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

Topic 4: Leveraging Europe's Expertise to accelerate Cell Therapy for Type 1 Diabetes

Expected outcomes

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

1) Researchers, industry, and healthcare providers will benefit from a standardized framework for impurity thresholds and manufacturing best practices, ensuring regulatory alignment, facilitating clinical translation, and supporting the scalable production of safe and effective beta-cell therapies for Type 1 Diabetes (T1D).
2) Regulatory authorities, academic researchers, healthcare professional (HCP) and industry partners will have access to validated immune-modulating strategies that enhance graft survival and promote immune tolerance, alongside advanced models and biomarkers for assessing engraftment success, metabolic function, and immune responses.
3) Pharmaceutical companies, regulatory bodies, and payers will benefit from established scalable and cost-effective manufacturing processes for beta-cell therapy, ensuring the production of high-quality, reproducible products that meet regulatory standards and support market approval and reimbursement.
4) Academic researchers, regulatory bodies, and healthcare providers will have improved preclinical models and clearly defined clinical criteria for different patient demographics, ensuring that beta-cell therapies are accessible, safe, and effective across diverse populations.
5) Healthcare providers, industry, and Information and Communication Technology (ICT) companies will utilize AI-driven predictive models and real-time monitoring technologies to enhance the assessment of transplant success, immune responses, and metabolic function, enabling personalized treatment plans, optimized immunosuppression regimens, and reduced therapy failure.
6) Healthcare providers and regulatory bodies will adopt patient-centered clinical endpoints as key indicators of treatment success, accurately reflecting quality of life and disease burden in T1D.
7) Health Technology Assessment (HTA) bodies, people living with diabetes, payers, and policymakers will benefit from cost-effectiveness assessments, pilot reimbursement programs, and policy recommendations that enable the establishment of a reimbursement framework, thus paving the way for the adoption of beta-cell therapies for T1D.
8) Healthcare providers, researchers, and policymakers will benefit from training programs for endocrinologists, diabetologists, and transplant surgeons, enhancing expertise in cell therapy, immunosuppression, and post-transplant care. Collaboration with professional societies will drive the development of clinical pathways, ensuring the generation of appropriate evidence for integrating cell-based therapies into standard diabetes care.
9) Academia, industry, regulatory agencies, patient organizations, people living with diabetes and policymakers will collaborate through fully operational European innovation hubs,

facilitating knowledge sharing, driving research advancements, and harmonizing regulatory practices to accelerate the adoption and implementation of beta-cell therapies across Europe.

10) People living with diabetes will benefit from all these outcomes, as they will lead to improved treatment options, enhanced long-term health outcomes, better access to innovative therapies, and an overall improved quality of life.

It is expected that certain existing assets, such as intellectual property (e.g. patents, know-how), preclinical and clinical data, registries, prospective studies, cell manufacturing technologies, gene editing platforms, and regulatory information, will be used as background in this action. Therefore, beneficiaries intending to participate in this project must acknowledge that ownership of specific deliverables or project results, which are considered direct improvements to a beneficiary's background assets, will need to be transferred back to the beneficiary who originally contributed the background asset. The provisions and conditions regarding such transfers should be clearly outlined in the project's consortium agreement.

Scope

Challenges and Background

T1D is an autoimmune disease that destroys insulin-producing pancreatic beta-cells, leading to lifelong insulin dependence. Despite advances in technology, achieving stable blood glucose levels remains challenging, increasing the risk of severe complications, negatively impacting daily life, work productivity, and mental health, and contributing to stress, anxiety, and depression.

Beta-cell replacement therapy offers a promising path towards a functional cure, but critical challenges must be addressed, including the need for renewable cell sources, optimized islet preparations, standardized manufacturing protocols, robust monitoring tools, sustainable reimbursement models, and trained healthcare professionals to manage complex treatments. These challenges align with key priorities from the Draghi Report[1], emphasizing harmonized regulatory pathways, early engagement with HTA bodies, standardized manufacturing processes, and patient-centric clinical endpoints. Without urgent action, the full potential of beta-cell therapies will remain unrealized.

Key Objectives:

1) Establishing Standardized Criteria and Analytical Methods:

This objective aims at developing standardized criteria and analytical methodologies to detect, quantify, and characterize unintended bystander cells and impurities in stem cell-derived or beta-cell therapies for T1D. This work is intended to support the field at large by generating reference materials, optimizing detection technologies, and defining regulatory-compliant thresholds that can inform future research and development—not to advance a specific product. The focus is on creating translatable, broadly applicable tools and standards that ensure safety, consistency, and quality. Engagement with the EMA is encouraged to facilitate the regulatory relevance and potential adoption of these methodologies in preclinical and clinical research settings.

2) Enhancing Graft Survival and Immune Tolerance:

This objective aims at developing immune-modulating strategies that support the long-term survival of beta-cell grafts and promote immune tolerance. This work is intended to generate insights, tools, and models that advance scientific understanding and inform future therapeutic approaches. Activities will include retrospective analyses of human cadaveric islet transplantation

[1] Mario Draghi, "The Future of European Competitiveness," European Commission, September 9, 2024

cohorts from different European countries and healthcare systems to support biomarker discovery and predictive modeling. Key biomarkers—such as continuous glucose monitoring (CGM) metrics, C-peptide levels, HbA1c, inflammatory cytokines, immune cell subsets, beta-cell-specific autoantibodies, and gene expression profiles—will be explored to identify indicators of graft survival, immune tolerance, and beta-cell function. In addition, a prospective study may be designed to identify novel biomarkers related to glycemic variability, immune regulation, insulin independence, beta-cell regeneration, and inflammatory pathways. These efforts are aimed at supporting the development of robust monitoring tools and decision-making frameworks, not at advancing a therapeutic candidate toward clinical use.

3) Advancing Manufacturing and Quality Control:

The objective is to establish robust cryopreservation techniques that preserve the viability and functionality of beta-cells post-thaw, with an emphasis on the identification and validation of biomarkers to guide and assess these processes. Building on this, the applicants should aim to develop and optimize scalable, cost-effective manufacturing methodologies and quality control frameworks that support the production of consistent, high-quality beta-cell therapy materials in a research and innovation context. The goal is to generate foundational knowledge, technical standards, and reference systems—not to develop specific commercial products. Additionally, the consortium should work toward establishing standardized criteria for the production and quality control of excipient raw materials used in beta-cell therapy delivery systems, to ensure their stability, safety, and suitability for future clinical applications.

4) Streamlining Preclinical and Clinical Development:

This object aims at enhancing preclinical models for allogeneic cell therapies, ensuring standardized approaches and consistent methodologies in transplantation science and surgery. The focus is on harmonized regulatory approval, defining patient demographics for broader accessibility, and tailoring treatment requirements for personalized care. Establishing definitions for insulin independence, refining primary endpoints such as Time in Range (TIR) and Time in Tight Range (TiTR), and optimizing clinical trial design for allogeneic therapies are essential components of the future project.

5) Implementing Advanced Monitoring and artificial intelligence (AI)-Driven Predictive Tools:

Leveraging real-time monitoring technologies like continuous glucose monitoring (CGM) and biosensors to assess transplant success and metabolic function, this objective aims to integrate advanced techniques from various fields, including oncology. Specifically, immune monitoring strategies used in oncology, such as immune checkpoint inhibitors and tumour biomarker profiling, will be explored to enhance the understanding of immune responses in beta-cell transplantation. AI-powered predictive models will personalize treatment plans and optimize immunosuppression regimens. Additionally, non-invasive imaging techniques, such as Magnetic Resonance Imaging (MRI) and positron emission tomography (PET), will track graft survival and immune responses, ensuring better monitoring and management of beta-cell therapies.

6) Defining Clinically Meaningful and Patient-Centred Endpoints Using Real-World Evidence:

This objective aims at leveraging real-world data to define clinically meaningful endpoints that capture quality of life and disease burden in T1D. This includes identifying surrogate endpoints to enable clinical trials that demonstrate long-term benefits without requiring extended study durations. Additionally, generating data on the advantages of achieving normoglycemia in individuals already within target glucose ranges will help refine treatment goals and support regulatory decision-making. A small pilot study must be conducted to test these endpoints and gather initial data on their feasibility and impact.

7) Exploring Reimbursement Models for Beta-Cell Therapies:

This object aims at developing initial cost-effectiveness models that highlight the potential financial and healthcare benefits of beta-cell therapies, focusing on key aspects like reduced

complications and improved quality of life. Early-stage collaboration with HTA bodies, payers, and policymakers must be sought to help build a foundation for understanding the value of these therapies, laying the groundwork for future integration into healthcare systems across Europe.

8) Integration of Cell Therapy into Diabetes Care and Collaborative Networks:
Beta-cell therapies should be integrated into standard diabetes care through specialized training for healthcare providers and the creation of a network of multidisciplinary centres across Europe. Clinical guidelines should be put in place to ensure a smooth transition from current treatments. Additionally, a network of European innovation hubs must be established to foster collaboration, knowledge exchange, and harmonized regulatory approaches, accelerating the development and clinical application of beta-cell therapies. It will also be crucial to collaborate with professional societies to define a clear clinical pathway, ensuring alignment with best practices and optimizing patient outcomes across the region.

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

Applicants are required to ensure transparent and open dissemination of outcomes, including models and tools, to enable their integration and reuse throughout the wider ecosystem.

The funded project is also expected to explore synergies with complementary initiatives to advance research and innovation in Europe, such as NHPIG[2], which is developing the first T1D autoimmune pig model, Vanguard-project[3], Islet-project[4], JOIN4ATMP[5], and relevant Horizon projects. Furthermore, the project should explore synergies with the European Pancreas and Islet Transplantation Registry (EPITR)[6], an initiative led by the European Pancreas and Islet Transplant Association (EPITA) to establish a pan-European registry collecting data on individuals who have received pancreas or islet transplants. By leveraging their insights and networks, the project aims to strengthen the impact of beta-cell therapy development, ensuring that these collaborations contribute to a more comprehensive and effective approach to tackling T1D through cell-based therapies.

Expected impacts

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

- To support the widespread adoption of beta-cell therapy, ensuring long-term efficacy, accessibility, and integration into healthcare systems;
- To accelerate the development of stem cell-based therapies through advancements in manufacturing, preclinical models, regulatory alignment, and predictive tools;
- To strengthen Europe's position as a leader in beta-cell therapy by fostering innovation hubs and clinical networks;
- Scientific and regulatory progress will advance regenerative medicine for other metabolic and autoimmune disorders beyond T1D;
- Patients, healthcare providers, regulators, policymakers, and industry stakeholders will all benefit from improved treatments, clearer guidelines, and increased investment;

[2] https://www.nhpig.eu/
[3] https://vanguard-project.eu/
[4] https://isletproject.eu/
[5] https://www.join4atmp.eu/
[6] https://esot.org/epita/epita-epitr/

- Boosting European industrial competitiveness by driving innovation in cell-based therapies, fostering cross-sector collaboration, and enhancing Europe's global leadership in regenerative medicine.

These impacts are expected to advance IHI JU's objectives of improving healthcare quality, accessibility, and sustainability while contributing to European health policies and initiatives.

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

- The European Health Union: addressing the chronic disease (diabetes) burden; accelerating groundbreaking therapies while drawing on the potential of digital and AI solutions; contributing to modern and innovative health policies (by working on models, tools and pathways enabling the adoption of innovative/breakthrough therapies by European healthcare systems);
- The Pharmaceutical Strategy for Europe → Advancing innovative cell therapies and improving patient access to cutting-edge treatments;
- A Competitiveness Compass for the EU: establishing Europe as a hub for cutting-edge scientific and research innovation; contributing to the announced EU Biotech Act as a forward-looking framework to leverage the potential that biotechnologies can bring to our economy;
- WHO Sustainable Development Goals (SDG 3: Good Health & Well-being): Reducing the impact of non-communicable diseases (NCDs) like Type 1 Diabetes.

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

The outcomes outlined can only be achieved through a cross-sectoral, multidisciplinary public-private partnership (PPP) like the IHI JU action, given the complexity of the challenges involved. The development of innovative immune-modulating strategies, scalable manufacturing processes, and advanced preclinical models requires collaboration across multiple sectors, including pharmaceuticals, academia, medical devices, health ICT, clinical societies and patient organizations. Europe's strong academic expertise in islet transplantation is critical for advancing beta-cell therapies, and academic institutions can provide the foundational research necessary to drive progress in this field. Collaboration with pharmaceutical companies, healthcare practitioners, and regulators ensures that beta-cell therapies are scientifically sound, clinically effective, and aligned with patient needs.

In addition to academic and industry expertise, patient organizations, payers, and HTA bodies play a pivotal role in making these therapies accessible and sustainable. Patient organizations provide valuable insights into real-world patient needs, helping shape therapies that focus on improving quality of life. Payers and HTA bodies ensure that beta-cell therapies are financially viable and can be integrated into healthcare systems across Europe. Their involvement helps secure reimbursement and fosters the widespread adoption of these therapies.

This public-private collaboration facilitates the efficient use of resources, combining scientific research, innovation, clinical expertise, regulatory guidance, and patient input. It enables the creation of therapies that are scalable, cost-effective, and accessible to diverse patient populations. By leveraging Europe's collective expertise, this model accelerates the development and integration of beta-cell therapies, making them a sustainable and viable solution for patients with Type 1 Diabetes across Europe.

Pre-identified industry consortium and contributing partners

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

Indicative budget

- The maximum financial contribution from the IHI JU is up to EUR 8 825 000. ***NB: this amount is indicative and subject to change, pending approval by the IHI Governing Board.***
- The indicative in-kind contribution from industry beneficiaries is EUR 2 300 000. ***NB: this amount is indicative and subject to change, pending approval by the IHI Governing Board.***
- The indicative in-kind and financial contribution from IHI JU contributing partners is EUR 7 340 000. ***NB: this amount is indicative and subject to change, pending approval by the IHI Governing Board.***

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

The allocation of the EUR 6 550 000 financial contribution (FC) from IHI JU contributing partner(s) will be decided by the full consortium at the second stage when preparing the full proposal. ***NB: this amount is indicative and subject to change, pending approval by the IHI Governing Board.***

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 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:

- Provision of training materials for healthcare professionals on cell therapy;
- Regulatory, R&D, and clinical expertise;

- Specialized knowledge in clinical protocol design and endpoint definition (e.g., TIR, TiTR);
- Expertise in defining clinically meaningful endpoints;
- Engagement with payers, policymakers, and regulatory agencies to support value-based healthcare adoption;
- Dissemination and communication efforts, including the open sharing of all relevant learnings, tools, and materials to maximise their accessibility and uptake across the healthcare ecosystem.

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:

1) **Scientific Expertise**
    - *Beta-Cell Biology & Immune Modulation*: Deep knowledge of immune tolerance, beta-cell biology, and strategies to prevent graft rejection and enhance long-term cell survival;
    - *Stem Cell Technology*: Proficiency in generating and assessing stem cell-derived beta cells in preclinical and clinical settings;
    - *Gene Editing & Advanced Therapies*: Expertise in gene-editing technologies (e.g., CRISPR) to improve cell compatibility and function, alongside immune-modulating therapies.
2) **Manufacturing & Quality Control Expertise**
    - *Cell Therapy Production*: Experience in scalable cell therapy manufacturing, cryopreservation, and adherence to Good Manufacturing Practices (GMP);
    - *Process Development*: Capability to design cost-effective, reproducible manufacturing systems with batch consistency.
3) **Regulatory Expertise**
    - *Regulatory Affairs*: Strong background in regulatory engagement with bodies like the EMA to facilitate beta-cell therapy approval;
    - *Clinical Trial Design*: Expertise in preclinical and clinical trial development, particularly for different age groups.
4) **Preclinical & Clinical Development Resources**
    - *Preclinical Models*: Access to predictive models that accurately simulate human T1D for assessing safety and efficacy;
    - *Clinical Trial Networks*: Established networks to support the transition from research to human trials, including patient recruitment;
    - *Retrospective & Prospective Data Analyses*: The applicants are expected to bring data from both retrospective and prospective analyses, including clinical, biomarker, and health outcomes data from cadaveric islet transplantation cohorts. This data should include samples from islet transplants that have successfully provided full

insulin independence, as well as those that have not, to support the development of models and biomarkers to assess engraftment success, metabolic function, and immune responses;

- *Access to Islet Transplantation Datasets*: Availability of and experience working with comprehensive datasets from islet transplantation registries, including long-term clinical outcomes, graft function, metabolic control, and immune response data. These datasets will be instrumental in developing predictive models and biomarkers for therapy success.

5) **Advanced Monitoring Technologies**
    - *Monitoring Systems Development*: Ability to create real-time tracking tools such as continuous glucose monitoring (CGM) and biosensors;
    - *AI & Machine Learning*: Expertise in predictive models for personalized treatment and immunosuppression optimisation;
    - *Imaging Technologies*: Access to non-invasive imaging (e.g., MRI, PET) for monitoring graft health and immune responses.
6) **Patient-Centered Research**
    - *Patient Engagement*: Integration of patient perspectives and real-world data to define meaningful clinical endpoints;
    - *Post-Transplant Care*: Development of protocols to minimize immunosuppression side effects and ensure long-term therapy sustainability.
7) **Economic & Policy Expertise**
    - *Health Economics*: Ability to assess cost-effectiveness and long-term viability of beta-cell therapies;
    - *Health Technology Assessment (HTA)*: Experience engaging with HTA bodies to secure reimbursement pathways.
8) **Multidisciplinary Collaboration**
    - *Healthcare Training*: Development of training programs for clinicians in cell therapy management;
    - *Collaborative Networks*: Existing partnerships with academic institutions, industry, regulators, and patient organizations.
9) **Infrastructure for Knowledge Sharing**
    - *Knowledge Exchange Platforms*: Capacity to organize workshops, webinars, and conferences for knowledge dissemination;
    - *European Networks*: Ability to participate in or establish innovation hubs dedicated to beta-cell therapy.
10) **Technological Capabilities**

- *Advanced Technologies*: Access to gene editing platforms, real-time monitoring systems, and imaging tools;
- *Data Sharing Infrastructure*: Capability for secure, multi-institutional data collaboration.

11) **Patient Advocacy & Public Engagement**

- *Engagement with Patient Groups*: Active collaboration with advocacy organizations to improve access, awareness, and policy influence.

These combined resources and expertise are essential for applicants to effectively contribute to achieving the objectives of advancing beta-cell therapies for T1D, ensuring successful clinical translation and adoption across Europe. Applicants must also document that these resources are shareable with the full public-private partnership from the beginning of the action to ensure broad impact across the European research and healthcare landscape.

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

Dissemination and exploitation obligations

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

Glossary

Acronym	Meaning
AI	Artificial Intelligence
CGM	continuous glucose monitoring
EMA	European Medicines Agency
EPITA	European Pancreas and Islet Transplant Association
EPITR	European Pancreas and Islet Transplantation Registry
FC	financial contribution
HCP	healthcare professional
HTA	Health Technology Assessment
ICT	Information and Communication Technology
ICT	Information and Communication Technologies
IHI JU	Innovative Health Initiative Joint Undertaking
IKAA	in-kind contributions to additional activities
IKOP	in-kind contributions to operational activities
MRI	Magnetic Resonance Imaging
NCDs	non-communicable diseases
PET	positron emission tomography

PPP	public-private partnership
SDG	Sustainable Development Goals
T1D	Type 1 Diabetes
TIR	Time in Range
TiTR	Time in Tight Range
WHO	World Health Organisation