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 2: From early endpoints to long-term outcomes: Healthcare decision-making on the use of surrogate evidence for timely patient access

Expected outcomes

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

1. **A consensus-driven, transparent and evidence-based patient-centred operating model** to assess when and how surrogate endpoints can be connected to longer-term clinical and patient relevant outcomes. Regulators, health technology assessment (HTA) bodies, international professional societies, patient advocacy groups, citizens and industry will benefit from this model, providing clear guidance and support for more consistent interpretation and use of surrogate endpoint evidence.

2. **Enhanced decision-making** for surrogate endpoint evidence and its role in health technology assessment by all healthcare decision-makers, clinicians, patients, and patient advocates, supported by clear guidance, capacity building, and standardised communication approaches.

3. **Harmonised alignment on the evaluation and interpretation of surrogate endpoints** between regulators and HTA bodies, where appropriate, to optimise patient access. This should contribute to a reduction of disparities in evidentiary expectations.

4. **A set of tested, consensus-based tools, case studies, and recommendations** that demonstrate how surrogate endpoint evidence and long-term outcomes can be connected, interpreted and communicated for regulatory, HTA, payer, clinician, patient and citizen decision-making across disease contexts.

Scope

Background and challenges to be addressed

In numerous disease areas, particularly oncology, definitive assessment of a treatment's effectiveness through long-term clinical endpoints such as overall survival may take several years. To avoid delaying access to potentially life-saving therapies, regulatory authorities may grant traditional or accelerated approvals based on surrogate endpoints, such as progression-free survival, disease-free survival, objective response rate, or biomarker response. However, current HTA frameworks may not place the same value on these endpoints as regulatory ones[1], as HTA often tends to take a long-term perspective that assesses the future impact in terms of health outcomes and the costs of introducing a new health technology for an acute or chronic condition in the healthcare system.

INDICATIVE TEXT

[1] Differences in Evidentiary Requirements Between European Medicines Agency and European Health Technology Assessment of Oncology Drugs—Can Alignment Be Enhanced? (Dec 2022): https://doi.org/10.1016/j.jval.2022.05.006

A substantial body of methodological and policy work has already examined the utility, validation and interpretation of surrogate endpoints. This includes the EUnetHTA methodological guideline on surrogate endpoints[2]; the independent Institute for Quality and Efficiency in Health Care (IQWiG) framework for validation of surrogate endpoints in oncology[3]; international reviews of HTA agency practice showing wide variation in evidentiary expectations[4]; the recent National Institute for Health and Care Excellence (NICE)-led international white paper on surrogate endpoints in health technology assessment[5]; the 2026 the Professional Society for Health Economics and Outcomes Research (ISPOR) Good Practices Report on methods for evaluating surrogate endpoints for HTA decision making[6]; and the European Medicines Agency (EMA) methodological guidance on the use of endpoints such as progression-free survival and disease-free survival in oncology development[7].

Despite this progress, important gaps remain that justify a coordinated European action. Validation standards are not applied consistently, and the underlying assumptions, uncertainty and limits of generalisability are not always quantified, transparently communicated, or presented in a way that supports consistent interpretation and decision-making by regulators, HTA bodies, clinicians, patients and other stakeholders. Methodological recommendations also remain insufficiently operationalised for routine use in submissions and assessments, particularly where surrogate evidence must be linked transparently to estimates of longer-term clinical benefit and, where relevant, health economic modelling. These challenges are especially important in the evolving European context, where joint clinical assessments (JCA) under Regulation (EU) 2021/2282[8,9] are increasing the need for greater methodological clarity, consistency and early cross-stakeholder alignment on endpoint relevance and evidence interpretation.

In addition, the use of surrogate endpoint evidence can be challenging for healthcare professionals, patients, patient advocacy groups, HTA bodies, and policymakers to interpret consistently in the absence of clear, agreed approaches for the utility, value and limitations of surrogate endpoint evidence across stakeholders.

INDICATIVE TEXT

[2] EUnetHTA Endpoints used in Relative Effectiveness Assessment: Surrogate Endpoints (2015): https://tools.eunethta.be/files/Endpoints%20in%20REA%20-%20Surrogate.pdf

[3] IQWIG [A10-05] Validity of surrogate endpoints in oncology (Rapid report): [A10-05] Validity of surrogate endpoints in oncology (Rapid report)

[4] Validity of Surrogate Endpoints and Their Impact on Coverage Recommendations: A Retrospective Analysis across International Health Technology Assessment Agencies - Oriana Ciani, Bogdan Grigore, Hedwig Blommestein, Saskia de Groot, Meilin Möllenkamp, Stefan Rabbe, Rita Daubner-Bendes, Rod S. Taylor, 2021: https://doi.org/10.1177/0272989X21994553

[5] Surrogate endpoints in cost-effectiveness analysis for use in health technology assessment
White paper (Nov 2024): Surrogate endpoints in cost-effectiveness analysis for use in health technology assessment (main report)

[6] Methods for Evaluation of Surrogate Endpoints for HTA Decision Making: Bujkiewicz S, Ciani O, Heeg B, et al. Methods for evaluation of surrogate endpoints for health technology assessment decision making: a Good Practices Report of an ISPOR Task Force. Value Health. 2026;29(5):711-724.

[7] EMA Evaluation of anticancer medicinal products - Scientific guideline: https://www.ema.europa.eu/en/evaluation-anticancer-medicinal-products-scientific-guideline

[8] Regulation (EU) 2021/2282 of the European Parliament and of the Council of 15 December 2021 on health technology assessment and amending Directive 2011/24/EU

[9] Health technology assessment (Regulation (EU) 2021/2282) framework for joint clinical assessments (JCA) at EU level. https://health.ec.europa.eu/health-technology-assessment/implementation-regulation-health-technology-assessment/joint-clinical-assessments_en

Objectives

The objective of this topic is to develop, test and validate a multi-stakeholder, patient-centred operating model approach for determining when surrogate endpoint evidence is useful, necessary, or insufficient, and for evaluating how surrogate endpoints can be connected to long-term clinical, patient-relevant and decision-relevant outcomes. The central research question is how surrogate evidence generated during clinical development can be interpreted, communicated and used consistently across regulatory, HTA, payer, clinical, patient and citizen decision-making without losing sight of uncertainty, disease specificity, and the outcomes that matter most to patients.

To fulfil this objective, the action funded under this topic should specifically aim to:

1. Create a validated, transparent and evidence-based operating model, including guiding principles and practical tools, for evaluating surrogate endpoints against patient-relevant clinical outcomes and for determining where surrogate endpoints are, or are not, appropriate. The approach should support assessment of biological plausibility, individual-level and trial-level evidence, appropriate quantitative methods, treatment of uncertainty, transferability across settings and disease areas, linkage to longer-term outcome prediction and, where relevant, health economic modelling. It should translate emerging international good practice into actionable methods, guidance and tools that can support more consistent evidence generation, interpretation and use, leading to greater alignment across regulatory and HTA decision-making.

   The operating model should be co-created across stakeholder groups, including patients and citizens, and pilot tested through purposefully selected use cases using existing clinical trial and/or real-world datasets. Because the challenges of surrogate endpoints are particularly salient in oncology, use cases may disproportionately represent oncology indications. However, although each use case is expected to rely upon detailed, rigorous quantitative methods to establish surrogacy in a way that addresses nuances specific to that use case, the overall approach is expected to be relevant to all disease areas and adaptable to non-oncology disease areas.

2. Establish best practices for the interpretation and communication of surrogate endpoint evidence so that regulators, HTA bodies, payers, clinicians, patients, citizens and other stakeholders can understand both the strengths and the limitations of the evidence base, including the extent to which surrogate endpoints are meaningfully connected to outcomes such as survival, quality of life, symptoms, functioning, treatment burden and uncertainty tolerance.

To achieve this, the action funded under this topic is expected to include, but not be limited to, the following key research and innovation activities:

- A comprehensive evidence, policy, literature and practice review of surrogate endpoint use, including regulatory precedents, HTA requirements, published validation studies, methodological guidance, and lessons from recent European and international assessments. The expected output of this review is to identify gaps and areas that could benefit from the harmonisation between surrogate endpoints with broad clinical and regulatory acceptability, but which have faced challenges of HTA acceptability.

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- Early and continuous multi-stakeholder engagement aimed at developing and testing an engagement model that brings together relevant stakeholders at appropriate stages of the project, including regulators, HTA bodies, payers, clinicians, patients, citizens, patient organisations, methodologists, and industry. The engagement model should support alignment on priority use cases, evidentiary requirements, terminology, endpoint relevance, uncertainty management, communication needs and implementation pathways. Methods of engagement and alignment will include advisory boards, workshops/panels, patient and citizen input mechanisms, and other engagement and support tools available at European and national levels, such as those coordinated by the EU-Innovation Network[10], among other methods.

- Development of a methodological and evidence-based decision-support operating model to outline the approach toward evidence generation that would be required to establish the link between a given surrogate endpoint and longer-term outcomes. This approach should use data available at or around product launch, including historical datasets, real-world data, and synthetic data approaches where justified (e.g., synthetic data could be used to augment sparse datasets to more robustly assess these relationships). The model should also include a roadmap to guide disease- and context-specific customisation where needed.

- Pilot testing through clearly framed use cases, initially focused on oncology indications where mature overall survival data, rather than surrogate endpoint evidence, is strongly preferred by HTA bodies / payers. The use cases will include multiple myeloma and another oncology indication to be selected by the full consortium during the preparation of the full proposal. Furthermore, the full consortium should explore including a use case from a non-oncology disease area to support the transferability of the operating model to other disease areas. Each use case should have a clearly stated purpose, for example to test the approach where surrogacy evidence is relatively mature, to explore contexts where surrogate evidence is uncertain or contested, to demonstrate when surrogate endpoints may not be needed, or to show how early endpoints can be connected to longer-term patient-relevant outcomes. Prospective data generation is not required as part of the use cases. The intention of these specific use cases is to provide practical examples and evidence for surrogate endpoint evaluation that is relevant to regulatory, HTA, payer, clinician, patient and citizen decision-making.

- Development and dissemination of practical outputs, such as guidance, stakeholder consensus-based recommendations, HTA/regulatory reporting templates, a decision tree for surrogate endpoint readiness, patient- and citizen-facing communication tools, an implementation roadmap, case studies and peer-reviewed scientific publications, to support uptake in evidence generation, assessment and decision-making.

- Development of a strategy to ensure adoption of the action's outputs (including the operating model and practical outputs) by healthcare decision-makers including, but not limited to, regulatory authorities, HTA bodies, payers, clinicians, patients, citizens, patient advocacy groups and industry.

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[10] EU-Innovation Network guidance on available scientific and regulatory support tools at national and European level for human medicinal products/technologies/methodologies: EU-IN Guidance on Support Tools

For clarity, validation of new surrogate endpoints (i.e., those without any HTA or regulatory precedent) is not within the scope of this action.

Applicants are expected to consider synergies with other relevant global, European and national initiatives to maximise impact, facilitate uptake and avoid duplication.

Applicants are also expected to consider the potential regulatory and HTA relevance of the operating model and methodologies developed and to outline a regulatory and HTA strategy and interaction plan, including appropriate engagement with European and national regulatory authorities, HTA bodies and national competent authorities. Whilst this action is focused within Europe, global alignment with relevant regulatory and HTA bodies should also be considered by the applicant consortium to reduce disparities in access to innovative therapies. Depending on the needs and maturity of the outputs developed during the project, the strategy may consider mechanisms such as scientific advice, methodological consultations, joint scientific consultations and other regulatory or HTA engagement and support tools available at national and European levels.

Expected impacts

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

- Earlier, more consistent and equitable patient access to innovative therapies, by enabling more credible use of early evidence when long-term outcomes are immature.
- Reduced uncertainty or alignment on how to address uncertainties in clinical and reimbursement decision making, through more robust and transparent validation, interpretation and communication of surrogate endpoint evidence.
- Greater convergence across European evidence assessment processes with streamlined evidence transition and optimal management of differences in evidentiary requirements, supporting more consistent regulatory, HTA and payer consideration of surrogate-based evidence.
- Improved efficiency of evidence generation and assessment, by delivering practical methods and tools that help industry, regulators and HTA bodies generate, assess and interpret surrogate endpoint evidence appropriately from the outset, reducing repeated analyses / submissions and fragmented evidentiary expectations.
- Stronger trust and transparency among clinicians, patients and decision-makers regarding what surrogate endpoints can and cannot reliably demonstrate.
- Strengthened EU leadership in science-based methodological innovation for access-relevant evidence generation and assessment and the competitiveness of the EU’s health industry.

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The actions are expected also to consider and contribute to EU programmes, initiatives and policies such as Europe's Beating Cancer Plan[11], the EU Mission on Cancer[12], the Regulation on the European Health Data Space (EHDS)[13], and the EU Regulation on Health Technology Assessment[14] where relevant

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

Addressing the complex challenges associated with surrogate endpoint validation and acceptance requires cross-stakeholder collaboration that cannot be achieved by individual organisations or sectors alone. An IHI JU action uniquely enables the combination of industry expertise, regulatory insight, HTA perspectives, academic methodologies, clinical experience, and patient input.

Industry partners bring access to historical datasets and expertise in clinical development, regulatory science and evidence generation. Public partners contribute independent scientific expertise, methodological innovation, and links to healthcare systems and patient communities (including patient organisations that can help define what outcomes are meaningful from a patient perspective). This will be particularly important to ensure that surrogate endpoint evidence is interpreted not only in terms of statistical or regulatory relevance, but also in relation to outcomes that matter to patients, unmet medical needs and treatment optimisation. Achieving meaningful and durable consensus will require active participation from regulators, HTA bodies, academia, professional societies, clinicians, patient organisations and industry.

Only a public–private partnership under the IHI JU framework can mobilise these complementary resources at the necessary scale, create neutral spaces for convergence, and deliver outputs with credibility and legitimacy across Europe.

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'):

- AstraZeneca
- Boehringer Ingelheim
- Bristol Myers Squibb
- Merck KGaA
- Novartis
- Novo
- Pfizer ('Lead')
- Roche
- Sanofi

INDICATIVE TEXT

- [11] Europe's Beating Cancer Plan: https://health.ec.europa.eu/system/files/2022-02/eu_cancer-plan_en_0.pdf
- [12] EU Mission on Cancer: https://research-and-innovation.ec.europa.eu/funding/funding-opportunities/funding-programmes-and-open-calls/horizon-europe/eu-missions-horizon-europe/cancer_en
- [13] Regulation (EU) 2025/327 of the European Parliament and of the Council of 11 February 2025 on the European Health Data Space and amending Directive 2011/24/EU and Regulation (EU) 2024/2847: https://eur-lex.europa.eu/legal-content/EN/TXT/?uri=OJ:L_202500327
- [14] EU Regulation on Health Technology Assessment: https://eur-lex.europa.eu/legal-content/EN/TXT/?uri=CELEX:32021R2282

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

Indicative budget

- The maximum financial contribution from the IHI JU is up to EUR 5 400 000.
- The indicative in-kind and financial contribution from industry beneficiaries is EUR 4 650 000 (target).

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 48 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:

- Access and value
- Health economics and outcomes research
- Clinical development
- Regulatory and HTA engagement and strategy
- Biostatistics and quantitative methods
- Data science and data stewardship
- Evidence generation and medical expertise
- Disease-area and product-development
- Patient engagement and communication

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- Suitable use cases and the associated relevant evidence from multiple myeloma, another oncology use case as well as from a non-oncology disease to be decided at the second stage when preparing the full proposal.

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:

- **Data science, analytics and biostatistics expertise**, including institutions with the capability to:
  - analyse large-scale datasets and heterogeneous data sources
  - perform cross-study and cross-disease analyses
  - curate, harmonise and interrogate structured and unstructured data
  - advanced analytical methodologies (including meta-analysis, causal inference and predictive modelling)
  - surrogate endpoint validation at individual- and trial-level
  - evidence synthesis, including systematic literature reviews and comparative effectiveness analyses
  - development of modular methodological and decision-support evidence pathway approaches applicable across disease areas while allowing for disease- and context-specific adaptation
- **Clinical and disease-area expertise**, including in oncology, and the proposed use case in multiple myeloma.

  The applicant consortium is not expected to provide proprietary clinical trial datasets, as access to historical datasets and relevant evidence assets will be primarily provided by the pre-identified industry consortium.
- **Qualitative research, patient and citizen engagement expertise**, including:
  - patient organisations and social science groups
  - experts in patient-centred outcomes, preference elicitation and risk communication
  - capability to conduct qualitative research (e.g. interviews, advisory boards, deliberative workshops, digital solutions such as social media listening or data from wearables) to capture patient, citizen and stakeholder perspectives on the interpretation, acceptability and communication of surrogate endpoints and related uncertainty
  - expertise in defining and prioritising patient-relevant outcomes, including quality of life, symptoms, function, treatment burden and preferences regarding uncertainty and risk
- **Policy, regulatory science, health technology assessment and stakeholder engagement expertise**, including organisations with experience in:
  - joint clinical assessments (JCA) under Regulation (EU) 2021/2282
  - PICO (Population, Intervention, Comparator, Outcomes) scoping, outcome selection and interpretation
  - assessment of relative clinical effectiveness and uncertainty
  - appraisal of surrogate endpoint-based evidence in reimbursement decision-making
  - facilitating multi-stakeholder consensus processes

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- translating methodological outputs into policy-relevant recommendations
- supporting alignment between regulatory and HTA perspectives

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

At the second stage, the applicant 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.

Glossary

Acronym	Meaning
EMA	European Medicines Agency
EHDS	European Health Data Space
EU	European Union
HTA	Health Technology Assessment
IHI JU	Innovative Health Initiative Joint Undertaking
IKAA	in-kind contributions to additional activities
IKOP	in-kind contributions to operational activities
ISPOR	Professional Society for Health Economics and Outcomes Research
IQWiG	Independent Institute for Quality and Efficiency in Health Care
JCA	Joint Clinical Assessments
NICE	National Institute for Health and Care Excellence

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