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: Towards precision medicine: platform for transdiagnostic stratification of brain dysfunction

Expected outcomes

The action generated by this topic is expected to contribute to all the following outcomes:

1. A sustainable and collaborative large, multimodal data platform that can identify novel transdiagnostic candidate markers and endpoints for the symptom domains of reward/motivation (including anhedonia) and impulsivity (RM&I) [1],[2] in neuropsychiatric, neurodegenerative, and physical health disorders. Relevant disorders include Alzheimer's disease (AD), major depressive disorder (MDD) and obesity (priority areas). Other relevant disorders/diseases include but are not limited to substance use disorders, schizophrenia, bipolar disorder, borderline personality disorder and Parkinson's disease. For a disorder/disease to be relevant, there must be evidence to show that reward/motivation and/or impulsivity are clinically significant symptom domains;
2. Novel transdiagnostic candidate markers and endpoints are identified and progressed towards validation. Learnings are applied in drug discovery to increase Probability of Success (PoS);
3. A clear roadmap to achieve full validation of candidate markers and endpoints by regulatory and health technology assessment (HTA) bodies. Clinical best-practice guidelines are developed, and recommendations are made to the current diagnostic classifications[1] to expedite the adoption of precision medicine;
4. A greater understanding of the biological foundations of RM&I symptom domains and their role in AD, MDD, obesity and other relevant disorders, enabling the generation of novel therapeutic approaches by industry;
5. Closer alignment between psychiatry, neurology, and physical health disciplines to enable dialogue between healthcare professionals (HCPs) and other medical specialists to optimise outcomes, particularly for individuals with complex healthcare needs and comorbidities.

Scope

Current diagnosis and patient stratification in health disorders with CNS-driven symptoms are based on DSM-5 / ICD-11 codes, which are not aligned with underlying biological processes and mechanisms. Subsequent suboptimal disease classification and patient stratification is a key reason for the low PoS of clinical development and the historical lack of new and more efficacious treatments. This topic aims to address these challenges by adopting a holistic, transdiagnostic approach [3] focused on the common underlying biology of RM&I symptom domains across the relevant disorders listed in the 1st expected outcome.

The topic seeks to build on an existing federated data platform to consolidate, curate, link and analyse robust, multimodal datasets from relevant patient populations. Thus, activities related to

1 Diagnostic and Statistical Manual of Mental Disorders (DSM) and International Classification of Diseases (ICD)

building a platform or a biorepository from scratch are out of scope. The data platform must enable advanced analytics and artificial intelligence (AI) technologies to illuminate the biological basis of the RM&I symptom domains and identify related candidate markers and endpoints. The hypotheses will be prospectively tested in clinical case studies focusing on but not limited to AD, MDD, and obesity. Post-project, the platform will be available as open access for ongoing research and validation.

The topic also priorities collaboration with relevant stakeholders, including people with lived experience (LE), carers, HCPs, providers, regulators, HTA bodies and payers, to prepare the healthcare system for this transformative shift. People with LE can provide unique insights and expertise that comes as the result of first-hand experience of health challenges. Integrating LE expertise improves research by bringing an understanding beyond academic and clinical knowledge. The perspectives of people with LE across the relevant symptom domains must be represented within the consortium and applied wherever appropriate.

Applicants must outline their approach to inclusive and equitable practices throughout the initiative, possibly through a risk register and appropriate mitigations. Example areas for consideration include data representation, bias mitigation, stakeholder engagement, ethics, and feedback mechanisms.

Objectives of the topic

Applicants are required to focus on four main objectives in their proposal:

1. Adapt and extend an existing federated data platform that is sustainable, enabling collaborative curation, access and analysis of clinical datasets and samples (as mentioned above). Consolidate existing multimodal datasets and samples from cohorts with relevant disorders[2] into the adapted platform;
2. Collect additional new clinical datasets and samples to address gaps and integrate these into the adapted platform;
3. Test hypotheses for candidate markers and endpoints within a defined context (e.g. patient selection, diagnosis, or treatment monitoring) in a transdiagnostic patient population presenting symptom domains of RM&I, including those with AD, MDD, and obesity;
4. Establish a collaborative platform to bring together people with LE, HCPs, regulators, HTA bodies and payers to achieve consensus on the value of candidate markers and endpoints, how to operationalize them into new diagnostic and treatment frameworks and achieve readiness in the healthcare system.

Activities under objective 1:

The success of this topic hinges on access to a large of amount of high-quality, multimodal data and biological samples collated from applicants and other partners (including industry). The applicants must list the datasets and samples that they will bring and confirm that they will be made accessible to the whole public-private partnership (PPP) from the start of the action.

1.1 Collate existing multimodal, longitudinal and transdiagnostic datasets at an individual level, including relevant parameters outlined under 1.2. These datasets can come from public or

2 Relevant disorders: Alzheimer's disease, major depressive disorder and obesity are priority areas for this topic. Other relevant disorders/diseases include but are not limited to substance use disorders, schizophrenia, bipolar disorder, borderline personality disorder and Parkinson's disease. For a disorder/disease to be relevant, there must be evidence to show that reward/motivation and/or impulsivity are clinically significant symptom domains.

private databases, observational studies, clinical trials, real-world evidence (RWE) studies, biobanks, electronic health records, registries, and/or other digital health technologies and platforms. Applicants must in their short proposal include a strategy to utilise relevant data from the European Platform for Neurodegenerative Diseases (EPND) catalogue[3] as much as possible as well as other relevant datasets available from previous projects.

1.2 Relevant multimodal datasets ideally include as many as possible from the following: neurophysiology data (e.g. electroencephalography (EEG), magnetoencephalography (MEG)), brain imaging data (e.g. functional magnetic resonance imaging (fMRI), MRI), qualitative subjective assessments, behavioural/language data, real-world data, medical claims and billing data, routine clinical data (from medical and psychological assessments including data on metabolic status), behavioural monitoring data (polysomnography, actigraphy, digital data from wearables, etc.), speech/language data, patient reported outcome data (e.g. questionnaires), molecular biodata (e.g. "-omics"). Biological samples (e.g. blood, urine, stools, cerebrospinal fluid) from biobanks should be leveraged. Datasets should be from individuals with relevant disorders as well as healthy controls.

1.3 Propose a strategy to integrate and connect the datasets from different sources.

1.4 Outline an approach to inclusive and equitable practices, including data representation, including but not limited to, gender, ethnicity, and age (e.g. paediatric and adolescent populations).

1.5 Adapt and extend a federated data platform by building on existing infrastructures proven effective in PPPs, including the AD Workbench[4] and the EPND hub[5] (made available via the pre-identified industry consortium). The adapted platform should leverage available resources (including standard operating procedures) from EPND [4]. The adapted platform must be scalable and adaptable to curate high-quality, multimodal, retrospective, prospective and longitudinal data as mentioned under 1.1 and 1.2. It must enable data/sample discovery, access, and support AI analysis, while ensuring interoperability with other global data platforms.

1.6 Ensure high data quality by verifying the robustness of methodologies before integration into the adapted platform. This could be achieved by establishing a Data Quality Assessment Committee.

1.7 Implement fair and transparent governance for data and sample sharing. Applicants must explain how they will develop a consensus on data sharing principles, complying with legal and ethical standards (e.g. General Data Protection Regulation (GDPR) and Intellectual Property (IP)) and ensuring robust protection of data volunteers' rights. For example, leveraging the Data Sharing Playbook[6] and setting up a Data Access Review Committee.

1.8 Review the collated dataset to identify key gaps and develop a strategy to guide new data collection under Objective 2.

1.9 Identify potential algorithms for activities under 3.3 in Objective 3.

1.10 Ensure platform sustainability by creating a strong value proposition and user ecosystem beyond the consortium, with a clear strategy for a long-term, AI powered

3 https://epnd.org/resources/announcing-the-enhanced-epnd-catalogue
4 https://www.alzheimersdata.org/ad-workbench
5 https://epnd.org/news-and-resources
6 Data Sharing Playbook:
https://www.ihi.europa.eu/sites/default/files/uploads/Documents/ProjectResources/IMI_IHI_DataSharingPlayBook_2024.pdf

platform accessible to the broader research community, including the healthcare industry. Relevant activities need to be in place from the start of the action.

Activities under objective 2

2.1 Collect new prospective multimodal and ideally longitudinal data from transdiagnostic cohorts, focussing on individuals affected by RM&I abnormalities in the relevant disorders, and ideally also collect biological samples. The datasets should close data gaps identified under 1.8 and be integrated into the adapted platform, meeting the same criteria described in Objective 1.

2.2 Continue to recognise and fill data gaps to expand and maintain the adapted data platform, keeping it current with technological and scientific advancements. Utilise AI, such as synthetic data generation, image analysis, natural language processing etc., to enhance the dataset.

2.3 Continue identification of potential algorithms for activities under 3.3 in Objective 3.

Activities under objective 3

3.1 The short proposal should propose an initial pilot clinical case study designed to test a scientifically robust and data-supported hypothesis on candidate markers and/or endpoints in RM&I symptom domains during the project's initial year. It must include transdiagnostic populations from AD, MDD, and obesity. The case study must include as a minimum neurophysiological data (e.g. EEG or MEG) and brain imaging data (e.g. MRI, fMRI) from each subject. In addition, datasets should include as many parameters as possible from the list described in 1.2. The precise scope of the initial clinical case study will be developed by the full consortium during the preparation of the full proposal. (Additional case studies are described under 3.4).

3.2 In the first 6 months, prepare a Systematic Literature Review (white paper) of available potential markers in RM&I symptom domains in relevant disorders to support hypothesis generation and subsequent testing throughout the action. This should be updated throughout the action.

3.3 Apply advanced AI analytics, modelling, and simulation across the multimodal data in the adapted platform to cluster biologically similar subjects, stratified independently of their conventional diagnostic classification to identify and confirm clinically significant, quantitative candidate markers for RM&I symptom domains in relevant disorders, incorporating hypothesis-driven and data-driven approaches. Establish the foundation for a new transdiagnostic framework based on phenotypes/biotypes to enable detection of factors for susceptibility, risk stratification, diagnostic precision, disease monitoring, treatment response prediction, and overall patient outcomes.

3.4 Test putative transdiagnostic markers and endpoints hypotheses derived from 3.2 and 3.3 through additional non-sequential pilot clinical case studies, incorporating insights from stakeholder consultations in Objective 4. These case studies must test the same transdiagnostic marker/endpoints in separate pre-defined patient populations in two or more of the relevant disorders to strengthen the transdiagnostic approach. As a preference, the three priority disorders should be included in at least one study each as a lead indication. For instance, one study with AD, one with MDD and one with obesity as the lead indication, each including at least one additional relevant disorder. Each study must include neurophysiological and brain imaging data and include as many other parameters as possible from the list outlined under 1.2. Studies must be powered sufficiently to allow

analyses both within and across the included disorders. All results must be integrated into the adapted platform. The studies should enhance the platform's ability to accelerate hypothesis testing of new candidate markers and endpoints within a defined context of use (e.g. patient selection, diagnosis, or treatment monitoring) in representative patient populations. These studies must not involve the development of new in-vitro diagnostic tools or digital sensors. The resulting evidence from pilot case studies (including the initial pilot clinical study under 3.1) should:

- be verifiable and applicable for patient stratification and/or monitoring in future clinical trials.
- demonstrate clinical utility to foster new patient pathways and clinical guidelines.
- contribute to bridging the gap between health care needs and capacity.

Activities under objective 4

4.1 Create an efficient collaborative platform to support seamless communication and collaboration among key stakeholders in the field of the relevant disorders. This includes innovators, researchers, clinicians, people with LE, carers, patient advocates, HCPs, regulators, scientific societies, HTA bodies, payers, and policy makers to collectively define and implement a new framework for the diagnosis and treatment of these disorders.

4.2 Form advisory/working groups comprising different stakeholders to support activities under Objectives 1, 2 and 3, and co-create solutions. Ensure active and meaningful participation of people with LE, carers, and advocacy organisations throughout the activities and governance.

4.3 Engage with regulators (via experts with relevant expertise), e.g. EMA Innovation Task Force and/or national competent authorities, proactively initiating early consultations as appropriate. This should set the basis for continuation towards full validation of markers and endpoints beyond the action. Develop a regulatory strategy and interaction plan early on to define a strategic approach to evidence collection and analysis where feasible (including case studies under Objective 3). Similarly, appropriately engage with HTA bodies and payers on the value of new transdiagnostic framework, candidate markers and endpoints when used to support claims of effectiveness of new therapies, paving the way for future reimbursement.

4.4 Craft evidence-based clinical guidelines through consultations with stakeholders, including people with LE, regulators, HTA bodies, payers, and medical organisations. Achieve consensus on best practices for implementing the new transdiagnostic framework. Develop recommendations and provide proposals for updates to the classification of disorders[4].

4.5 Design and implement a comprehensive training program for HCPs to adopt the new transdiagnostic framework. Create educational materials and implement trainings for people with LE, families and carers in multiple languages, ensuring readiness across the healthcare system for the paradigm shift in healthcare delivery throughout Europe.

Applicants are expected to leverage and build on the learnings and outputs from previous and ongoing relevant PPPs[7] and other relevant global, European and national initiatives. They should consider synergies with the **future European Genomic Data Infrastructure (GDI)[8],**

7 EPND, PRISM/ PRISM2, RADAR-CNS, RADAR-AD, MOBILISE-D, IDEA-FAST, EU-PEARL, SOFIA, READI, AIMS-2-TRIALS, EHDEN, PROMINENT, PREDICTOM, AD-RIDDLE, among others.
8 Synergies with the future European Genomic Data Infrastructure (GDI) are encouraged. https://gdi.onemilliongenomes.eu/

part of the European 1+Million Genomes Initiative[9], and other relevant upcoming projects[10].

Expected impacts

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

Data platform for precision medicine: A comprehensive, sustainable data-driven health platform linking behaviours and symptoms to quantitative biological markers. This will deliver much-needed refinements to existing diagnostic frameworks and treatment paradigms, providing a clear step towards personalised healthcare for CNS-driven symptoms. This platform could be a model for other disease areas where there is need for more biology-driven precision medicine.

Advancing mechanistic understanding: Clarification of the biological basis of CNS transdiagnostic symptoms expediting the identification of novel and more effective precision therapies across the relevant disorders, boosting the competitiveness of European industry and beyond. Advanced mechanistic understanding will also galvanise innovation in diagnostics.

Patient outcomes and stigma: A significant improvement in care quality (more integrated and personalised care) and in health outcomes for people within the RM&I driven relevant disorders. This includes healthcare innovations arising from improved understanding of the relationship between psychiatric and physical health (e.g. for obesity, understanding the interplay between metabolic disturbances, mental health and eating behaviours) and their underlying biology with far-reaching implications for patient health beyond psychiatry and neurology. This will also lead to reduction of stigma and provide opportunities for early intervention.

Efficiency in the healthcare system: Precision treatments reduce avoidable waste in healthcare resources, leading to overall cost reduction, higher productivity, and a positive economic impact on the European health care budget. Overall, a transformative shift towards a more integrated and personalised approach to healthcare will benefit patients across Europe and beyond.

The action will also improve European competitiveness and contribute to a number of European policies/initiatives, which include the European Commission's proposal for the European Health Data Space (EHDS) and the European Commission's Communication on a comprehensive approach on mental health[11] and the Healthier Together- EU Non-Communicable Diseases initiative[12].

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

The development of a scalable, sustainable, public-private federated data and biobanking infrastructure, as well as the collation of multimodal, transdiagnostic data, is crucial to address the current marker/endpoint challenges in neuropsychiatric, neurodegenerative, and physical health disorders including AD, MDD and obesity. Acquisition and harmonisation at this scale is beyond the capacity of a single organisation. The Innovative Health Initiative (IHI) provides an ideal model for creating such an initiative, integrating all relevant stakeholder groups in a focussed and collaborative framework. This public-private consortium will collate resources,

9 https://gdi.onemilliongenomes.eu/ ; https://digital-strategy.ec.europa.eu/en/policies/1-million-genomes
10 IHI Call 11 T1: Understanding how infections foster and induce non-communicable diseases as well as relevant projects funded under IHI Call 9.
11 https://commission.europa.eu/strategy-and-policy/priorities-2019-2024/promoting-our-european-way-life/european-health-union/comprehensive-approach-mental-health_en
12 https://health.ec.europa.eu/non-communicable-diseases/healthier-together-eu-non-communicable-diseases-initiative_en

share knowledge, and coordinate efforts to transform the diagnosis, treatment, categorisation and understanding of disorders driven by the RM&I symptom domains.

Pre-identified industry consortium and contributing partner(s)

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 19 962 600. ***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 13 320 000. ***NB: this amount is indicative and subject to change, pending approval by the IHI Governing Board.***
- The indicative in-kind contribution from IHI JU contributing partners is EUR 6 642 533. ***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 EUR 2 600 000 financial contribution (FC) from industry beneficiaries and EUR 5 940 550 from the contributing partner is further described under the section Contribution of the pre-identified industry consortium and contributing partners. ***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 partner

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

- The AD Workbench, which has already been leveraged in EPND, will be made available as well as facilitation of access to EPND hub infrastructure including the EPND catalogue[13];
- Expertise and capabilities for data management, biostatistics and data science, development of processes for data and sample collection, quality assurance/control, and data analyses; contributions to implementation of data analysis algorithms and Large Language Model (LLM) and other AI methodologies;
- Contributions to Systematic Literature Reviews;
- Activities to make available multimodal datasets and (if possible) samples collected from historical clinical trials and activities to collect data in prospective clinical trials (e.g. placebo and potentially comparator data from Phase I/II/III trials in relevant disorders);
- Clinical trial, translational, digital health, and medical expertise and guidance related to clinical protocol design, clinical operations, clinical and real-world data collection and analysis;
- Expertise in legal, ethics, compliance, and representativeness in research/study design;
- Expertise in regulatory strategy, policy and decision making, HTA assessment and reimbursement, involvement of LE expertise; support for integration of their requirements;
- Contribution to the elaboration of educational and training programmes for HCPs, people with LE and carers.

Furthermore, the industry consortium will provide the Project Leader and legal support and help with data and knowledge management and communication/dissemination of results. It will also provide contributions to joint meetings and steering committees, networking, exploitation and sustainability.

Full details regarding the FC of EUR 2 600 000 from industry partners and of EUR 5 940 550 from the contributing partner will be provided in the full proposal. A part of the FC from industry beneficiaries will be allocated to activities related to the pilot clinical case studies. ***NB: this amount is indicative and subject to change, pending approval by the IHI Governing Board.***

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 and/or resources:

- Project management expertise and capabilities in running multi-stakeholder cross-sector projects;

13 https://discover.epnd.org/catalogue/studies

- Data platform expertise and capabilities to leverage the AD Workbench to establish an extended version of the EPND platform, including data privacy, ethics, and legal expertise, development of principles and processes for data and sample collection, ensuring equitable and inclusive data practices, quality assurance/control, and an approach for the platform's sustainability;
- Data capture / data management and analysis expertise and capabilities to import, curate and integrate existing and prospective datasets and ideally samples from public and private sources into the data platform; expertise and capabilities in data science, to develop and apply advanced AI supported analytics, modelling and simulation, and bias mitigation, and conduct multimodal analyses at scale to develop hypotheses of new candidate markers and endpoints;
- Proven expertise and capabilities in the conduct of transdiagnostic pilot clinical case studies: i) expertise in RM&I symptom domains, translational, digital and clinical science, development and validation of new markers/endpoints; ii) Systematic Literature Reviews of potential transdiagnostic markers and endpoints and hypotheses generation; iii) design and conduct of all pilot studies including regulatory and ethics approvals, setting up sites, recruitment in AD, MDD and obesity, collection and storage of data and samples, and measurement of all parameters described above. The outline of the first pilot clinical case study must be included in the short proposal (to be finalised by the full consortium during the preparation of the full proposal; study protocols of additional pilot clinical studies will be finalised by the full consortium during the proposed action);
- Involvement of LE and patient advocacy groups/organisations as consortium members;
- Resources to engage with people with LE, carers, HCPs to prepare training programmes and educational materials;
- Expertise and capabilities in interacting with regulatory authorities, HTA bodies, payers, policy makers, medical societies, organisations of people with LE, and patient advocacy groups.

At the second stage, the selected public consortium, the predefined industry consortium and contributing partners will form the full consortium. The full consortium will develop the full proposal in partnership, including the overall plan and the work packages, based on the selected short proposal.

Dissemination and exploitation obligations

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

References

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[3] Towards a consensus roadmap for a new diagnostic framework for mental disorders, European Neuropsychopharmacology, 2025, 90: 16-27, https://doi.org/10.1016/j.euroneuro.2024.08.515

[4] The European Platform for Neurodegenerative Diseases (EPND) https://doi.org/10.1002/alz.079164

Glossary

Acronym	Meaning
AD	Alzheimer's disease
AI	artificial intelligence
CNS	central nervous system
EEG	electroencephalography
EHDS	European Health Data Space
EMA	European Medicines Agency
EPND	European Platform for Neurodegenerative Diseases
fMRI	functional magnetic resonance imaging
GDI	Genomic Data Infrastructure
GDPR	General Data Protection Regulation
HCPs	healthcare professionals
HTA	health technology assessment
IHI	Innovative Health Initiative
IHI JU	Innovative Health Initiative Joint Undertaking
IKAA	in-kind contributions to additional activities
IKOP	in-kind contributions to operational activities
IP	Intellectual Property
LE	lived experience
LLM	Large Language Model
MDD	major depressive disorder
MEG	magnetoencephalography
MRI	magnetic resonance imaging
PoS	Probability of Success
PPP	public-private partnership
RM&I	reward/motivation and impulsivity

RWE	real-world evidence