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 pre-identified industry consortium expects to contribute to the IHI JU project by providing the following expertise and assets:

- ongoing pilots (including models, management, or coordination platforms)
- data from prospective observational studies
- necessary health interventions: medical devices (e.g. wearables), diagnostics, medicines
- support to the organisations of meetings, workshops, conferences and setting up the coordination and dissemination platform (including IT systems where appropriate)
- expertise in the field of R&D in relevant science fields, clinical development, medical and regulatory affairs, medical education, health economics, data management, communication.

Applicant consortium

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

This may require mobilising the following expertise in:

- clinical practice in CVD in both primary and secondary care
- clinical investigators/researchers in CVD
- health economics and outcomes
- economic modelling and financial tools
- data and knowledge management
- artificial Intelligence
- communication and awareness raising campaigns
- healthcare systems organisations
- complex project management
- telehealth and remote patient management
- health impact of living conditions/urbanism.

Key resources might include: data, data platforms, diagnostic and monitoring tools, education and training infrastructure, communication platforms (including social media and other).

Key stakeholders to be involved include (but are not limited to): public health and research institutions, learned societies, hospitals, health providers, health systems managers, medical associations, patient organisations, community leaders. Connectivity with competent authorities responsible for planning and deployment of programmes targeted by the action is a must (in an advisory role or as participants in the action).

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

References

[1] Kotseva K, Gerlier L, Sidelnikov E, Kutikova L, Lamotte M, Amarenco P, Annemans L. Patient and caregiver productivity loss and indirect costs associated with cardiovascular events in Europe. Eur J Prev Cardiol. 2019 Jul;26(11):1150-1157. doi: 10.1177/2047487319834770. Epub 2019 Apr 6. PMID: 30955367.

[2] Reiker et al., "Population health impact and economic evaluation of the CARDIO4Cities approach to improve urban hypertension management," Plos Global Public Health. April 2023.

[3] Luengo-Fernandez et al, "Economic burden of cardiovascular diseases in the European Union: a population-based cost study." National Library of Medicine. December 2023.

Topic 2 : Novel endpoints for osteoarthritis (OA) by applying big data analytics

Expected outcomes

The action under this topic must contribute to all the outcomes listed below, by integrating existing data sets (clinical registries, prospective observational trials and real-world evidence data, for example from medical claims and biobanks as well as genotypic and epigenetic information), and data collections from historical and ongoing clinical trials (provided by industry partners).

- Algorithms and models, including Artificial Intelligence (AI)-based models, that are adaptable to differences in data availability have been developed and validated in different datasets to allow for the identification of osteoarthritis (OA) patient subpopulations (phenotypes/endotypes) that will benefit from specific, targeted treatment approaches. The identification of subpopulations will be based on:
  a) the patient-specific burden of osteoarthritis with focus on underlying drivers (e.g. metabolic disease) and multi-morbidity/holistic patient profiles;
  b) the evaluation of underlying pathways driving local vs. centralised pain in joint disease and the correlation of symptoms to joint tissue pathology;
  c) the identification of key risk factors for pain in joint disease that can be linked to structural disease progression providing insights into the symptom–structure discordance in OA;
  d) the detection of joint areas at risk of progression and quantification of structural progression to a more advanced stage;
  e) the measures from existing innovative tools such as functional assessments with mobility and activity assessing devices (including algorithms) to reflect independence, gait measures, and assessments of muscular strength and function, as well as balance and coordination to subtly measure functional changes;
  f) evaluating the differences and commonalities of osteoarthritis (OA) and inflammation-driven joint diseases such as psoriatic arthritis (PsA), rheumatoid arthritis (RA), erosive hand osteoarthritis (eHOA).
- A validation strategy is provided for a selected set of novel endpoints to measure and predict OA disease progression that enables planning of regulatory implementation pathways. This validation strategy supports innovative outcome-based and patient-centred development approaches for medicines and other therapeutic options to be discussed by regulatory authorities, health technology assessment (HTA) bodies, healthcare providers, patients, scientists and industry, shaping new approaches to the development of efficient treatments in OA and respective regulatory frameworks.
- A decision tool is developed – based on the predictive models – that supports shared decision-making for patients, their caregivers and healthcare providers according to the predicted disease progression, the most likely associated OA disease drivers and the current disease burden.
- A robust, trustworthy, and interpretable AI framework is established, that enables the development of guidelines or determines any boundaries for predictive modelling at various stages of value generation e.g. biological discovery, patient subgrouping, and clinical trials enrichment. Measures to mitigate the risk of bias and discrimination are implemented including, but not limited, to:
  a) careful consideration of data sets to ensure diversity and inclusion (or account for the lack thereof);
  b) the running of bias-unaware AI models and provision of fairness metrics;
  c) applying AI models within frameworks mitigating bias and promoting fairness during the pre-processing, in-processing and post-processing phases.
- Data platform(s) are designed and implemented to allow a workable and efficient collaboration across the participating organisations in their respective geographies, respecting each data contributor's access, privacy and consent approaches, which can be facilitated by federated data sharing. This

outcome may serve as a blueprint for other data collaborations under the umbrella of the EU's newly implemented AI act and data policies[24, 25].

It is expected that certain existing assets like clinical data, algorithms, and data storage infrastructure will be used as background in this action. Therefore, beneficiaries intending to participate in this data-driven action need to be comfortable with the principle that ownership of specific deliverables / project results which would be considered direct improvements to a beneficiary's background asset, will need to be transferred back to the beneficiary who contributed the background asset to the project. Provision for, and conditions relating to such transfers should be specified in the project's consortium agreement.

Scope

Osteoarthritis (OA) has no cure and affects the lives of more than 500 million people worldwide with widespread individual, societal and economic consequences. Economic consequences pertain on one hand to health care utilisation and health care spending, OA is however also associated with relevant economic impact on the individual due to missed days at work, early retirement, and substantial out-of-pocket expenditures. Since OA primarily affects the elderly, females, patients with lower levels of education and socio-economic status and certain ethnicities, the associated economic risk hits already vulnerable populations. OA has long been underestimated in its impact; the disease negatively affects social functioning and ranks 7th for years lived with disability in people over 70 years. With its impact on activities of daily living, OA is a major risk factor for loss of independence. Additionally, OA is associated with increased mortality.

Despite major research efforts and increasing insights into the mechanism, epidemiology, risk factors and natural history of OA, various development efforts over the years have failed to provide a disease-modifying treatment. The epidemiology as well as clinical and biological insights strongly suggest the existence of several pheno- and endotypes of osteoarthritis; failure to account for those differences critically hampers progress in the field. The implementation of innovative approaches to stratify the patient population, predict the course of disease and define patient-relevant endpoints is specifically relevant in an ageing society with a high prevalence of obesity, metabolic syndrome, and multi-morbidity. Furthermore, there is an increasing prevalence of post-traumatic secondary OA in relatively young individuals affected at the prime of their lives. First studies towards the clustering of patient groups and development of predictive models have been published suggesting the feasibility of these approaches. Bringing all those insights together requires the collaboration of experts from various fields and can only be achieved in the concerted action of a public-private partnership, including existing initiatives.

The overall aim of this topic is to build a public-private partnership that is able to integrate and leverage the plethora of existing and currently collected data on OA, as well as the increasing insights and expertise gathered over decades of research. Further, the goal is to use a data driven approach to significantly progress the field by leveraging the novel opportunities that have emerged thanks to increased computing power and innovative methodologies in big data analysis, in order to:

1) integrate different perspectives to improve the understanding of osteoarthritis as a complex disease;
2) foster progress towards regulatory validation of patient-relevant endpoints to measure and predict OA disease progression as well as alternative endpoints to measure response to treatment;

[24] Proposal for a Regulation of the European Parliament and of the Council laying down harmonised rules on artificial intelligence (Artificial Intelligence Act) and amending certain Union legislative acts (2021/0106(COD), 26 Jan. 2024, pdf (europa.eu), last accessed 04.04.2024

[25] Proposal for a regulation - The European Health Data Space Proposal for a regulation - The European Health Data Space - European Commission (europa.eu), last accessed 04.04.2024

3) allow predictive modelling while actively seeking feedback to incorporate the perception of patients, care givers, primary care physicians and regulators.

The action generated by this topic should pave the way towards transforming the current isolated research efforts and static late-stage development approaches into a more patient-centred and simplified (more inclusive/enriched patient population, shorter study duration, potential enablement of the evaluation of preventive or early therapeutic strategies based on predicted outcomes, cost-effectiveness etc.) as well as sustainable part of clinical research and development. This aim is supported by increasing the insights into OA as an heterogenous disease with various underlying patient risk profiles, patho-mechanistic pathways and underlying genotypic/epigenetic/ metabolomic/transcriptomic phenomena based on big data. Such insights will allow for the creation of integrated risk profiles combining clinical and multi-omic approaches (e.g. clinical characteristics, transcriptomics, proteomics, genetic markers, and in-depth multimodal imaging data).

These advances are needed to support the development of patient-relevant and cost-efficient integrated health care solutions including focused, individualised treatments for specific patient segments. The use of AI-based approaches is crucial for the integration of the totality of existing patient datasets and mechanistic disease insights to better understand disease drivers in various tissues of joints thereby upscaling, broadening and/or sharpening current methodology.

The proposed action must:

- gather and provide access to high quality data – including clinical data from trials (mainly data from placebo arms from studies run outside the project) provided by the pre-identified industry consortium and by applicants as well as prospective observational data, registry data and cohort data including genetic, imaging, soluble biomarker, and data from wearables among others;

- provide a flexible federated data lake house with appropriate tools for access, management and governance, data curation, integration, and augmentation for consequent high-performance analytics using for example new or contributed AI (foundation) models and modelling workflows. This infrastructure will deploy existing or newly developed approaches or implementations to host and analyse disparate data assets ranging from public, commercial, and not-for-profit observational and trial clinical data to -omics, images, or data from wearables. In their proposal applicants should address key challenges around federated data collection, data privacy, data transfer, data storage, data processing, curation, and harmonisation of data, etc. to achieve a comprehensive understanding of OA by upscaled, big data analytics from:
  1) genetic analyses (GWAS);
  2) AI-driven big data analyses for identification of clinical patterns in phenotypes and endotypes;
  3) algorithm-based imaging analyses of whole joints and peri-articular tissues;
  4) the evaluation of performance assessments using novel technologies and devices.
- generate and provide a validation strategy for a risk model of disease progression by evaluating whether and to which extent risk factors and predictive models identified in the literature and the above-mentioned data sets are reliably predictive for the progression of structural joint changes as evidenced by imaging, pain and functional decline documented by patients and ultimately leading to joint replacement surgery. The combination of surrogate markers such as imaging [1] with medical history and medication, as well as with predictive markers (plasma-based multi-omics, polygenic risk scores) [2][3], patient reported outcome data and data from wearables or performance tests [4], will generate a more refined predictive engine in analogy to, for example, established fracture risk prediction algorithms in osteoporosis;
- work towards a broad consensus between all stakeholders especially linking patients, caregivers and healthcare providers' perspectives to regulatory and health technology assessment (HTA) bodies. This

will enable the elaboration of a set of endpoints relevant to these groups depending on the phase of development of treatments (i.e. early phase trials for medication or device efficacy, while late-stage development needs to prove effectiveness, which may necessitate different sets of outcomes), incorporating the various domains of assessments, and taking into account the predominant effect (structural or symptomatic) of the evaluated treatment. This will help to shape new regulatory frameworks for accelerated targeted OA treatment development based on big data analyses, in-silico trials, digital twin approaches and similar innovative trial designs;

- use data analysis and modelling to provide evidence and knowledge that could enable the evaluation of existing innovative tools (such as functional assessments, imaging approaches etc.) and innovative treatment solutions for OA, based on their scientific validity and feasibility as a prerequisite. Design a strategy to progress them towards regulatory validation and implementation. The action should provide an exploratory and interactive platform to evaluate the validity and user-preference of novel methods of evidence generation, such as the use of data from wearable devices, innovative imaging, and surrogate markers for joint replacement surgery;
- model short- and long-term economic and public health impact from OA including morbidity and mortality. These new risk models should support benefit/risk assessment as well as quality and efficacy assessments of therapeutic interventions in patients diagnosed with OA to prevent or delay the onset of disease progression, but also avoid overtreatment and thereby optimise the use of health care resources;
- develop a decision tool based on predictive models that can support shared decision-making between physicians, patients and their caregivers to select the intervention best suited to address the various stages and symptoms of OA in an individual patient, integrating also patient reported outcome and experience measure (PROMs and PREMs) data as well as patient preferences. The diversity of patients at risk or affected by the disease must be considered when discussing patient-relevant outcomes to enable the focused development of treatments and healthcare solutions specific to the needs of individual patients;
- leverage real-world evidence (RWE) data to address the diversity of patients including sex and gender, ethnicity, and race disparities to develop patient engagement strategies. This should enable engagement with specific groups for the design of OA outcome trials and better promotion of OA management.

The action should contribute to addressing the research needs outlined in the Regulatory Science Research Needs initiative[26], launched by the European Medicines Agency (EMA), assessing the utility of real-world healthcare data to improve the quality of randomised controlled trial simulations and patient and public involvement and engagement.

Therefore, applicants are expected to consider the potential regulatory impact of the results and – as relevant – develop a regulatory strategy and interaction plan for generating appropriate evidence as well as engaging with regulators in a timely manner (e.g. national competent authorities, EMA Innovation Task Force, qualification advice).

Consideration should be specifically given to patient and public involvement and engagement in the implementation of all of the above activities. The applicants are expected to leverage prior learnings, for example, previous experiences that have demonstrated the importance of transparent and accessible structures to receive input from patients, caregivers and health care providers as key stakeholders and integrate expertise from various fields relevant in this context [5]. The continuous and active engagement of all groups is indispensable to meet patients' and providers' needs and leverage synergies between practitioners and scientists, especially to ensure the sustainability of potential outputs.

[26] https://www.ema.europa.eu/en/documents/other/regulatory-science-research-needs_en.pdf, last accessed March 19th 2024

Applicants should provide in their proposal evidence that they have in place all permissions (legal, ethical) needed for accessing the data necessary to implement the action.

Note that the implementation of prospective clinical studies is not supported by this topic.

Expected impacts

The project should contribute to all of the following impacts:

- the federated integration of big data from disparate data sources including the use of digital twin and similar methodological approaches will lay the foundation for advanced clinical trial designs that allow for more efficient and smaller trials, as well as the reduction of patients' burden and exposure to placebo;

- the development of predictive models for disease progression and joint replacement, which are crucial to efficiently discuss treatment strategies, support assessments of quality in health care and equitably plan and allocate health care resources. In addition, such predictive models can revolutionise outcome trial designs, shortening the trial duration and patient burden as well as reducing development costs. The aspired modular flexibility to data availability allows for their sustained use in various settings and economic circumstances;

- the stratification of different patient groups and targeting of treatments to patients' needs and preferences, which enables the development of successful therapies, informs development strategies, improves patient and caregiver engagement and optimises trial designs. This stratification also supports data-based shared decision making for health care solutions in clinical practice;

- availability of tools that enable specific functional measurements and reflect the real-life treatment benefit for patients. These tools have been positively evaluated for practicality and scientific validity and could be used for systematic assessments complementing clinical and patient reported information. All of the above will allow for better trial designs that can demonstrate the treatment benefits of medicines and health care solutions in early development programmes with limited numbers of patients.

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

Millions of patients suffer from osteoarthritis but only a limited number of symptomatic treatment options are available. Efforts to develop insights into disease drivers and to develop disease-modifying treatments that address pain, function and joint survival have been fragmented and futile for decades. In addition, small sample sizes in early trials, the lack of stratification, the limited sensitivity of traditional biomarkers and outcome measures such as conventional x-rays, the vulnerability to confounders specifically of patient reported outcomes for pain, as well as a certain ignorance of patient preferences have also contributed to this failure. After countless failed trials in the industrial and academic setting, and in view of increasing patient numbers and the devastating impact from OA, it is high time to assemble an interdisciplinary team of clinical and scientific experts, health technology innovators, affected patients, their caregivers, HTA bodies and regulators to tackle this complex pathology leveraging AI that finally allows for the management and analytics of an important amount of data.

Only a concerted action with patients in a cross-sectoral public-private partnership incorporating various fields of expertise and from different academic fields and industry sectors can bring together the necessary skills to unravel and link the hidden insights from the plethora of existing data and translate this newly generated knowledge into tangible strategies to treat this underestimated disease.

The IHI JU provides a framework for bringing together the various public and private stakeholders as well as facilitating a structured dialogue including patients, caregivers, physiotherapists, nursing home specialists, primary care physicians and regulatory authorities. The action generated by this topic can provide a safe space in which patient stratification, endpoint development and the implementation of digital assessments can be discussed at a pre-competitive level breaking down existing silos and establishing a common ground and framework for guiding future trials. This not only leverages short-term synergies to reach the individual project goals but also opens the opportunity to reach a broad consensus for endpoint composition in different stages of drug development.

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'):

- Imorphics /Stryker
- GlaxoSmithKline (GSK)
- Nordic Biosciences
- Novartis (Lead)
- Novo Nordisk
- Rottapharm Biotech
- Sanofi
- Siemens Healthineers

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

- Capgemini
- Nordic Biosciences Clinical Development (NBCD)
- Pacira

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 regarding 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 IHI is up to EUR 14 000 000.
- The indicative in-kind contribution from industry partners is EUR 11 416 000.
- The indicative in-kind contribution from IHI JU contributing partners is EUR 4 260 000.

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 partners 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 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 partner(s) expect to contribute to the IHI JU project by providing the following expertise and assets:

- Data: data from clinical trials (such as patient profiles, soluble or imaging biomarkers, genetics at baseline and follow up information especially from placebo arms or observational cohorts), biobank data, real world data, biomarker data;
- Expertise: medical expertise, bioinformatics, data science, public health, patient input, clinical and regulatory expertise, data & AI experts, technology architects, data privacy experts;
- Technology: data science and imaging platforms and tools, including pre-developed imaging algorithms.

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 partner(s).

This requires mobilising the following expertise:

- OA disease-specific expertise including all of the following domains: clinical and patho-mechanistic expertise, imaging (software) analyses of whole joints and peri-articular tissues, evaluation of performance assessments using novel technologies, evaluation of patient reported outcome and experience measures, outcome quality;
- AI-driven big data analyses, data science, bioanalytics, bio-statistics/risk modelling, drug development;
- epidemiology, genetic analyses (GWAS), (epi)genetics;
- demonstrated experience in generating and analysing data from new digital tools that enable specific functional measurements and reflect the real-life treatment benefit for patients including expertise in movement science;
- proven experience with prior patient engagement: patient and caregiver networks including institutions such as nursing homes or assisted living facilities as well as networks with primary care physicians and physiotherapists are specifically valuable in this context to meet the needs and preferences of these primary target groups and support the development of sustainable, patient-centred and accepted solutions;
- experience with regulatory aspects especially with respect to endpoint validation, and previous experience with interaction with regulators;
- data privacy and ethics;
- health economics and outcome research, evidence-based medicine, quality, and efficiency in health care.

Furthermore, the applicant consortium is expected to provide the below resources:

- Timely access to data from registries, cohorts and any other relevant data collection is critical for the success of the action generated by this topic and has to be clearly documented in the proposal.
- Technology: data lake infrastructure, tools to curate, enrich and augment the data for AI models readiness.

Moreover, applicants are expected to give regard to previous activities / consortia on national/EU level such as the Digital Health Catalyst[27], a co-creation from two IMI projects (MobiliseD[28] and IDEA-FAST[29]), aiming to maximise insights from real-world digital measurements and remote monitoring options – or the BigData@Heart[30] [6] initiative (IMI2 call 7) – that similarly to this topic aims at leveraging big data to gain insights into phenotypes and pathologic mechanisms or EUROPAIN[31] among others (please see some additional examples listed below, this is however not an exhaustive list).

At the second stage, the consortium selected at the first stage and the predefined industry consortium and contributing partner(s) will form the full consortium. The full consortium will develop the full proposal in partnership, including the overall structure of the work plan and the work packages, 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.

Additional information (examples only)

Links to project-related EU programmes:

https://www.imi.europa.eu/projects-results/project-factsheets/approach

https://www.approachproject.eu

https://www.ihi.europa.eu/news-events/newsroom/computational-modelling-shows-promise-predicting-mortality-risk-after-knee

https://www.ehden.eu

https://www.ihi.europa.eu/projects-results/project-factsheets/idea-fast

https://health.ec.europa.eu/ehealth-digital-health-and-care/european-health-data-space_en

Links for more information on OA as a serious disease:

https://oarsi.org/sites/oarsi/files/library/2018/pdf/oarsi_white_paper_oa_serious_disease121416_1.pdf

https://cdn.vev.design/private/BCwBc9ZFZyVz8yQQKr9VeLxSnjf1/d6Jx2OYBUF_Unmet%20needs%20in%20Europe_EIU%20Briefing%20Paper_Pfizer.pdf.pdf

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[28] Home - Mobilise-D, last accessed March 19th 2024

[29] IDEA-FAST, last accessed March 19th 2024

[30] BigData@Heart > Home (bigdata-heart.eu) , last accessed March 19th 2024

[31] EUROPAIN_summary_final_report.pdf, last accessed March 19th 2024

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[5] Keogh A, et al., L, Mobilise-D consortium. **Mobilizing Patient and Public Involvement in the Development of Real-World Digital Technology Solutions: Tutorial**. J Med Internet Res 2023;25:e44206, URL: https://www.jmir.org/2023/1/e44206, DOI: 10.2196/44206

[6] Gill SK, et al. Artificial intelligence to enhance clinical value across the spectrum of cardiovascular healthcare, European Heart Journal, Volume 44, Issue 9, 1 March 2023, Pages 713–725, https://doi.org/10.1093/eurheartj/ehac758

Topic 3 : Modelling regulatory sandbox mechanisms and enabling their deployment to support breakthrough innovation

Expected outcomes

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

- A horizon scanning for potential sandbox candidates including how sandboxes provide an additional tool to existing frameworks and identified examples to model the process.
- Analysis of how regulatory sandboxes can drive science and health technology innovation in an evolving environment.
- Recommendations for end-to-end operations of regulatory sandboxes to inform healthcare innovation developers, regulators, and other decision makers.

Scope

While there is no concrete definition, regulatory sandboxes generally refer to regulatory frameworks that provide a structure for healthcare innovation developers to test and experiment with new and innovative products, services, or approaches under the oversight of a regulator for a limited period of time. These adaptive tools are meant to address challenges arising from the acceleration of technological/scientific advances and the mechanisms intended to regulate them. It offers customisation in terms of how a regulatory framework can be applied, combined with appropriate safeguards.

Regulatory sandboxes, first tested in the fintech sector (2015), are starting to transform the traditional methods used by regulatory agencies in the health sector to accompany the development of safe, efficacious, and high-quality health technologies[32], which, due to their level of novelty, challenge the current regulatory framework. The mechanism enables breakthrough developments and the testing of alternative regulatory approaches for disruptive innovations for medicinal products, related platforms and their combinations, including where appropriate medical and digital technologies. Regulatory sandboxes are mentioned as important future-proofing elements in the legislative proposal[33] of the European Commission on the general pharmaceutical legislation. The European Commission's communication to boost biotechnology and biomanufacturing in the EU further promotes the establishment of regulatory sandboxes that allow the testing of novel solutions in a controlled environment for a limited amount of time under the supervision of regulators as a way of quickly bringing more of them to the market[34]. Regulatory sandboxes are not featured in the medical devices and *in vitro* diagnostics regulations (MDR and IVDR)[35], but the artificial intelligence (AI) Act[36] creates an opportunity for regulatory sandboxes focused on case studies for AI-enabled medical devices. Regulatory sandboxes entail a shared learning objective for innovators (finding a pathway and getting regulatory predictability) and regulators (understanding the technology and defining how best to regulate it). The mechanism helps to inform future regulation through experimentation and evidence generation and minimises the risks of regulating ex-ante innovative and novel approaches prematurely or inappropriately. For the same reasons regulatory sandboxes also potentially facilitate the

[32] 'health technology' means a medicinal product, a medical device or medical and surgical procedures as well as measures for disease prevention, diagnosis or treatment used in healthcare.

[33] Proposal for a Regulation of the European Parliament and of the Council laying down Union procedures for the authorisation and supervision of medicinal products for human use and establishing rules governing the European Medicines Agency, amending Regulation (EC) No 1394/2007 and Regulation (EU) No 536/2014 and repealing Regulation (EC) No 726/2004, Regulation (EC) No 141/2000 and Regulation (EC) No 1901/2006 Chapter IX Regulatory Sandbox (Articles 113-115)

[34] https://research-and-innovation.ec.europa.eu/document/download/47554adc-dffc-411b-8cd6-b52417514cb3_en

[35] Regulation (EU) 2017/745 of the European Parliament and of the Council of 5 April 2017 on medical devices and Regulation (EU) 2017/746 of the European Parliament and of the Council of 5 April 2017 on in vitro diagnostic medical devices.

[36] Regulation of the European Parliament and of the Council laying down harmonised rules on artificial intelligence (Artificial Intelligence Act)

more efficient or rapid subsequent adaptation of the legislation either through translation into an adapted regulatory framework and/or through recommendations when the time comes for revising existing or developing new legislation.

Regulatory sandboxes should be able to experiment and draw on several relevant healthcare innovation related frameworks other than pharmaceutical products (i.e. medical devices, *in-vitro* diagnostics, AI, digital health technologies, and substances of human origin among others). Due to their anticipatory and adaptive nature, regulatory sandboxes are well placed to address gaps and complexity within and across regulatory frameworks. Indeed, as the number of drug and device combinations increases, and technology integration becomes the norm rather than an exception in healthcare innovation R&D, manufacturing and healthcare delivery, the current siloed technology-specific frameworks may not provide a clear path forward. To that end, when considering an innovation, it is important to consider all relevant legislative frameworks including MDR and IVDR, the Clinical Trials Regulation[37], the General Product Safety Regulation[38] and AI ACT among others.

Although still new to the healthcare and pharmaceutical sector, there are a few examples of regulatory sandboxes such as the Sante Canada sandbox for advanced therapeutic products or the Singapore sandbox to test telemedicine. More recently, the UK launched the MHRA AI-airlock to assist in the development and deployment of software and AI medical devices, safely providing patients with earlier access to cutting edge innovations that improve care.

The overall aim of this IHI topic is to contribute to the progression and successful implementation of regulatory sandboxes for healthcare innovations by developing a comprehensive and shared understanding of their value and process of implementation. The topic should also enable the development of a cross-sectoral community of stakeholders including pharma and medical device companies, regulators, and health technology assessment bodies (HTAs), among other stakeholders.

To fulfil this aim, the proposal should:

1. **Scan the horizon for potential sandbox candidates including how sandboxes provide an additional tool to existing frameworks, and use the examples identified to model the process.**

To this end, a key objective is to identify a number of healthcare innovation case studies to better understand how a regulatory sandbox could be used to solve further-defined challenges at an existing regulation level and inform recommendations for end-to-end operations. These cases could draw from the past, present and from horizon scanning activities (the EMA's work in this area already provides a hint[39]) to anticipate future innovations, looking across their development value chain.

2. **Analyse how regulatory sandboxes can drive science and health technology innovation in an evolving environment.**

The proposal should do this by:

- anticipating consequences for health technology development under a regulatory sandbox mechanism, acknowledging its time-limited scope and the consequences (considering the technical particularities of healthcare innovation) for other downstream activities e.g., standardisation, health technology assessment;
- proactively identifying any guardrails and mitigation measures.

[37] Regulation (EU) No 536/2014 of the European Parliament and of the Council of 16 April 2014 on clinical trials on medicinal products for human use

[38] Regulation (EU) 2023/988 of the European Parliament and of the Council of 10 May 2023 on general product safety

[39] Health horizons: Future trends and technologies from the European Medicines Agency's horizon scanning collaborations: https://doi.org/10.3389/fmed.2022.1064003

3. **Develop recommendations for end-to-end operations of regulatory sandboxes to inform healthcare innovation developers, regulators and downstream decision makers.**

The proposal should do this by:

- mapping out conceptual elements and operationalisation features of future sandbox mechanisms based on existing experiences in other fields such as governance, conditions fostering dialogue and collaboration, access to the right type of expertise, support, regulatory customisation, sharing/communicating lessons learned and their translation via the appropriate frameworks into new standards, among other elements to be further defined;
- modelling how to operationalise the sandbox(es) (including governance, operations, principles) and how they could be used in healthcare innovation development and evaluation in conjunction with existing regulatory mechanisms to advance innovation at European and national levels.

Part of the topic entails modelling a regulatory sandbox. The proposal should therefore consider good practices for designing and evaluating the necessary operating models to ensure the robustness and future applicability of the output of the project.

The project outcomes could also offer directions for the translation of the resulting recommendations into digital tools and systems deemed necessary for the functioning of regulatory sandboxes (e.g. ensuring collaboration between different health authorities' triage mechanisms, horizon scanning, fitness check evaluations), as relevant.

When developing a comprehensive and shared understanding of the value of regulatory sandboxes, applicants will have to explore key aspects across the life-cycle of healthcare innovations with the objective of accompanying their ultimate adoption, which could include as appropriate R&D, regulatory authorities, HTA bodies, payers, governments, clinicians and patients. Ethical considerations would also have to be considered as some innovations could trigger questions in this field.

A shared objective should include to develop a regulatory strategy and interaction plan for generating appropriate evidence, enabling engagement across all the different decision makers in a timely manner (e.g. national competent authorities, EMA and the respective Innovation Task Force, qualification advice) and identifying aspects that can be leveraged by existing regulatory tools, as well as the limiting aspects and the flexibilities that would be required under a regulatory sandbox to achieve the timely development and access of healthcare innovations.

Expected impacts

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

- Meaningful contributions to the successful implementation of regulatory sandboxes through developing a comprehensive and shared understanding of their use and value among key stakeholders in the healthcare ecosystem.
- Support the future-proofing of the EU regulatory framework by design, enabling the efficient implementation of regulatory sandboxes where and when appropriate, and thus helping to make Europe more attractive as place of innovation.
- Enhancing and enabling the cooperation of key healthcare stakeholders, including patients, clinicians, small and medium-sized enterprises (SMEs) and academics, with regulators in developing a competitive and innovation-friendly landscape.
- Fostering interaction with regulators to develop healthcare solutions when it is not possible to develop them within the current framework.

The action will also contribute to a number of European policies/initiatives, which include:

- the European Commission's Pharmaceutical Strategy for Europe, specifically the pillar on competitiveness, innovation and sustainability;

- related measures under the ongoing revision of the Pharmaceutical legislation;
- the European Commission innovation agenda (published in 2022) flagship initiative "*Enabling innovation through experimentation spaces and public procurement*" facilitating innovation through improved framework conditions including experimental approaches to regulation (e.g. regulatory sandboxes);
- the EU biotech strategy;
- the green and sustainability agenda.

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

As health innovation happens at the interface of disciplines and will be increasingly driven by technology, regulatory challenges will arise at the interface of the regulatory frameworks that govern these disciplines.

Engagement across sectors and multi-disciplinary collaboration are essential to support the deployment of regulatory sandboxes within different fields and across regulatory frameworks.

Therefore, a wider cross-sectorial community of stakeholders is needed to achieve the topic objectives. Innovators from the academic sector and from the various developer organisations (including biotech and start-ups) are increasingly coming together in areas such as medical devices, *in-vitro* diagnostics, AI, digital health technologies, and substances of human origin, among others.

Regulatory science and oversight are at the heart of regulatory sandboxes, so regulatory authorities and the wider regulatory science community including notified bodies are at the centre of the project. Downstream decisions makers such as HTA bodies and payers as well as solution recipients like patients and healthcare professionals should also be involved. This diversity reflects the actors of the ecosystem and is essential to ensure the uptake of innovation in a holistic manner.

A public-private partnership is the ideal framework for such a multi-sectorial and disciplinary endeavour and the diversity of representation in a neutral collaborative platform like an IHI consortium would help to build trust which is essential to ensure the adoption of the resulting mechanisms and future outputs.

Pre-identified industry consortium

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'):

- Astellas
- Biogen
- CSL Behring
- EFPIA
- Eli Lilly
- F. Hoffman-La Roche (co-lead)
- Johnson & Johnson
- Merck KGA
- MSD (co-lead)
- Novo Nordisk
- Novartis
- Pfizer

- Sanofi
- Takeda
- Teva

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 5 200 000
- The indicative in-kind and financial contribution from industry beneficiaries is EUR 4 261 096

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 (IKOP) from those countries that are neither part of the EU nor associated to the Horizon Europe programme.

The allocation of the EUR 100 000 financial contribution (FC) from industry beneficiaries will be decided by the full consortium at the second stage when preparing the full proposal.

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 36 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 pre-identified industry consortium expects to contribute to the IHI JU project by providing the following expertise and assets:

- expertise in manufacturing/CMC (chemistry, manufacturing, and controls) in healthcare innovation development R&D, clinical development, clinical trials, benefit/risk assessment;
- expertise in regulatory, HTA/pricing and reimbursement, legal and intellectual property, medical and health affairs and communication;
- expertise and input on impact on decision-making;
- risk assessment and risk management expertise;
- expertise in organisational design (design thinking);
- contributions to case simulation.

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.

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

- project management expertise in running cross-sectorial projects;
- broad expertise in R&D of healthcare innovation;
- expertise in simulation set-up to design appropriate conditions to run the simulation exercises;
- expertise in organisational design (e.g. design thinking) to inform the architecture of the regulatory sandbox mechanism;
- regulatory and legal expertise are core to a number of activities ranging from the fitness check evaluation of the regulatory framework against identified innovations to the development, simulation and design of the regulatory sandbox operating principles;
- healthcare professionals and patient perspectives, including a dimension on ethical considerations, would be beneficial;
- HTA and payer perspective;
- innovation, its management and foresight to inform horizon scanning activities and the identification of innovations susceptible to present challenges to their development and deployment;
- expertise in risk management to inform the anticipated consequences of the use of regulatory sandboxes (e.g. via scenario design) and contribute to defining mitigation solutions;
- IT and digital expertise.

Applicants are also expected to propose case studies in their short proposals. The pre-identified industry consortium would also propose case studies, to be aligned and decided by the full consortium at the second stage when preparing the full proposal.

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

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:

  - 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;
  - describe the potential relationships among COAs, patient-centred DHT-derived endpoints and other common types of clinical study endpoints;
  - 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;
  - 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;

- 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:
  - 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;
  - understanding the relationships between COA data and patient-centred DHT-derived endpoints in diverse therapeutic areas;
  - using DHTs (e.g., apps, smart personal devices, smart drug-delivery devices, therapeutic medical technologies, etc.) to collect PPI and COA data;
  - 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:
  - include a range of digital measurement domains (e.g., physical activity, sleep, cognition, fatigue, or others) and address differences between passive and interactive DHTs.
  - include a range of patient ages (e.g., paediatric, adolescent, younger adults, and older adults).
  - address issues related to diversity in patient populations (e.g., disease type, disease stage, health literacy, cultural factors, underserved patient populations, etc.)
  - 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).
  - 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:
  - 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.
  - 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.
  - 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:
  - 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;
  - existing frameworks and guidance documents related to patient-focused drug development such as those from FDA and EMA;
  - 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.