innovative health initiative

IHI

13th Call for proposals

Two-stage call

COCIR efpia EuropaBio MedTech Europe from diagnosis to cure Vaccines Europe

Co-funded by the European Union

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Introduction

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

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

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

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

Topics Overview

HORIZON-JU-IHI-2026-13-01 **IHI European HealthCare Incubator Network**	The maximum financial contribution from IHI JU is up to EUR 35 000 000. The indicative in-kind contribution from industry partners is EUR 10 696 000. The indicative in-kind contribution from IHI JU contributing partners is EUR 4 328 750. 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-2026-13-02 **An AI Foundation Toxicology Model and Framework to Support Waiving a Second Species in Drug Safety Studies**	The maximum financial contribution from IHI JU is up to EUR 9 000 000. The indicative in-kind contribution from industry partners is EUR 7 300 000. The indicative in-kind contribution from IHI JU contributing partners is EUR 100 000. The indicative in-kind contribution from industry partners may include in-kind contributions to additional activities.	Research and Innovation Action (RIA). Two-stage submission and evaluation process. Only the applicant consortium whose proposal is ranked first at the first stage is invited for the second stage.
HORIZON-JU-IHI-2026-13-03 **Decode the Immuno-science of age-related diseases**	The maximum financial contribution from IHI JU is up to EUR 9 200 000. The indicative in-kind contribution from industry partners is EUR 9 200 000. 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.

Call conditions for single stage and two-stage calls

For Call 13 please refer to the conditions relevant to the two-stage call

The submission deadline for short proposals (SPs) will be 08/10/2026 and the full proposals (FPs) submission deadline will be 21/04/2027.

Scientific evaluation of the SPs and FPs under the two-stage call will run in 2026 and 2027, respectively. GAP will be completed within 3 (three) 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).

A. 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 IHI JU is established to address complex cross-border challenges that require an integrated approach, making it possible to address the transformational, systemic and market failures, and to contribute to strengthening the competitiveness of the Union's health industry, a cornerstone of the Union's knowledge-based economy, to an increased economic activity in the development of health technologies, in particular of integrated health solutions, and thus serve as a tool for increasing technological leadership and fostering the digital transformation of our societies.

This aim can be achieved only by bringing together a broad range of players across the value chains and ecosystems, enabling efforts and resources to be concentrated on common priorities to solve the complex challenges.

To deliver on such priorities and impact, and to respond to the essential nature of the partnership, the IHI JU calls are developed through a broad involvement of relevant stakeholders across Europe, including industry partners and those other entities who are not IHI members or their constituent or affiliated entities, but are interested in supporting the IHI JU in their specific areas of research (defined as contributing partners).

Considering:

- Article 5(2)(a) of the Council Regulation (EU) 2021/2085 allows the participation of pre-identified members of the joint undertaking or their constituent or affiliated entities in duly justified cases as specified in the work programme in order achieve the Innovative Health Initiative Joint Undertaking's strategic objectives and tasks set out in Articles 115 and 116 of Council Regulation (EU) 2021/2085;
- Article 125(4) of the Council Regulation (EU) 2021/2085 provides that, with reference to Article 5(2)(a)'s requirement for duly justified cases, legal entities identified by the Innovative Health Initiative Joint Undertaking may participate in specific indirect actions. Those pre-identified legal entities shall not be eligible for funding from the Innovative Health Initiative Joint Undertaking;
- The utilisation of a two-stage call encompassing a pre-identified industry consortium composed of the private members of the IHI JU (and/or their constituent or affiliated entities) and contributing partners, duly identified in the work programme and integrating unique industry expertise in such areas as regulatory affairs and the concomitant allocation of industry resources which are primarily full time employees (FTEs), and the provision of access to propriety industry assets such as internal assays and research infrastructure, allows the achievement of both those activities of the specific call topic and the wider strategic IHI JU objectives in articles 115 and 116 of Regulation (EU) 2021/2085. The IHI JU two-stage calls remain fully open to all applicants provided such applicants meet the eligibility conditions per this section (see below).

The General Annexes to the Horizon Europe Work Programme 2026 - 2027 shall apply *mutatis mutandis* to the calls for proposals covered by this amended Work Programme, including the "Restrictions for the protection of European communication networks" under General Annex B. In accordance with Article 5(2)(a) and Article 125(4) of Council Regulation (EU) 2021/2085 of 19 November 2021 establishing the Joint Undertakings under Horizon Europe, 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 amended 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, and in Council Regulation (EU) 2021/2085 of 19 November 2021 establishing the Joint Undertakings under Horizon Europe.

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 2026 - 2027 shall apply *mutatis mutandis* for the calls for proposals covered by this amended 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 2026 – 2027 shall apply *mutatis mutandis* for the calls for proposals covered by this amended Work Programme unless otherwise provided in this amended Work Programme.

Per the above and by way of derogation from General Annex B of the Horizon Europe Work Programme 2026 – 2027 the following shall apply:

According to Article 119 of the Council Regulation (EU) 2021/2085, for indirect actions selected under calls for proposals covered by this amended 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;
- In accordance with article 119.3 of the Council Regulation (EU) 2021/2085, the 45% threshold may be lowered at the level of individual indirect actions ('project level') when properly justified.
- Per the above, for Call 13, topic 01 'IHI European HealthCare Incubator Network' the threshold is duly lowered to 30% at the project level to reflect that:
  - ❖ some of the resources to be contributed by the members of IHI JU, their constituent or affiliated entities, and contributing partners and which are considered crucial for the success of the project do not fall under the category of eligible costs per article 6 of the Horizon Europe Model Grant Agreement and therefore cannot be properly accounted.
  - ❖ The third parties attached to the project are not known in advance, and it is impossible therefore to determine the capacity for contributions under article 119 in advance.
- at project level, the maximum amount of non-EU IKOP is set to:
  - i. Twenty percent (20%) for IHI JU Call 12.
  - ii. One hundred percent (100%) for IHI JU Call 13.

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[1].

ENTITIES ELIGIBLE FOR FUNDING

In relation to the single-stage calls for proposals covered by this amended Work Programme, the relevant provisions of the General Annex B to the Horizon Europe Work Programme 2026 – 2027 shall apply *mutatis mutandis*.

By way of derogation, in relation to the two-stage calls for proposals covered by this amended 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:

[1] 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.

- 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 2026 – 2027,

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.

Where specified in the call topics conditions, with reference to the Trade and Cooperation Agreement between the EU and the UK including its Protocol I, establishing the UK's association to the Horizon Europe Programme, more particularly to article 2(2) of that Protocol; and Regulation (EU) 2085/2021, more particularly article 174.14, and Commission Delegated Regulation (EU) 2019/887, specifically article 6.5 ('Principle of Annuality'):

- legal entities established in the UK shall not be eligible to receive funding.

Where specified in the call topic's conditions, with reference to the agreement between the European Union and Canada on the participation of Canada in Union programmes, more particularly to articles 6 and 19; and Regulation (EU) 2085/2021, more particularly article 174.14; and Commission Delegated Regulation (EU) 2019/887, specifically article 6.5 ('Principle of Annuality'):

- legal entities established in Canada shall not be eligible to receive funding.

Where specified in the call topic's conditions, with reference to the agreement between the European Union and the Republic of Korea on the participation of the Republic of Korea in Union programmes, more particularly to articles 6 and 17; and Regulation (EU) 2085/2021, more particularly article 174.14; and Commission Delegated Regulation (EU) 2019/887, specifically article 6.5 ('Principle of Annuality'):

- legal entities established in the Republic of Korea shall not be eligible to receive funding.

Where specified in the call topic's conditions, with reference to the agreement between the European Union and the European Atomic Energy Community and the Swiss Confederation on the participation of the Swiss Confederation in Union Programmes, more particularly to articles 7 and 18; and Regulation (EU) 2085/2021, more particularly article 174.14; and Commission Delegated Regulation (EU) 2019/887, specifically article 6.5 ('Principle of Annuality'):

- legal entities established in Switzerland shall not be eligible to receive funding.

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 amended Work Programme will take into account any application of Article 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 2026 – 2027 shall apply *mutatis mutandis* for the calls for proposals covered by this amended Work Programme.

EVALUATION RULES

General Annex D ('Award Criteria') to the Horizon Europe Work Programme 2026 – 2027 shall apply *mutatis mutandis* for the calls for proposals covered by this amended Work Programme with the following additions:

- the relevant calls for proposals launched under this amended 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 to the extent that the proposed work corresponds to the topic description in the amended work programme:	Impact Aspects to be taken into account to the extent that the proposed work corresponds to the topic description in the amended work programme:	Quality and efficiency of the implementation Aspects to be taken into account to the extent that the proposed work corresponds to the topic description in the amended work programme:
First stage evaluation of two-stage procedure	a) 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. b) Soundness of the overall methodology.	c) Credibility of the pathways to achieve the expected outcomes and impacts specified in the amended work programme, and the likely scale and significance of the contributions due to the project.	d) Quality and effectiveness of the outline of the work plan. e) 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 amended 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 (including risk of falling below 45% contribution threshold), 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 establishes a public-private collaboration and brings together the necessary expertise. If relevant, capacity and role of the contributing partner(s) to the consortium. • Clearly defined and effective integration of in-kind and financial contributions of IHI JU private members, their constituent or affiliated entities to enable a successful public-private partnership. If relevant, clearly defined and effective integration of in-kind and financial contribution of contributing partner(s).

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 procedure, evaluated proposals will be ranked in one single list.
With the exception of those provisions herein for establishing priority order for proposals with the same score within the same budget envelope, General Annex F ('Procedure') to the Horizon Europe Work Programme 2025 shall apply *mutatis mutandis.*

For proposals with the same score within a single budget envelope (with the exception of the first stage of two-stage submissions) the method to establish the **priority order** is as follows:

Starting with the group achieving the highest score and continuing in descending order:

- Proposals that address aspects of the call that have not otherwise been covered by more highly ranked proposals will be considered to have the highest priority.
- The proposals identified under 1), if any, will themselves be prioritised according to the scores they have been awarded for 'Excellence'. When those scores are equal, priority will be based on scores for 'Impact'.
- Proposals that include the highest number of IHI JU private members and constituent and affiliated entities of the IHI JU private members.
- Proposals that provide the highest percentage of contributions (IKOP, IKAA and financial contributions) from the IHI JU private members and contributing partners and the constituent and affiliated entities of both, of the proposal's eligible costs and costs for the related additional activities.
- If necessary, the gender balance among the researchers named in the researchers table in the proposal will be used as a factor for prioritisation.
- If necessary, any further prioritisation will be based on geographical diversity, defined as the number of Member States or Associated Countries represented in the proposal, not otherwise receiving funds from projects higher up the ranking list (and if equal in number, then by budget).
- If a distinction still cannot be made, the panel may decide to further prioritise by considering other factors related to the objectives of the call, or to IHI JU in general. These may include, for example, enhancing the quality of the project portfolio through synergies between projects or, where relevant and feasible, involving SMEs. These factors will be documented in the panel report.
- The method described in 1) to 6) will then be applied to the remaining equally ranked proposals in the group.

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 by 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[2].

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 2026 - 2027 shall apply *mutatis mutandis* for the calls for proposals covered by this amended Work Programme.

BUDGET FLEXIBILITY

General Annex F to the Horizon Europe Work Programme 2026 – 2027 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.

[2] 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.

PROPOSALS INCLUDING CLINICAL STUDIES[3]

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[4].

SPECIFIC CONDITIONS ON AVAILABILITY, ACCESSIBILITY AND AFFORDABILITY (3A)[5]

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 the project ends, use their best efforts to ensure that those products or services that are developed by any of the participants and are totally or partly based on the results of clinical studies performed as part of the activities of the selected project, will be broadly[6] available and accessible, at fair and reasonable conditions.
- In particular, and always to the extent permitted by applicable competition law:
    - At the proposal stage[7], and as part of the Plan for the Dissemination, Exploitation, and Communication Activities ('PDECA') which forms part of the proposal, the applicant consortium must identify potential and expected project results that may be subject to the 3A conditions and broadly outline their strategy to achieve the above objectives.[8]
    - At the project interim review stage, if relevant[9], the PDECA should be updated with a revised 3A strategy. This update should be based on the progress of the clinical studies conducted or to be conducted as part of the project and include any pertinent action to be implemented both during the project and over the four years after project end.
    - At the end of the project, the PDECA should be updated, to provide the expected planning for further product development and (if already scheduled) product launch, within the timeframe of four years after the project end and in order to meet those objectives laid out under point 1 above.[10]

[3] 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).

[4] 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

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

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

[7] For those 3A specific projects, the 3A content in the PDECA will be checked during the evaluation stage. Omission/inadequate treatment of 3A would be identified as a shortcoming. The content however, once considered adequate, will not be utilised for positive scoring and will not contribute towards any evaluation criteria.

[8] Suggested components would be 1) Identification of planned clinical studies that might generate results for which the provisions are relevant; 2) Confirmation that the consortium members are aware of the provisions and will consider them accordingly. 3)Tentatively identifying markets/areas where the product/service could be made affordable, accessible, available. These points could be checked at the evaluation stage.

[9] 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.

[10] Per the Model Grant Agreement ('MGA') Article 16, the beneficiaries must complete the Results Ownership List ('ROL') which identifies each result generated in the project and the owner thereof. The ROL should inform on the relevant results for which owners implement the 3A strategy in the PDECA for the four years following the project.

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

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 2026 – 2027 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 to third parties in IHI projects is allowed for Call 13, topic 1 "A network to boost the next wave of European innovations in healthcare" subject to the conditions set out below:

- The provisions set out in the General Annexes to the Horizon Europe Work Programme 2026 – 2027, particularly General Annex B and General Annex G therein, shall apply *mutatis mutandis*.
- Beneficiaries may provide financial support to third parties only in the form of grants.
- The maximum amount to be granted to each third party is EUR 2 000 000 (EUR 1 000 000 + EUR 1 000 000). The maximum amount of financial support reflects the financial needs of early-stage healthcare innovators and the complexity of activities such as regulatory preparation, clinical validation and proof-of-concept translation. It is necessary to support progress towards scale-up and market readiness, including activities such as preclinical studies and model development. The justification is further detailed in the relevant topic text.

B. Country-specific eligibility rules

Following the Horizon Europe Programme Guide, participation in IHI JU indirect actions will be open but eligibility for funding will be however limited to legal entities established in an EU Member State,

[11] 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:

    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:
    a) The planned measures to be taken into effect the 3A obligations;
    b) That the owning beneficiary will undertake all necessary actions to adhere to the 3A provisions to the best of its capacity;
    c) That the owing beneficiary will keep the IHI JU updated on a yearly basis on the progress.

Associated Country or Low- and Middle-Income Countries (please consult the list in the Horizon Europe Programme Guide[12]).

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

Topic 1 : A network to boost the next wave of European innovations in healthcare

Expected outcomes

This call topic responds to the pressing need for a collaborative approach to accelerating the research-to-market pathway and fostering innovation and competitiveness in the European healthcare sector. Accordingly, the action under this topic must contribute to all of the following outcomes:

1. **A sustainable European HealthCare Incubator Network** (hereafter, the 'Network') linking incubators from the public sector (academia, foundations etc.) and industry (pharma, medtech, biotech) to leverage and catalyse otherwise fragmented efforts and increase the reach of early-stage healthcare companies and academic players across Europe. By providing tailored mentorship and networking, resources and funding mechanisms, the Network will identify high-potential innovations and establish clear pathways for the scale-up and sustainable development of early-stage healthcare companies, supporting the next wave of European innovations.
2. A **strong programme for de-risking pipelines and mentoring high potential start-ups,** with the objective of making start-ups more attractive as investment propositions, and more capable of attracting essential scale-up finance through private or public investors. This should be achieved by leveraging the Network's unique access to multi-sectorial corporate expertise and mentorship from multiple large-cap companies with tailored funding.
3. An **agile framework for funding promising start-ups** through the mechanism of Financial Support to Third Parties ('FSTP' or 'cascade funding').
4. **Access to high-quality services and infrastructures**, provided by the consortium, to accelerate the most promising innovations.
5. **A framework of collaboration** with other relevant funding and innovation programmes (e.g. the European Innovation Council (EIC), EIT Health, and national and regional initiatives) to raise selected start-ups' awareness of potential future additional opportunities for support.
6. An 'industry quality seal' marking **industry-validated promising start-ups**, de-risked and connected to potential future funders and venture capital funds, that should enhance their ability to secure follow-on financing and successful further development.
7. New **opportunities for strategic partnerships** between selected start-ups and partner companies, incubators, investors, venture capital funds, and other interested third parties.
8. A portfolio of early-stage companies with **improved business, market and technological readiness**. This is achieved through targeted access to expertise, infrastructure and services, mentorship, training, and FSTP-supported resources, culminating in sustainable innovations that can be implemented at scale.

The immediate and direct relationship between start-ups and the Network creates not only a support mechanism for start-ups, but also a coordinated platform delivering high value, non-financial industrial expertise that is not available through existing EU funding instruments.

Definitions for the purpose of this call topic:

Early-stage company

- Early-stage company / start-up refers to a new, fast-growing business that is typically in the early stages of development[13].
- The Technology Readiness Level (TRL) is a scale (from TRL 1 to TRL 9) used to assess the maturity of a technology or innovation. For the purpose of the topic, only early-stage companies at TRL 3 to TRL 5 are considered, meaning those in the early-stage development phase, where the technology is still being refined but has moved beyond basic concepts. The table below gives more specific examples.

Type of product	TRL 3	TRL 4	TRL 5
A medical device	Initial proof of concept demonstrated with a limited number of *in vitro* & *in vivo* trials including the expected device characteristics.	Proof of concept and safety of the device is demonstrated *in vitro, ex vivo* or *in vivo* conditions (non-GMP, Good Manufacturing Practice). System components integrated and tested regarding preliminary efficiency and reliability.	Pre-clinical studies include GLP (good laboratory practice), animal safety, and toxicity. GMP manufacturing process and quality controls identified. Classification of the device by the appropriate regulatory body established. Accreditation when appropriate initiated.
A drug	Initial proof of concept demonstrated with a limited number of *in vitro* & *in vivo* models.	Proof of concept and safety of the candidate is demonstrated in a laboratory or animal model.	Pre-clinical studies including GLP, animal safety & toxicity to support the Investigational New Drug (IND) application or similar EU process.

Incubator means an organisation that provides support and resources to early-stage companies to help them grow, develop their business models, and succeed. Incubators offer services like office and lab space, mentorship, training, and access to networks of investors and professional services.

Private or public funder means an investor who provides grants and/or capital to early-stage, high-growth potential companies in exchange for equity. A Venture Capital ('VC') investment as an example, offers a combination of funding and strategic support, such as business guidance and industry connections, to help new companies grow and achieve a significant return on investment. A relevant example of a public funder is the European Innovation Council Accelerator[14].

Scope

Specific Challenges

Europe has world-class research especially in the field of healthcare but continues to lag in commercialising its scientific output. This negatively impacts timely access to novel health technologies for European patients and healthcare systems, especially in areas of unmet healthcare need. Early-stage companies, which are the main engines of innovation, struggle due to structural barriers that inhibit innovation and scale-up. In general, early-stage companies often lack structured support, impeding their development and survival. The EU is positioning itself as a strategic hub for innovative start-ups/ early-stage companies by launching several key

[13] In line with the European Commission recommendation on the definition of innovative enterprises, innovative startups and innovative scaleups: https://research-and-innovation.ec.europa.eu/document/download/4e3cd140-47ed-4de2-be02-af1f344a2990_nl

[14] https://eic.ec.europa.eu/eic-funding-opportunities/eic-accelerator_en

initiatives and funding instruments to this end, such as the Start-up and Scale-up Strategy[15] and the Scale-up Europe Fund[16].

Additionally, Europe is rich in public incubators dedicated to healthcare start-ups, and many healthcare industry stakeholders have established dedicated incubators/venture accelerators.

However, the landscape of such initiatives, both public and private, is fragmented and not easily accessible to all early-stage companies across Europe, nor is it able to provide the necessary know-how and support at a scale that is necessary for generating a step change in bringing innovations to market in Europe and increasing Europe's competitiveness.

Consequently, the whole healthcare ecosystem is negatively impacted. Investors face difficulty identifying scalable ventures in a fragmented landscape. Industry lacks opportunities for early engagement with meaningful innovative projects that will bring novel therapies and medical technologies to patients. Additionally, regulators and policymakers must balance public safety with the need to reduce delays and complexity for innovators. This, in turn makes it very difficult for young and inexperienced innovators, who often lack relevant knowhow, to navigate the regulatory framework. Ultimately, this implies that European health systems and patients are missing out on timely access to innovative diagnostics and treatments.

Objectives

The overall aim of this call topic is to create a **European HealthCare Incubator Network** ('the Network') that should address the above challenges by delivering a structured support framework to enable more effective progression of outputs of early-stage healthcare companies toward deployable innovations in the healthcare ecosystem. The Network should create a unique, multi-sectorial network of business leaders and funders across the whole health industry and be exceptionally well placed to provide cross-industry business support and networking to promising start-ups. In practice, this should be achieved by providing both financial support (via FSTP) and direct interactions with large-cap pharmaceutical and medical technology industries/ companies.

The opportunities for start-ups to engage with major pharmaceutical and med-tech companies are unique within the Network, while remaining fully complementary to other EU funding instruments (e.g., the EIC).

The applicants in their proposal should ensure that through its design, the Network will:

- **Provide early, industry-informed insights** into whether a start-up's concept or product has the potential to address an unmet clinical/healthcare need and therefore represents a viable market opportunity.
- **Offer access to specialised mentorship and coaching**, including expertise from large-cap pharma and med-tech on pre-clinical development, regulatory pathways, market access considerations, and overall technology maturation.
- **Facilitate potential access to industrial capital, facilities, and infrastructural resources**.
- **Connect start-ups with high-quality early-stage innovators** across the ecosystem, stimulating collaboration and shared learning.
- **Strengthen fundraising prospects** through association with leading industry partners as well as enhanced visibility to venture capital funds, major buyers, and other investors.

By fostering a cohesive, innovation-friendly ecosystem, the action should aim to foster retention of talent, reinforce Europe's technological leadership, and improve access to novel health technologies for patients and

[15] https://research-and-innovation.ec.europa.eu/strategy/strategy-research-and-innovation/jobs-and-economy/eu-startup-and-scaleup-strategy_en

[16] https://eic.ec.europa.eu/eic-fund/scaleup-europe-fund_en

healthcare systems. The action generated from this topic should help to **bridge the first** '**valley of death**' in innovation[17], where promising technologies often fail due to lack of funding, know-how, and support mechanisms for reaching clinical efficacy and regulatory readiness.

The objectives of the topic are in response to IHI JU Strategic Research and Innovation Agenda (SRIA)[18] specific objective 2 - *Integrate fragmented health research and innovation efforts by bringing together health industry sectors and other stakeholders. This will enable the development of tools, data, platforms, technologies and processes that will in turn facilitate the prevention, diagnosis, treatment and management of diseases, especially in areas where there is an unmet public health need.*

The applicants are expected to address all the following strategic objectives in their proposal:

Objective 1 – Establishment and governance of a Europe-wide Incubator Network:

The Network should establish a lean and effective governance structure for the action with clear operational processes and collaboration mechanisms among the project partners and stakeholders (universities, industry, regulators, funders, other incubators etc), with the ultimate mission of guiding the selected start-ups and boosting the uptake of their innovative solutions into healthcare systems.

Activities to be performed in the context of this objective:

- Establish the **Network Coordination Forum** (composition, terms of reference, meeting cadence) as the main governing and decision-making body of the consortium, including an even split between public and private partners.
- Establish an **Advisory Board (AB)** to provide advice on the Network's activities including: the implementation of the eligibility and award criteria, the nomination of independent experts in the FSTP evaluation committee, and the overall evaluation process for awarding the FSTP. The AB should include representatives from relevant European Commission Executive Agencies such as the European Innovation Council (EIC), and independent experts with relevant European-wide innovation expertise.
- Develop a formal EU incubator network partner map as well as a mechanism for collaborating with further incubators as relevant.
- Create and update throughout the duration of the action an integration plan detailing how existing incubators are connected and leveraged.

Objective 2 – Selection & monitoring:

Attract, identify, evaluate, fund and monitor a project portfolio of high-potential early-stage healthcare companies selected through open, competitive, widely published calls that conform to EU standards concerning transparency, equal treatment, conflict of interest and confidentiality.

Activities to be performed in the context of this objective:

- Prepare and implement the call, publish and launch the first call by month 6, and co-ordinate the evaluation and selection of third parties in line with the '**Financial Support to Third Parties (FSTP)**' section of this topic; publish and launch additional calls as needed.
- Implement objective criteria when an additional milestone-based follow-on grant could be made available to accelerate development, validation, and industrial uptake.

[17] https://research-and-innovation.ec.europa.eu/document/download/2f76a0df-b09b-47c2-949c-800c30e4c530_en

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

- Establish a standardised contract template for third-party engagements via FSTP (including the relevant Intellectual Property (IP) considerations such as measures to safeguard it), milestone-based funding release schedules and clear oversight/audit protocols.
- Prepare a transparent onboarding workflow for early-stage companies funded through the project (timelines, governance guardrails).

Objective 3 – Growth catalyst:

Develop a comprehensive infrastructure support programme for early-stage companies that receive funding by providing mentoring, access to infrastructure, business development resources and regulatory navigation (CE marking, European Medicines Agency (EMA) processes, Medical Device Regulation / In Vitro Diagnostic Regulation (MDR/IVDR)); and training on commercial readiness ((pre)clinical validation, reimbursement strategies, business model development). By fostering early regulatory preparedness, the action should aim to improve time-to-market and increase the likelihood of regulatory acceptance of the outputs of the activities supported via FSTP.

Activities to be performed in the context of this objective:

- Create a mentoring programme for the FSTP recipients. The mentoring programme should be performed by expert consortium members. The applicants should identify a structure, mentor rota, matching process, milestones and evaluation for the mentoring programme. The mentoring programme is free of charge for the FSTP recipients, and additional to the FSTP funding.
- Provide regulatory navigation support (e.g. regulatory guidance on CE marking and clinical evidence generation, support with General Data Protection Regulation (GDPR)[19] and ethical approvals, CE/ EMA pathway support, MDR/ IVDR training). Early engagement with regulators, such as EMA and national authorities, should be actively promoted and facilitated.
- Provide mentoring for (pre)clinical validation, go-to-market planning, reimbursement strategies and commercial considerations. Such mentoring should be delivered by relevant experts from the pre-identified industry consortium and contributing partners.
- Provide expertise related to securing investments and ensuring readiness for commercialisation and market deployment (market research, value proposition, business case and business model, prospects for growth, intellectual property protection, competitor analysis etc.).
- Provide access to infrastructures, facilities and specialised services, thereby strengthening selected start-ups' research and development capacity, accelerating technology maturation and validation, and supporting the translation of innovative ideas into robust, market-relevant solutions.
- Build up an infrastructure access catalogue (labs, equipment, shared services) and hybrid R&D options.
- Design and implement visibility, outreach and networking opportunities for the selected start-ups, to match them with relevant venture capital funds, big buyers, accelerators and other industry players within and outside the consortium, with the final objective of providing growth and/or exit opportunities to the selected start-ups.
- Establish a collaboration with relevant European Commission services/agencies, to enhance alignment across respective funding portfolios, for example channelling FSTP awarded start-ups towards subsequent fast track applications to EU funded initiatives and programmes, such as the European Innovation Council (EIC) or EIT Health programmes.

[19] Regulation (EU) 2016/679 of the European Parliament and of the Council of 27 April 2016 on the protection of natural persons with regard to the processing of personal data and on the free movement of such data, OJ L 119, 4.5.2016, pp. 1–88.

Objective 4 – Sustaining network growth:

Develop the sustainability, impact measurement, and long-term viability of the platform to maintain ecosystem networking, expert guidance, and virtual incubation by delivering a strategy for sustaining the incubator network beyond the IHI JU funding period.

Activities to be performed in the context of this objective:

- Create a funding and collaboration map (VCs, corporate investors, public bodies) with regional/broad reach to support start-up networking during the project's lifespan.
- Develop training modules on (pre)clinical validation and develop a business development toolkit (go-to-market plans, reimbursement strategies, commercial models).
- Industry quality seal: start-ups incubated through the action should receive, at the end of their participation in the action, a signal of validation and endorsement from the Network, in recognition of the start-up's value and investment worthiness for the whole health industry sector. The 'quality seal' can be provided in the form of a letter of intent or any other form deemed appropriate by the applicants, insofar as the quality seal would increase the start-up's visibility and credibility with potential investors and provide market validation that could help unlock future interest in the selected start-ups. This would not constitute a formal commitment or investment decision by the action's beneficiaries, but rather a form of industry endorsement signalling that the startup is credible, promising, and valuable to the broader sector.
- Develop a sustainability strategy for the Network beyond the funded period (business case, governance, revenue / hosting model), with the objective of identifying scenarios to ensure long-term sustainability of the Network and the continuous accessibility of the deliverables implemented in the project.
- Design project-wide key performance indicators (KPI) and implement a dashboard with agreed metrics by category. Examples of categories are:
  - commercial and economic viability of the Network,
  - scientific and/or technological progress of the start-ups,
  - IP applications,
  - talent and human capital development,
  - ecosystem effects between start-ups, universities and industry.
- Develop annual impact and lessons-learned reports as well as go-to-market playbooks for incubated early-stage companies.
- Support an alumni network of start-ups that have progressed through the Network, designed to facilitate connections between the start-ups and potential investors and funding partners.
- Prepare training and knowledge transfer materials to ensure ongoing operation of the Network.
- Develop and validate a framework/guidance to support early-stage engagement with regulators in a simpler and more accelerated way, including the development of recommendations for policy makers.

Financial Support to Third Parties (FSTP)[20]

In addition to providing structured access to industry expertise and complementing existing EU and national funding instruments, the Network would offer **milestone-based financial support**, governed by the Network Coordination Forum.

[20] The additional conditions contained in General Annex B and General Annex G to the Horizon Europe Work Programme 2026-2027 for Financial Support to Third Parties shall apply *mutatis mutandis*.

Applicants should provide, as a key activity of the proposed action, financial support to early-stage companies via the mechanism of Financial Support to Third Party (FSTP). This mechanism should allow the necessary financial support for early-stage companies to perform research and innovation activities with sufficient agility while limiting the administrative burden. This will effectively boost the progress of high potential third parties (start-ups) working on enabling technologies that will support innovation in areas of unmet healthcare need.

IHI JU estimates that, to achieve all outcomes and impacts of this topic, at least 75% of the IHI JU funding supplemented with Financial Contribution (FC) from the pre-identified industry consortium and/or contributing partners should be allocated for financial support to third parties selected through dedicated calls.

Scope of the FSTP call(s)

The FSTP open calls should target European early-stage companies developing transformative healthcare technologies at TRL3-TRL5 to tackle unmet public health needs, including but not limited to new modalities or new screening platforms & technologies, early clinical validation, AI/ML for drug discovery, quantum, advanced biologics, next generation screening technologies, novel delivery systems, enabling computational tools, other transformative platform technologies – that can be applied across multiple indications or therapeutic areas.

The text for the call(s) will have to be submitted to IHI JU for approval prior to launch.

The FSTP must be used exclusively to support TRL 3-5 start-ups in the advancement of their core innovative technologies. Such funding must not, under any circumstances, be used directly or indirectly for ancillary, non-core, or unrelated purposes.

Maximum amount per third party:

The maximum amount to be granted to each third party is EUR 2 000 000 (EUR 1 000 000 + EUR 1 000 000 as detailed below).

The programme should provide funding through a two-stage grant structure: an initial grant followed by a **potential** follow-on grant.

- **Initial Grant:**
  Via a competitive FSTP call, each startup could receive a milestone-based grant ranging from EUR 100 000 to EUR 1 000 000. Funding is disbursed only when agreed technical and development milestones are met.
- **Follow-on grant:**
  Those start-ups receiving an initial grant which demonstrate **exceptional potential and strategic relevance** could unlock an additional grant. This **follow-on grant** may also range from EUR 100 000 to EUR 1 000 000, is also tied to milestones, and aims to accelerate further development, validation, and industrial adoption.

The maximum funding available to each start-up is up to EUR 1 000 000 for the initial grant, with the possibility of an additional EUR 1 000 000 follow-on grant, which should already be flagged at the time of the initial grant application, bringing the total potential support to a maximum of EUR 2 000 000 per start-up. This is necessary to achieve the objectives of the third parties (start-ups) funded via FSTP which would otherwise be impossible or overly difficult to reach.

It reflects the financial needs of early-stage healthcare innovators, enabling sub-projects to deliver meaningful, scalable and sustainable impact across the European healthcare landscape while supporting validation and maturation as well as attracting follow-on investment. The funding level is aligned with the scope and complexity of sub-projects advancing technologies that require significant resources for regulatory preparation, clinical validation, and business development. This support is essential to strengthen proof-of-concept

translation and enable progress toward scale-up and market readiness, including high-cost activities such as preclinical studies and model development.

Mechanisms to select and fund third parties via FSTP

The Network Coordination Forum should select and fund third parties through FSTP based on excellence, meaningful impact and avoiding duplication.

Accordingly, the applicants should provide as part of their proposal the following information:

- specify how FSTP will be managed;
- provide a list of the different types of activities for which a third party may receive financial support and describe the results to be obtained;
- detail the role of the Advisory Board in line with the tasks indicated above;
- detail how it will organise the call(s) to select the third party and lay out the cadence of calls – note that the timing of the call(s) should allow for the completion of the awarded sub-projects within the lifetime of the main action;
- describe the organisation of the team launching and implementing the FSTP call(s);
- detail how the principles of transparency, equal treatment, non-conflict of interest and confidentiality will be respected;
- clearly delineate / detail the calls' logic, including:
    - evaluation, selection and award procedure for FSTP subprojects;
    - implementation of the eligibility and award criteria indicated below (including contribution to the achievement of the general objectives of IHI JU and consideration for the scale of innovation and the strategic importance of the supported technologies, quality of the proposed plan of activity and alignment with the funding request);
    - costs eligibility criteria;
    - maximum funding per call;
    - procedure for the selection of experts.
- specify how it will advertise the call(s) including the following requirements:
    - the call(s) should at least be published on the project website and the EU Funding and Tenders portal for a minimum of 2 months;
    - the results of the call(s) should be published at least on the Network public website, in particular: the name and country of the third parties, the dates, the nature of the sub-projects funded and their duration.

Applicants to FSTP calls should comply with the following minimum eligibility criteria:

- operate at Technology Readiness Level (TRL) 3, 4, or 5 at the time of submission;
- have NOT previously received FSTP funding under this action;
- are NOT receiving other EU funding for the proposed subproject.

Proposed FSTP sub-projects shall be evaluated against the following minimum award criteria:

- scientific and technical excellence addressing unmet healthcare needs and contributing to the achievement of the IHI JU general objectives21;
- innovation and differentiation and quality of the regulatory strategy and pathway to market;
- team capabilities, investment readiness and compatibility with industry in-kind offering.

Additional follow-on funding may be awarded on the basis of the following minimum follow-on award criteria (as applicable):

- successful completion of initial FSTP grant, including achievement of pre-defined technical milestones from the initial grant and demonstrated advancement along the agreed TRL pathway;
- demonstrated exceptional potential and strategic relevance and a clear justification that additional funding will materially accelerate outcomes.

Evaluation

Applicants should include in their proposal the establishment of an independent expert evaluation committee composed of expert representatives nominated and selected by the Network in consultation with the Advisory Board. This committee will evaluate sub-projects under the FSTP scheme in a transparent, objective and fair manner based on clear criteria, aligned with the minimum criteria set out above, and subject to appropriate safeguards against conflicts of interest.

Form of Financial Support to Third Parties

- Beneficiaries may provide Financial Support to Third Parties only in the form of grants.
- Additional cascade funding is not foreseen. Third parties receiving financial support should not allocate or transfer the financial support, whether partially or in full, to another entity.
- The indicative duration of the sub-projects is up to 36 months. Nonetheless, this does not preclude submission and selection of proposals requesting other durations to allow for the proper level of funding for maturing of business plans and solutions. However, the duration of the sub-projects will not exceed the duration of the Grant Agreement.
- The FSTP should be reimbursed to the third party on a milestone-based approach:

  A milestone-based disbursement combined with a technical and financial reporting scheme would ensure accountability and the efficient use of resources. Specifically, the applicants should describe in the proposal the technical and financial reporting frequency (which should, at minimum, be the same as those of the grant agreement) as well as the payment scheme it will design for payment to the third-party. The

[21] Article 115 of Council Regulation (EU) 2021/2085 of 19 November 2021 establishing the Joint Undertakings under Horizon Europe, OJ L 427, 30.11.2021, pp. 17–119:

'*Additional objectives of the Innovative Health Joint Undertaking*

1. In addition to the objectives set out in Articles 4 and 5, the Innovative Health Initiative Joint Undertaking shall reach the following general objectives by 2030:

a) contribute towards the creation of a Union-wide health research and innovation ecosystem that facilitates translation of scientific knowledge into innovations, in particular by launching at least 30 large-scale cross-sectoral projects, focusing on health innovations;

b) foster the development of safe, effective, people-centred and cost-effective innovations that respond to strategic unmet public health needs, by exhibiting, in at least five examples, the feasibility of integrating health care products or services, with demonstrated suitability for uptake by health care systems. The related projects should address the prevention, diagnosis, treatment or management of diseases affecting the Union population, including contribution to Europe's Beating Cancer Plan;

c) *drive cross-sectoral health innovation for a globally competitive European health industry and contribute to reaching the objectives of the new Industrial Strategy for Europe and the Pharmaceutical Strategy for Europe'*.

payment scheme should be designed carefully to avoid any cashflow shortage and take into account the timing of payments from IHI JU.

- Applicants should also detail the procedures regarding the nature and frequency of controls to ensure that third-parties respect the costs eligibility criteria and other compliance obligations and outline how they will support third parties, ensuring they are informed of the reporting and compliance requirements, particularly the cost eligibility criteria.
- The beneficiaries should be able to provide evidence of the FSTP disbursements, in particular extracts from their accounts and extracts from the third-party accounts as well as the bank statements of both beneficiaries and third-parties showing the financial support amount.

Additional guiding principles

1. **Access to external partnerships for start-ups awarded funding**
   Start-ups (TRL 3 to 5) that are awarded funding through the Network should be permitted to initiate partnerships within the broader innovation ecosystem—including with pharmaceutical companies, venture capital funds, and other relevant stakeholders subsequent to the finalisation of Network grant funding. These partnerships may be structured on a non-dilutive or dilutive basis, as appropriate to support the start-up's development and commercialisation pathway.
2. **Eligibility of start-ups hosted by participating incubators**
   A start-up hosted by a participating incubator should remain eligible to participate in FSTP calls, provided that respective hosting costs are not financed through EU funding (they can be part of the in-kind provided and thereby part of the project budget and reported costs). For example: Startup A is hosted at private incubator B. Lab rental fees are part of a grant from incubator B. Startup A is still eligible for FSTP funding excluding the lab rental fees to avoid double funding.
3. **Equal rights and opportunities for all industry**
   In all cases, industry inside and outside consortium should have equal rights and opportunities to negotiate access rights, collaboration arrangements, and other partnership structures.

Expected impacts

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

- deliver innovative, early technology solutions that contribute to addressing strategic unmet public health needs across multiple therapy areas to improve prevention, early diagnosis, and treatment;
- leverage the unique network and scale of IHI JU members to create a pipeline to support innovative startups in the health industry, fully integrated into European initiatives in support of start-ups and entrepreneurship;
- drive early cross-sector health R&D and innovation to strengthen the European healthcare industry's global competitiveness, contributing to the EU Industrial Strategy and Pharmaceutical Strategy objectives;
- create a sustainable network of European healthcare incubators to guide and support highly talented and innovative early-stage companies;
- harness digital health and data-sharing technologies (e.g., AI and big data) to enable interoperable health solutions, contributing to the European Health Data Space (EHDS) and improved evidence-based care;

- the action should generate a portfolio of early-stage companies that have undergone rigorous multi-industry validation, significantly increasing their credibility with investors, regulators, and healthcare systems. This ‘industry quality seal’ should enhance the selected startups’ ability to secure follow-on financing;
- by integrating corporate expertise into a pan-European incubator network, the action should reduce fragmentation, support faster clinical and eventually commercial decision-making, and enable more innovators to navigate regulatory and reimbursement pathways successfully. This should contribute to the objectives of the EU to accelerate the translation of research into deployable health technologies. The Network should serve as a feeder mechanism into wider EU support structures, ensuring that promising companies can transition smoothly into later-stage funding and scale-up opportunities. This complementarity should maximise the added value of EU public funding while avoiding duplication and reinforcing Europe’s position as a globally competitive hub for health innovation.

The action under this topic should synergise with relevant EU programmes and contribute to several key EU strategies and policies: Life Science strategy, the proposed Biotech Act (especially the biotechnology development accelerators as referred to in article 5 of the Commission proposal), Industrial strategy, Pharmaceutical strategy, EU4Health Programme, Digital Europe Programme, Testing and Experimental Facility for Health AI and Robotic (TEF-Health), European Innovation Council (EIC) programmes, EU Competitive Compass, Choose Europe initiative, Startup and Scale-up strategy by the European Commission.

Additionally, the action under this topic should synergise with the forthcoming European Startup and Scaleup Hubs and, in particular, encourage connection into the Network from the Call ‘European Startup and Scaleup Hub Pilot Call – HORIZON-EIE-2026-02-CONNECT-01’.

Furthermore, the action has the potential to support Europe’s Beating Cancer Plan, EU Mission on Cancer, Healthier Together – EU Non-Communicable diseases initiative, Joint Action for Cardiovascular Disease and Diabetes in Europe, or the Cardiovascular Health Plan.

Applicants should demonstrate in the proposal how these synergies will avoid duplication, ensure complementarity with existing EU efforts, and provide early-stage companies with continuity and scale-up pathways.

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

The fragmentation of Europe’s early-stage health innovation landscape – across incubators, investors, national programmes, and regulatory actors – cannot be addressed by public initiatives alone. Achieving the expected outcomes of this topic requires the integrated, cross sector model uniquely enabled by an IHI JU action.

The positioning and added value of the Network should be clearly articulated within the wider European innovation and funding landscape. Public and private collaboration is equally vital. Its distinctiveness lies in the provision of targeted industry in-kind support to a defined subset of start-ups developing enabling technologies (e.g. AI for biologics screening) with clear relevance to pharmaceutical and medical technology applications. This includes expertise and assets that cannot be replicated within public incubators or grant schemes, including access to infrastructure, clinical datasets, regulatory specialists, and corporate venture perspectives. These capabilities enable early-stage companies to receive actionable, market aligned guidance that significantly improves feasibility, derisks development, and accelerates time-to-market.

An IHI JU action brings these actors together under a shared governance model, ensuring alignment, mutual commitment, and faster translation of innovation.

Without this level of integration, efforts may remain fragmented. This model is uniquely positioned to deliver the coordination, ambition, and impact required to address these complex challenges in a stream-lined and accelerated manner bringing sustainable and continued investment in Europe.

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'):

- Astra Zeneca
- Boehringer Ingelheim
- Johnson & Johnson (co-lead)
- Novo Nordisk (lead)
- Pfizer(co-lead)
- Sanofi
- Servier
- UCB

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

- BioInnovation Institute Fonden
- OBELISQUE IMMOBILIER SARL

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 35 000 000.
- The indicative in-kind and financial contribution from industry beneficiaries is EUR 10 696 000.

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 allocation of the EUR 850,000 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).

- The indicative in-kind contribution from IHI JU contributing partners is EUR 4 328 750.

Justification for lowering the 45% threshold for this individual action

- The topic foresees a maximum of EUR 35 000 000 in IHI JU funding over five years, with the majority delivered through cascade funding to downstream innovators via calls targeting early-stage-healthcare companies. 75% of the IHI JU funding is expected to be reserved for FSTP, in line with the anticipated support needs of healthcare startups operating at early Technology Readiness Levels (see below).
- The indicative in-kind and financial contribution from the pre-identified industry consortium is EUR 15 024 750 (30% of the total project budget – justification below)
- Industry and contributing partners contributions for this topic will primarily consist of advice and guidance on business development, market access and technical expertise, access to lab facilities, platforms and data, for the IKOP component. This is unlike other IHI JU actions which often include significant time spent by postdocs and specialists from industry partners contributing to the actual work packages.
- Article 119(3) of Council Regulation (EU) 2021/2085 (the 'Single Basic Act') states that 'contributions provided by participants to indirect actions funded by the Innovative Health Initiative Joint Undertaking shall amount to at least 45 % of an indirect action's eligible costs and costs of its related additional activities. When justified, the work programme may exceptionally allow a lower proportion of contributions at the level of an individual indirect action and its related additional activities.'
- In line with the above-mentioned Single Basic Act provision, industry is investing significantly in IHI JU incubator activities and, as such, will seek to maximise relevant project-level IKAA, however, providing 45% or more of the requested eligible cost is unlikely to be achieved for the following reasons:
    - some of the necessary resources contributed by companies and contributing partners (data, equipment, offices, general infrastructure) will not be considered as eligible costs in accordance with Article 6 of the Horizon Europe Model Grant Agreement[22] and therefore will not be reported;
    - for all industry and contributing partners involved given the nature of the topic, it is not known in advance who the third parties are that will take part. This makes it challenging to predict upfront at individual company level the maximum in-kind levels that could be contributed to support them.
- Commitments from industry and contributing partners must represent at least 30% of total project resources. This is likely to match the IHI JU funds reserved and required for eligible consortium partners to receive funding for coordination, implementation, and support activities, but is insufficient to match the cascade funding component and fully achieve the topic outcomes.
- Therefore, given its unique, strategic and systemic importance for the European innovation ecosystem, the project funded under the present topic satisfies the conditions for a justified exceptional request for lowering the 45% threshold for an individual action.
- Expected budget distribution:

Total Action	Industry and contributing partners contributions	IHI Funding	FSTP	Project coordination
50 024 750	15 024 750	35 000 000	26 250 000*	8 750 000

*75% of IHI JU funding + to be complemented with financial contributions from industry.

[22] https://ec.europa.eu/info/funding-tenders/opportunities/docs/2021-2027/common/agr-contr/general-mga_horizon-euratom_en.pdf

Indicative duration of the action

The indicative duration of the action is 60 months.

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

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 that are essential to achieving the aims of the action and cannot be provided through public mechanisms alone.

- Technical and scientific knowledge across therapeutics, medical devices, diagnostics, digital health, and enabling technologies
- Specialised regulatory, legal and IP expertise.
- Commercial readiness and market access insight, ensuring that supported companies develop solutions aligned with real-world unmet needs and adoption pathways.
- Infrastructure, facilities, datasets, and platforms enabling early experimental validation, prototyping, and data-driven development.
- Corporate venture and investor-readiness support, enhancing visibility and credibility for startups seeking follow-on funding.
- Partnership opportunities, including testing environments, early pilots, and potential strategic collaborations or co-development agreements.
- Multi-corporate mentorship, ensuring that start-ups benefit from cross-industry perspectives rather than single-company viewpoints.

These contributions constitute the core added value of Network and differentiate the action fundamentally from existing funding and acceleration programmes. Industry involvement will enable Network to act as a European-level catalyst, delivering de-risked innovations with strong potential for scale-up and integration into healthcare systems.

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:

a) **Core leadership and operational, financial, and grant management**

- Strategic leadership and stakeholder engagement: Expertise in overall strategy development, stakeholder management, and fundraising.
- Operational and administrative management: Capability to manage day-to-day operations, program execution, and logistics.
- Third-party funding management (FSTP): Proven ability to select, fund and manage the full life cycle of third-party projects via FSTP. Sufficient operational and financial capacity will have to be clearly documented.

- Community building and engagement: Experience in organising events, networking activities, training sessions, and expert workshops for early-stage companies.
- Financial and grant management: Proficiency in budget planning, grant administration, and financial reporting. Demonstrated track record in managing large financial budgets and public-private partnerships.
- Start-up selection and support: Expertise in selecting, contracting, mentoring, and monitoring early-stage companies.

b) **Technical and business support**

- Business development and commercialisation: Skills in corporate partnerships and commercialisation strategy.
- Investment and funding expertise: Experience in due diligence, investment readiness, and investor network engagement.
- Regulatory, legal and IP strategy: Knowledge of regulatory frameworks, IP management, and contract negotiation.
- Technology expertise: Competence in AI, data science, enabling technologies, and digital health solutions.
- Public health and policy: Understanding of public health impacts and policy development.
- Technology tools: Customer Relationship Management (CRM) / portfolio management system; data rooms for due diligence; cloud computing resources; KPI tracking systems; portfolio monitoring capabilities; impact assessment framework

c) **Physical incubator infrastructure (complementary to industry in-kind facilities)**

- Flexible office/co-working spaces (hot-desking options).
- Meeting rooms and collaboration spaces.
- Wet lab facilities (for biotech-focused startups).
- IT infrastructure and cybersecurity advisory.
- Access to specialised lab facilities.

d) **Experience in enabling key capabilities and partnerships**

- Pharma partnership development: Ability to establish and maintain strategic collaborations with pharmaceutical companies; Access to industry experts and opportunities for technology validation.
- Investor network management: Strong connections with venture capital firms, corporate venture arms, and grant agencies; Expertise in facilitating funding opportunities for early-stage ventures.
- Academic and research collaboration: Partnerships with universities and research institutions for talent acquisition and intellectual property development; Capability to leverage academic resources for innovation.
- Service provider ecosystem: Established network of legal, accounting, Contract Research Organisations (CROs), and regulatory consultants; Ability to provide or broker specialised support services for startups.
- Pan-European networking: Links to other incubators and innovation hubs across Europe for knowledge sharing and collaboration; Experience in fostering cross-border partnerships.

- Health incubator programme expertise: Proven track record in designing and operating med-tech and pharma incubator programs; Ability to deliver structured support for early-stage health ventures.
- Early-stage company engagement: Deep expertise in partnering with and mentoring early-stage companies; Capability to guide startups through commercialisation and growth phases.
- Sustainability and growth: Deep expertise in shaping and implementing a roadmap to sustain long-term value beyond the project timelines

At the second stage, the applicant consortium selected at the first stage and the pre-identified industry consortium and contributing partners will form the full consortium. The full consortium will develop 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 2 : An AI Foundation Toxicology Model and Framework to Support Waiving a Second Species in Drug Safety Studies

Expected outcomes

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

1. **A validated Artificial Intelligence (AI) Foundation Toxicology Model*[23]** that provides transparent probabilistic predictions for industry and regulator stakeholders to determine when a second species in chronic (>90 days) and sub-chronic (90 days) small molecule medicine repeat-dose studies is unlikely to provide additional safety relevant information, including risks of missed toxicity, organ-specific findings, and divergence in No Observed Adverse Effect Level (NOAEL). The goal would be to enable waiving the need for two-species chronic testing for small molecules and other modalities e.g. oligonucleotides.
2. **A standardised, transparent weight-of-evidence framework** for industry, regulator and academic stakeholders that enables reproducible assessment of evidence quality, consistency, relevance, and uncertainty across regulatory submissions, supporting the wider adoption of the AI Foundation Toxicology Model and New Approach Methodology (NAM)-based toxicology strategies in general.
3. **Functional tools, templates, and training materials** that support the real-world implementation, sustainability and evolution of the foundation model and weight-of-evidence framework including guidance on explainability, provenance, governance, ethical use, and alignment with AI requirements, tailored to industry, regulator and academic stakeholder needs.
4. **Enhanced industry and regulator stakeholder confidence in second species waiver applications**, particularly for small molecule medicines, supported by empirical, calibrated evidence and a framework enabling predictable adjudication, more consistent global waiver decision-making and timely progression of medicine development without compromising patient safety. This confidence should be gained through the model and framework's application for regulator validation and acceptance, with the longer-term goal, beyond the action's scope, of a revision of the regulatory guidelines ICH M3(R2) **[1]** taking onboard the future project's outcomes. This topic should provide the opportunity to extend this confidence to waiving chronic testing in a single species beyond small molecule medicines and to other study types.

Scope

Regulatory guidelines e.g. ICH M3(R2) for nonclinical safety assessment of new small molecule medicines have historically required toxicity studies in two species, typically one rodent and one non-rodent, to maximise the likelihood of detecting adverse effects, improve the translatability to humans and guide patient dosing and monitoring. This two species approach is increasingly challenged by ethical considerations, long and costly study durations, limited reproducibility, and uncertainty regarding human relevance **[2]** **[3]**. In parallel, scientific progress in mechanistic toxicology, advanced *in vitro* systems (e.g. organoids and micro-physiological systems), multi-omics technologies, and AI-based modelling is enabling NAMs to help reduce reliance on animal models without compromising patient safety. Within the context of this topic, the AI Foundation Toxicology Model will be considered a NAM, facilitating NAM-enabled second species waivers.

[23] An AI Foundation Toxicology Model is a large-scale, pre-trained machine learning system that learns generalisable representations of toxicological biology and chemistry from diverse, multimodal datasets, enabling broad applicability across safety assessment tasks with minimal task-specific training.

In addition, the policy landscape across global jurisdictions is evolving rapidly. The European Commission is preparing a roadmap towards phasing out animal testing for chemical assessment safety, expected in 2026[24]; the European Medicines Agency (EMA) has increased its focus on emerging NAMs through horizon-scanning and dedicated working groups[25]; the UK Government has published the Replacing Animals in Science strategy[26] and the United States Food and Drug Administration (FDA) has published a dedicated roadmap for reducing animal testing in preclinical safety studies[27]. Collectively, these initiatives highlight the need for robust evidence, data integration, validated methods and coordinated stakeholder action to support credible alternatives to animal testing.

A weight-of-evidence approach can eliminate unnecessary animal tests by integrating and assessing diverse data sets as well as determining whether the available evidence is sufficient or additional nonclinical testing is required to address potential safety concerns. The value of this evidence depends on its quality, consistency, human relevance, and the nature and severity of observed effects. Currently, the absence of standardised, data-driven methods means decisions can vary across reviewers and jurisdictions, creating an uncertainty which discourages changes from being made to the current process. A more structured, reproducible, validated, and evidence-based approach would support consistent, transparent, and well-justified decision-making on whether second species studies could be waived.

This topic aims to address and standardise the waiver process for second species chronic and sub-chronic small molecule general toxicology studies by developing a transparent, AI-driven Foundation Toxicology Model. The model should be underpinned by diverse, standardised, high quality *in vivo* datasets, encompassing all modalities of medicines, and supported by a robust weight-of-evidence framework.
The most appropriate single species should be selected early in the drug development programme based on target affinity and functions, metabolite profiling, etc. The main context of use of the AI Foundation Toxicology Model is to predict whether testing in a second species will provide additional safety-relevant information.
If toxicity predictions are equal across rodent and non-rodent species, priority should be given to the reduction of non-rodent chronic toxicity testing.

Although the context of use for this topic should be focused on waiving second species testing for chronic and sub-chronic small molecule studies, the project's actions, sustainability plan plus the ongoing development and evolution of the model should provide the opportunity to assess appropriate single species selection and encompass the broadening of the context of use to enable the waiving of single species chronic testing in small molecules and other modalities, such as oligonucleotides. Therefore, relevant data sources and their provision should enable this broader and longer-term goal. Selection of the appropriate single animal species for preclinical safety evaluations for biotechnology-derived pharmaceuticals in line with ICH S6[28] should be considered within the scope of this project if the relevant data provision is sufficient to enable this functionality.

This topic should build upon, among others, the outcomes, learnings, data sharing structures, and methodologies of previous IMI/IHI projects that improve the predictability, feasibility and reliability of

[24] European Commission – Roadmap towards phasing out animal testing
https://single-market-economy.ec.europa.eu/sectors/chemicals/reach/roadmap-towards-phasing-out-animal-testing_en
[25] EMA – New Approach Methodologies Horizon Scanning Report
https://www.ema.europa.eu/en/documents/report/new-approach-methodologies-eu-horizon-scanning-report_en.pdf
[26] UK Government – Replacing Animals in Science Strategy
https://www.gov.uk/government/publications/replacing-animals-in-science-strategy
[27] FDA – Roadmap to Reducing Animal Testing in Preclinical Safety Studies
https://www.fda.gov/files/newsroom/published/roadmap_to_reducing_animal_testing_in_preclinical_safety_studies.pdf
[28] Preclinical Safety Evaluation of Biotechnology-Derived Pharmaceuticals:
https://database.ich.org/sites/default/files/S6_R1_Guideline_0.pdf

pre-clinical safety assessments — such as BigPicture[29], eTRANSAFE[30], eTOX[31], imSAVAR[32], and VICT3R[33] — as well as other relevant European, international and national initiatives such as Animal-free safety assessment of chemicals: Project cluster for implementation of novel strategies (ASPIS)[34] and NC3Rs-led efforts like the Virtual Second Species[35] initiative and the Two Species project[36]. Preliminary analysis from the NC3Rs Two Species project predicts that it would be possible to avoid conducting studies in non-rodents (e.g. dog or non-human primate) in >60% of the small molecule drugs that enter Phase II globally each year **[4]**.

By fostering collaboration among pharmaceutical companies, regulatory agencies, academic institutions, SMEs, and patient advocacy groups, the action generated by this topic should seek to enhance patient safety, reduce reliance on animal testing, streamline medicine development timelines, lower associated costs, and boost the global competitiveness of the pharmaceutical industry within the European Union.

To fulfil this aim, the proposal should:

1. **Consolidate and evaluate data sources**
    - Identify, curate, and assess the quality and suitability of data from multiple pharmaceutical companies and other organisations within the consortium with a priority focus on general toxicology studies (14-day, 28-day, 90-day and chronic toxicity studies) in the form of structured toxicity data in CDISC SEND[37] format as well as in unstructured study reports. Secondary focuses for additional data should also be considered, including *in vivo* toxicity study data, chemistry (e.g. structure information, where permitted), pharmacokinetic and exposure data, mechanistic *in vitro* systems, *in silico* models, multi-omics datasets, licensed content, prior consortia outputs, and public regulatory databases.
    - Develop a new database to host and analyse data, encompassing principles to support a common or federated data model that enables sensitive data preservation and multisource analysis that can allow NAM-enabled second species waivers. Additionally, sensitive data should undergo various levels of blinding from full blinding to structural alerts as a surrogate for the full structure and structural embeddings with noise introduction among other approaches.
    - Applicants are expected to consider the potential regulatory impact of the project's results and develop a regulatory strategy and interaction plan for generating the required evidence to support regulatory decision-making, linked to the data sources used, as well as engaging with regulators in a timely manner for their input (e.g. national competent authorities, EMA, etc). The goal is to gain, by the end of the project, endorsement of the AI Foundation Toxicology Model from the regulatory authorities (e.g. EMA, FDA, including potential Innovative Science and Technology Approaches for New Drugs (ISTAND)[38] submission) to enable second species waivers for chronic

[29] BigPicture: https://bigpicture.eu/

[30] eTRANSAFE: https://etransafe.eu/

[31] eTOX: https://www.ihi.europa.eu/projects-results/project-factsheets/etox

[32] imSAVAR: https://imsavar.eu/

[33] VICT3R: https://www.vict3r.eu/

[34] ASPIS: https://aspis-cluster.eu/

[35] NC3Rs Virtual Second Species - Applying advanced computational and mathematical modelling approaches to develop a suite of virtual dog tissues and organs to model toxicological endpoints for new chemical entities https://nc3rs.org.uk/crackit/virtual-second-species

[36] Review of the use of two species in regulatory toxicology studies | NC3Rs: https://nc3rs.org.uk/our-portfolio/review-use-two-species-regulatory-toxicology-studies-ichm3#two-species-phase-ii-ich-m3r2

[37] SEND specifies a way to collect and present non-clinical data in a consistent format, a requirement for data submission to regulators

[38] Innovative Science and Technology Approaches for New Drugs (ISTAND) Program, FDA: https://www.fda.gov/drugs/drug-development-tool-ddt-qualification-programs/innovative-science-and-technology-approaches-new-drugs-istand-program

and sub-chronic small molecule testing. The longer-term goal, beyond the action's scope, of revising the regulatory guidance ICH M3(R2) in line with this project's outcomes should also be taken into consideration when designing the regulatory strategy. The opportunity to broaden the scope of the AI Foundation Toxicology Model to encompass waiving single-species chronic testing beyond small molecules (e.g. oligonucleotides) should be part of the longer-term and sustainability planning.

2. **Select and optimise AI methods**

- Conduct a systematic review of existing AI and AI-supported foundation modelling approaches.
- Select and optimise AI methods able to perform probabilistic predictions estimating the likelihood of novel safety-relevant information being identified in longer-term studies and/or in a second species, including risks of missed toxicity, organ-specific findings, and divergence in NOAEL. The potential to select the appropriate single species for biological medicines should also be considered in the AI method selection and optimisation.
- Ensure transparency, interpretability, traceability, and data provenance to meet regulatory expectations.

Applicants should ensure that, in order to support regulatory acceptance and the scientific robustness of the AI Foundation Toxicology Model, it is built using a structured and transparent AI methodology encompassing:

- Data harmonisation and representation learning
  - Feature extraction pipelines appropriate to each data modality (unstructured study reports, molecular structures, omics datasets, mechanistic assays).
  - Multimodal representation learning (e.g., contrastive learning) to create unified latent spaces across biological, toxicological, and metadata features.
  - Federated learning and privacy preserving techniques to enable secure, multi-organisation data contributions without exposing proprietary information.
- Predictive modelling approaches
  - Probabilistic supervised models (e.g., Bayesian neural networks, Gaussian processes, calibrated ensembles) to estimate the probability of missed toxicological findings under a single-species approach.
  - Mechanistic-informed modules integrated via knowledge graph neural networks, causal inference frameworks, and multi-task predictors for endpoints such as drug-induced liver injury, cardiotoxicity, and genotoxicity.
  - Uncertainty quantification methods to ensure transparent confidence intervals suitable for risk-based decision-making.
  - Scenario simulation engines (Monte Carlo, generative models, causal models) to test counterfactuals relevant to second species value.
- Transparency and explainability
  - Use of explainable AI techniques to identify key drivers of model predictions.
  - Comprehensive provenance tracking to ensure every model output is traceable.
  - Human interpretable decision layers to support weight-of-evidence narratives.

- Long-term evolution
    - Ability for continuous learning, single-species chronic testing waivers beyond small molecules and modular updates as new data types and methods emerge.

In parallel, other approaches should be assessed in case a foundation model does not provide the solution. This could encompass decision-tree approaches, Bayesian statistical methods and/or more classical Machine Learning (ML) approaches.

3. **Develop and validate the AI Foundation Toxicology Model**

    - Design, train, and validate an AI Foundation Toxicology Model that produces probabilistic predictions across multiple dimensions: 1) study duration (sub-acute, 14–28 days; sub-chronic; and chronic), 2) species (rodent and non-rodent), and 3) outcome type including the likelihood of identifying a novel target organ, a significantly divergent toxicity profile and/or a significantly divergent NOAEL. For example, the model should predict the likelihood (0-100) that running a 9-month non-rodent study would identify a divergent toxicity profile, including significantly increased severity of pathology findings as compared to the toxicity profile identified in earlier, shorter-term studies or projected to be identified in the rodent 6-month study yet to be conducted. These specific outputs should be defined depending on the data provided and the AI methods, which will be established within the early stages of the project.
    - Industry, academic and SME stakeholders with consistent regulator engagement and input should define representative use cases and performance metrics, including accuracy, robustness, explainability, extensibility and trustworthiness, to validate the model. Formal benchmarking and rigorous testing are essential for ensuring consistency of results, to build trust in the model's recommendations.

4. **Establish a standardised weight-of-evidence framework**

    - Create a transparent, reproducible, weight-of-evidence decision support framework that integrates diverse data types and model outputs into standardised reasoning steps, including the direct model outputs (e.g., probability and significance of novel findings in a longer-term second species study) and model context (e.g., narrative rationale supporting the probabilistic output) from the AI Foundation Toxicology Model as well as orthogonal internal programme and external literature support. *In vitro* NAMs, target knowledge and literature mining would all help supplement and increase confidence in the AI Foundation Toxicology Model outputs and recommendations.
    - Define how uncertainty, evidence quality, consistency, severity, and human relevance including potential impact on or risk for the clinical programme should be evaluated, compatible with regulatory reasoning, to support second species waiver submissions.
    - Test the AI Foundation Toxicology Model, through use cases, together with the weight of evidence framework with relevant diverse stakeholder groups, including pharmaceutical and biotechnology companies, regulators and academics/SMEs working at the interface of drug safety research and regulation to ensure consistency across reviewers and jurisdictions.

5. **Prepare for regulatory uptake and long-term sustainability**

    - Develop recommendations and practical tools for real-world implementation, including regulatory strategy and guideline revision as required, alignment with ethical and legal principles plus a governance structure for ongoing model evolution and ecosystem adoption. For instance,

trustworthy AI, human oversight and verifications will follow regulatory frameworks such as the Assessment List for Trustworthy Artificial Intelligence (ALTAI)[39].

- Devise a sustainability and evolution plan for long-term hosting, maintenance, continuous data harmonisation and improvement of the AI Foundation Toxicology model and weight-of-evidence framework, enabling broad and sustainable ecosystem adoption.

Expected impacts

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

- Faster and more informed decision-making through the use of an AI-driven NAM (AI Foundation Toxicology Model) and increased efficiency through rapid processing of vast amounts of data[40]
- Increased consistency and standardisation in a NAM-based approach, specifically an AI model, used by industry in the efficient development, testing and production of safe and effective innovative health technologies, improving industrial competitiveness.
- Regulatory adoption of a NAM-enabled second species waiver model (AI Foundation Toxicology Model) and weight-of-evidence framework, in line with recommendations and more consistent global decision-making on waiving second species testing.
- Reduction in animal use, accelerated timelines and lower costs, enhancing the competitiveness of the European health industry through economical and ethical benefits.
- Improved public health as patients will benefit from safe and effective medicines developed faster using validated NAMs.

The action is expected to contribute to the EU Directive (2010/63/EU)[41] on the protection of animals used for scientific purposes and the implementation of the 3Rs principles to replace, reduce and refine the use of animals. The action is expected also to consider and contribute to EU programmes, initiatives and policies on New Approach Methodologies (NAMs) such as the future European Research Area (ERA) action on accelerating NAMs to advance biomedical research and testing of medicinal products and medical devices.

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

Achieving regulator-trusted, NAM-enabled second species waivers requires large, heterogeneous datasets; federated collaboration across multiple pharmaceutical companies and other relevant stakeholders; cross-disciplinary expertise in toxicology, data science, regulatory sciences, and ethics; and early, coordinated engagement with regulatory authorities. These conditions cannot be met by individual organisations acting independently. IHI JU public-private partnerships provide the framework, scale, and infrastructure required to deliver impact, ensure sustainability, and build broad stakeholder confidence in AI-driven weight-of-evidence approaches.

[39] Assessment List for Trustworthy Artificial Intelligence (ALTAI): https://digital-strategy.ec.europa.eu/en/library/assessment-list-trustworthy-artificial-intelligence-altai-self-assessment

[40] Transforming animal study toxicology reports into structured, harmonized data using large language models: https://pubmed.ncbi.nlm.nih.gov/42133063/

[41] European Directive on the protection of animals used for scientific purposes: https://eur-lex.europa.eu/eli/dir/2010/63/oj/eng

Pre-identified industry consortium and contributing partner

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
- Bayer
- Bristol Myers Squibb
- Eli Lilly
- Gilead
- Novartis
- Pfizer (Lead)
- Servier

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

UNITED KINGDOM RESEARCH AND INNOVATION – National Centre for the Replacement, Refinement and Reduction of Animals in Research ('UKRI NC3Rs').

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 9 000 000.
- The indicative in-kind contribution from industry beneficiaries is EUR 7 300 000.

Due to the global nature of the participating industry partners, it is anticipated that some elements of the contributions will be in-kind contributions to operational activities (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).

- The indicative in-kind contribution from the IHI JU contributing partner is EUR 100 000.

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 may jointly agree on a different duration when submitting the full proposal.

Contribution of the pre-identified industry consortium and contributing partner

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

- proprietary toxicology and mechanistic datasets;
- expertise in CDISC SEND standards, AI/ML, mechanistic toxicology, pharmaceutical and regulatory sciences, and federated analytics;
- infrastructure for federated learning;
- leadership in model development, validation, and regulatory engagement.

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.

This may require mobilising the following expertise:

- pharmaceutical and toxicology data management, engineering and integration including:
    - managing chemical structure and properties, structured (SEND-formatted) and unstructured (study reports) *in vivo* toxicology study data, *in vitro* assay results and flexibility to handle other data types and formats (e.g., omics);
    - mapping of diverse terminology to ontologies and controlled vocabularies for enhanced data integration at scale via automated methods (i.e., LLM-driven).;
    - extraction of key values and text from unstructured reports (e.g., treatment-related findings and NOAEL/LOAEL values);
    - hosting federated data / learning platforms or other data security and privacy platforms/approaches
- AI/ML model development capabilities including:
    - core machine learning, artificial intelligence, data science applied to health and biological sciences;
    - advanced AI techniques including the ability to develop large-scale models (multi-billion parameter networks);
    - experience with multi-modal model development.
- experience with complex probabilistic predictions as outputs from foundation models or fine-tuned versions;
- regulatory and compliance Framework Standard Operating Procedures (SOPs): expertise for AI model validation and monitoring;
- regulatory packages and weight-of-evidence decision-making in pharmaceutical toxicology studies;
- project management experience for large multi-stakeholder European public-private partnerships.

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

- technological infrastructure:
    - high-performance computing for processing large volumes of data;

    - data storage solutions to securely store and manage data from various sources during the project duration and beyond to enable sustainability of the project's outcomes;
    - federated data platform that enables sharing and/or analysis of data in a blinded manner.
- provision of proprietary toxicology and mechanistic datasets or other relevant data, where available.

All project members need to have access to data in a GDPR-compliant manner.

The applicant consortium is expected to enable effective collaboration with regulatory authorities, national competent authorities, and may consider, for instance, engaging them as consortium partners, or in an advisory capacity.

At the second stage, the consortium selected at the first stage and the predefined industry consortium and contributing partner 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.

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Topic 3 : Decode the immuno-science of age-related immune-mediated diseases

Expected outcomes

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

1. Researchers will benefit from a **better understanding of the potential causal links between chronic inflammatory diseases and biological ageing**, and the predictiveness of the accompanying biomarkers could allow for the definition of precise risk profiles for age-associated immune disease onset and exacerbations.
2. Patients will benefit from **new early detection strategies as well as new diagnostic approaches to differentiate disease onset in elderly people from onset in younger adults**. This will inform a personalised medicine approach to treatment and will in turn help to prevent disease progression.
3. Patients and healthcare professionals will benefit from the **repurposing or development of novel therapies for ageing populations with chronic inflammatory diseases** and precision medicine approaches that prevent health decline while reducing healthcare costs.
4. Researchers and industry will benefit from **the establishment of systematic collaborative approaches for the use of available biobanks across age ranges**, immune diseases and comorbidities to adopt innovative approaches (by integration of multi-omics, immunophenotyping, digital biomarkers, ageing clocks, and artificial intelligence (AI) with comprehensive patient information).
5. Patients and healthcare professionals will benefit from **deeper insights into treatment response** and the evaluation of the impact of ageing on treatment effectiveness.
6. Industry and researchers will benefit from **the establishment of regulatory pathways for novel intervention strategies and biomarkers,** leading to the faster clinical development of drugs that improve age-associated disease exacerbations, ultimately enabling the translation of research findings into therapeutic solutions for vulnerable patient populations. This includes the field of digital biomarkers and their use in monitoring activity, strength and fatigue as exemplary readouts.

Scope

The global population is undergoing an unprecedented demographic shift, with the number of individuals aged 65 and older projected to double by 2050, presenting one of the most significant public health challenges of our time. The transition to an ageing society is accompanied by a parallel rise in the prevalence of chronic diseases, multimorbidity, and years lived in poor health, placing immense strain on healthcare systems worldwide [1]. Central to this phenomenon is the progressive decline of immune function with age which not only increases susceptibility to infections and malignancies, but also drives chronic low-grade inflammation, known as "inflammaging" [2].

The profound age-related changes to the immune system are collectively termed immunosenescence. These changes include thymic involution, reduced naive T-cell production, expansion of memory T-cells with limited repertoire diversity, increased inflammatory cytokine production (inflammaging), and broad dysregulation of innate immunity [3] [4]). In parallel, senescent cells accumulate and secrete SASP cytokines—such as IL-6, IL-1β, and TNF—which further amplify inflammaging and contribute directly to age-related immune dysfunction [5] [6]. Concurrently, there is a rising incidence of immune-mediated diseases with initial onset in elderly populations, including late-onset rheumatoid arthritis [7], elderly-onset

inflammatory bowel disease (IBD) [8], late-onset systemic lupus erythematosus (SLE) [9] and late-onset respiratory diseases [10] [11].

Critically, advanced age is associated with the increased incidence of autoimmune and inflammatory diseases [12]. Moreover, older adults exhibit heightened vulnerability to immune-mediated pathologies ranging from late-onset autoimmune disorders to vaccine hyporesponsiveness and impaired tissue repair Error! Reference source not found.[13] [14]. Despite the clear clinical burden, the mechanistic underpinnings of how ageing reshapes immune homeostasis and disease susceptibility, and concomitantly, of how diseases reshape the ageing-process and the immune system, remain incompletely understood. A comprehensive understanding of the bidirectional relationship between immune system dysfunction and the ageing process is therefore imperative to develop targeted interventions that can prevent, delay, or reverse age-associated immune diseases and ultimately extend health span.

Despite their clinical significance, elderly-onset immune diseases remain poorly understood compared to their younger adult-onset counterparts. Evidence suggests that they may represent distinct disease entities with unique pathogenic mechanisms, clinical presentations, and treatment responses [15] [16]. The intersection of immunosenescence with pathological immune dysregulation presents both challenges and opportunities for targeted interventions.

Industry, regulators, researchers, and other stakeholders should address the critical gap in our understanding of how ageing-related immune changes contribute to disease pathogenesis in the elderly. New evidence-based findings should help to elucidate the molecular drivers of both elderly-onset immune diseases as well as immune disease exacerbations during ageing. In addition, these findings should help to identify predictive biomarkers, leading to age-appropriate therapeutic and prevention strategies accounting for the unique immunological context of older patients, and ultimately reducing the socio-economic burden for society.

The action funded under this topic therefore aims to elucidate the key biological determinants that drive healthy ageing and immune-mediated disease, with a particular focus on how age-associated immune system remodelling shapes these outcomes.

Applicants are expected to address all of the following objectives of the topic in their proposal:

Understanding molecular and clinical differences between younger adult-onset and elderly-onset diseases: The focus of the action should be on immune-mediated diseases with a peak of onset in elderly patients, such as inflammatory bowel disease and respiratory diseases, and specifically directed to diseases with mainly elderly onset.

Therefore, in summary the proposal should cover the following immune-mediated diseases:

- gastroenterological diseases: IBD like Crohn's disease, ulcerative colitis;
- respiratory diseases: like asthma, chronic obstructive pulmonary disease, immune-mediated interstitial lung disease;
- rheumatoid diseases: like rheumatoid arthritis, giant cell arteritis, polymyalgia rheumatica, Sjögren's disease, SLE.

The focus and the combination of these disease types would limit the risk of dispersion but still reflect different organ systems and enable crucial cross-disease comparisons.

Identify drivers of elderly-onset immune diseases: Determine the specific cellular and molecular mechanisms that trigger immune dysregulation uniquely in elderly populations.

Characterise factors driving disease exacerbations with ageing: Investigate how age-related physiological changes influence disease progression and flare frequency/severity.

Evaluate biological age as a driver of disease: Distinguish chronological from biological ageing in disease pathogenesis and identify predictive biomarkers for onset and exacerbations, including the influence of comorbidities.

Discriminate the molecular phenotypes and associated patient characteristics between chronologically aged versus biologically aged adults and elderly-onset disease patients. Understand patient heterogeneity in elderly-onset disease, both in regard to treatment response and molecular signatures.

Define the relevance of immunosenescence on biological and chronological ageing and whether there is a **causal link between age, senescence and chronic inflammatory diseases** including treatment response.

Identify common immunosenescence signatures across elderly-onset immune diseases: Elucidate shared pathways that might represent universal therapeutic targets.

Evaluate how **vaccination history can contribute to reducing disease onset and/or exacerbation** in older populations. Moreover, assess the translatability of system serology or other immunological endpoints as senescence markers.

Pathway identification and validation: AI / machine learning (ML)-assisted identification of underlying biological pathways and biomarkers from the gathered datasets. Evaluation of the impact of ageing on treatment effectiveness. Assessment of the predictiveness of identified biomarkers in ageing populations independent of underlying chronic inflammatory diseases.

Applicants should envisage the following activities as part of the action funded under this topic:

1. Applicants are expected to define a strategy to assess age-related disease phenotypes and related biomarkers, incorporating a modelling perspective alongside AI-assisted data mining, appropriate statistical methodologies, and prioritisation approaches for the exploration of mechanisms of action (MoA).
2. Applicants should detail their methodological approach, including verification strategies and data collection procedures, providing preliminary data to show potential for success and strategies for mitigating the main methodological risks and limitations.

   The action should leverage both the wealth of existing cohorts, as well as the data from a new targeted observational cohort, which is expected to be set up by the consortium, and to include appropriate age-ranges and disease onset groups. New and existing observational cohorts should be used to evaluate the impact of standard of care treatments on the chosen diseases to define a path forward towards precision medicine and understanding age-dependent impacts of therapy response.

   The analysis of existing and new bio-specimens (peripheral blood mononuclear cells, white blood cells, stool, saliva, urine, diseased tissues and exhaled breath condensate) should allow for the conduct of deep molecular profiling of the targeted chronic inflammatory diseases across various age ranges with appropriate age-matched control groups.

   The wealth of data (both existing as well as newly created via the observational cohort), including participants' clinical characteristics and health records (e.g. disease, comorbidities, frailty assessment, vaccination and infection history) gathered through state-of-the-art methodologies and technologies will enable the comprehensive analysis of chronological ageing, biological ageing markers, and immune signatures through:

   - Immunological profiling: systems serology, immunophenotyping, T/B cell repertoire analysis, immunopeptidome.
   - Molecular profiling (systemic and organ-specific) including RNASeq, scRNASeq, spatial transcriptomics, proteomics, metabolomics, epigenome.

- Evaluating and comparing multiple ageing clocks e.g. IMM-AGE, iAge, proteomic, somatic DNA mutations e.g. CHIP associated mutations, epigenetic (DNAm), RNA, and metabolic clocks.
- Metagenomic: Microbiome/Virome. The gut, lung and tissue-resident microbiomes are key modulators of immunosenescence and inflammaging and influence the onset and exacerbation of elderly-onset immune diseases. Integrated metagenomic and metabolomic profiling will be combined with immunophenotyping, ageing clocks and digital biomarkers to identify microbiome-driven signatures of biological ageing and disease risk. Incorporating host–microbiome interaction modelling will enable identification of modifiable pathways to support targeted prevention and early intervention strategies in ageing populations.
- Leveraging population-wide electronic health records with comorbidities, but also vaccination history, viral/bacterial infection data, and immunogenicity profiles as functional metrics to define immunosenescence.
- Applying AI-driven computational approaches to integrate multi-omics data with electronic health records and population-based disease registries to identify potential disease-agnostic senescence pathways and reveal both disease-agnostic as well as disease-specific mechanisms by which immunosenescence may drive the onset and progression of autoimmune diseases in elderly populations. The action should link identified changes with patient characteristics including disease severity, treatment response, comorbidities, age, and age at onset of disease. Appropriate verification strategies to bridge the gap between computational and biological outcomes should be developed whenever possible.
- Applying digital health technologies (e.g. wearables, in-soles, hand grip, sleep monitoring) and related digital biomarkers to assess physical function, track sleep and to correlate with molecular markers.

3. 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. Additionally, applicants should anticipate engaging regional healthcare systems and authorities to prepare for clinical implementation and outcome acceptance when necessary.
4. Applicants should include in their proposal a strategy to ensure sustainability of the outputs of the project, including data and samples collected, beyond the funding period.
5. Applicants should leverage experience from the European research infrastructures (ERICs) already working on the areas mentioned in this call topic to avoid overlaps and increase the impact of results.

The action funded under this topic is expected to consider potential synergies with projects that work on the area of interest of this topic.

Expected impacts

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

- **Accelerate EU access** to more cost-effective interventions in an increasingly ageing population by identifying personalised treatment approaches for elderly-onset immune diseases.
- **Decrease disease risk** later in life by defining specific prevention strategies based on ageing biomarkers and risk factors.
- **Halt age-associated disease exacerbation** by the identification of predictive and digital biomarkers that can stratify patients for early intervention.

- **Improve quality of life** for healthy individuals and patients by preventing further health decline, avoiding escalating care costs, and properly stratifying individuals earlier in the diagnostic pathway.
- **Accelerate adoption** of innovative diagnostic, preventative, and therapeutic strategies, strengthening the EU's position as a healthcare innovator.
- Evaluate **digital biomarker as potential regulatory endpoints** in the ultimate goal to develop medicines for 'healthy ageing'.
- **Integrate fragmented research efforts** by bringing together health industry sectors and stakeholders to develop clinical and multi-omics data integration capabilities.
- **Enable new data-driven research** by building AI infrastructure on existing data and cohorts that no single organisation could develop independently

Patients and citizens will benefit from improved medical practice and healthcare solutions, new targeted prevention strategies and ultimately healthier ageing.

The action will support EU policy and priorities including the European Health Data Space Regulation (EHDS) and the EU Artificial Intelligence Act, while contributing to European competitiveness in addressing one of society's major challenges.

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

Elucidating the complex relationships between ageing and chronic inflammatory diseases requires a multi-disciplinary approach that transcends traditional research boundaries. The interconnected nature of immunosenescence and age-related disease onset or exacerbations demands collaboration between academic researchers with expertise in ageing biology, epigenetics, immunometabolism, and multi-omics approaches, and private companies pursuing therapeutic options in chronic inflammatory diseases.

Collaborations built under IHI offer the following advantages: Cross-sectoral collaboration: The project requires unprecedented collaboration between disease expertise, ageing and immunology research, communities that traditionally do not overlap. IHI's model facilitates this essential partnership between academic and industry expertise.

Data access, integration and federated analysis: The greatest advantage of the IHI model is increased access for all ecosystem players to:

- existing research cohorts and biobanks;
- electronic health records and real-world evidence;
- digital biomarker data and computational resources;
- large genetic consortia and validation datasets.

Resource pooling: No single organisation possesses the comprehensive resources needed, including:

- multi-disease expertise across inflammatory conditions;
- advanced multi-omics capabilities (immunoproteomics, spatial transcriptomics, metabolomics);
- AI/ML computational power for complex data integration;
- regulatory expertise for novel (wet lab and digital) biomarker development;
- patient recruitment capabilities across multiple age groups and diseases.

Timeline feasibility: Traditional research structures would require decades to achieve these outcomes. The IHI model enables parallel execution of data mining (existing cohorts & data) and prospective cohort preparation/recruitment, making translational outcomes feasible within the project timeframe.

Sustainability and impact: The collaborative framework ensures sustainability beyond the funding period through established industry-academic partnerships and shared data infrastructure that will continue to generate insights for the ageing population's healthcare needs.

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'):

- Eli Lilly
- Novartis
- Novo Nordisk
- Sanofi (Lead)

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 9 200 000.
- The indicative in-kind contribution from industry beneficiaries is EUR 9 200 000.

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 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

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

- expertise in target discovery, biomarker identification, AI-driven analysis, regulatory sciences and therapeutic development;
- expertise and scientific resources in the disease areas of interest – rheumatology, gastroenterology, respiratory – of immune mediated origins, as well as in immunology, ageing and translational science and medicine;
- enabling access to retrospective datasets, e.g. FinnGen UK Biobank, OpenTarget including federated analysis opportunities;
- proprietary datasets of related patients or control cohorts (baseline, placebo data) for verification and validation via federated analysis models;
- real world evidence (RWE) datasets;
- computational analysis support;
- support with (digital) biomarker expertise;
- molecular analytical support with certain technologies like CHIP.

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:

- academic research capabilities in ageing biology and immunosenescence;
- clinical expertise in gastroenterology and pulmonology and rheumatology;
- expertise in ageing biomarkers, immunophenotyping and immunogenetics and epigenetics;
- omics expertise, generation and analysis across immunology, epigenetics, microbiome, metabolism and spatial technologies;
- clinical trial set-up, logistics and conduct, including multi-omics analytics;
- AI- and big data development and handling / data management;
- expertise on digital biomarkers;
- project management experience for large multi-stakeholder European public-private partnerships;
- biobanks (systemic as well as tissue datasets) including longitudinal cohorts (for example but not limited to Milieu Interieur, INSPIRE-T, NutriNet, SNAC-K and EHDEN) combined with epidemiology data and broad patient information database including the immune-mediated diseases mentioned above, treatment history, comorbidities;
- registries such as, but not limited to, UK IBD registry, Initiative on Crohn and Colitis registry, FranceCoag registry, product related registreies (e.g. REMISMA registries), other data sources (e.g. French database SNDS);

- data inventories and strong IT, AI and bioinformatics expertise to integrate datasets and build data infrastructure;
- bio-sample handling and storage.

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.

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Glossary

ACRONYM	MEANING
AI	Artificial Intelligence
ALTAI	Assessment List for Trustworthy Artificial Intelligence
ASPIS	Animal-free Safety assessment of chemicals: Project cluster for Implementation of novel Strategies
EFPIA	European Federation of Pharmaceutical Industries and Associations. See https://www.efpia.eu/
EHCIN	European Healthcare Incubator Network
EHDEN	European Health Data & Evidence Network
EHDS	European Health Data Space
EIC	European Innovation Council
EMA	European Medicines Agency
ESR	Evaluation Summary Report
ERICS	European Research Infrastructures
EU	European Union
EUR	Euro
EUROPABIO	European association representing corporate and associate members across sectors, plus national and regional biotechnology associations which, in turn, represent over 2 600 biotech companies, 2 300 out of them are SMEs. See https://www.europabio.org/
FC	Financial contributions
FDA	Food and Drug Administration
FP	Full Proposal
FSTP	Financial Support to Third Parties
FTES	Full time employees
GA	Grant agreement
GAP	Grant agreement preparation
GB	IHI JU Governing Board

ACRONYM	MEANING
GDPR	General Data Protection Regulation
GMP	Good Manufacturing Practice
HORIZON EUROPE	Horizon Europe is the EU's key funding programme for research and innovation. See https://ec.europa.eu/info/funding-tenders/find-funding/eu-funding-programmes/horizon-europe_en.
IBD	Inflammatory Bowel Disease
ICT	Information and Communications Technology
IHI JU	Innovative Health Initiative Joint Undertaking
IKAA	In-kind contributions to additional activities
IKOP	In-kind contributions to operational activities
IMI2 JU	Innovative Medicines Initiative 2 Joint Undertaking
IT	Information Technology
IVD	*in vitro* diagnostics
IVDR	*In vitro* Diagnostic Regulation
IVDS	*in vitro* diagnostic medical devices
JUS	Joint Undertakings
KPI	Key performance indicator
LLM	Large Language Model
LOAEL	Lowest Observed Adverse Effect Level
MDR	Medical Device Regulation
MEDTECH EUROPE	European trade association for the medical technology industry including diagnostics, medical devices and digital health. See https://www.medtecheurope.org/
ML	Machine Learning
MOA	Mechanisms of Actions
NAMS	New Approach Methodologies
NOAEL	No Observed Adverse Effect Level

ACRONYM	MEANING
NON-EU IKOP	Eligible costs incurred by private members, their constituent or affiliated entities, and contributing partners for implementing project activities carried out in third countries outside of the EU Member States and countries associated to Horizon Europe.
PDECA	Plan for the Dissemination, Exploitation, and Communication Activities
PSCI	Pharmaceutical Supply Chain Initiative (PSCI)
R&D	Research and development
RIA	Research and innovation actions
R&I	Research & Innovation
RWE	Real World Evidence
SEDIA	Single electronic data interchange area (SEDIA), the funding & tender opportunities portal of the European Commission. See here https://ec.europa.eu/info/funding-tenders/opportunities/portal/screen/home
SLE	Systemic Lupus Erythematosus
SMES	Small and medium-sized enterprises
SOS	Specific Objectives
SRIA	Strategic research and innovation agenda
TRL	Technology Readiness Level
TTG	Time to grant
UK	United Kingdom