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

## Expected outcomes

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

- Algorithms and models, including Artificial Intelligence (AI)-based models, adaptable to differences in data availability have been developed and validated in different datasets to allow the identification of osteoarthritis (OA) patient subpopulations (phenotypes/endotypes) that will benefit from specific, targeted treatment approaches. The identification of subpopulations will be based on:
    a. the patient-specific burden of osteoarthritis with focus on underlying drivers (e.g. metabolic disease) and multi-morbidity/holistic patient profiles
    b. the evaluation of underlying pathways driving local vs. centralised pain in joint disease and the correlation of symptoms to joint tissue pathology.
    c. the identification of key risk factors for pain in joint disease that can be linked to structural disease progression providing insights into the symptom–structure discordance in OA.
    d. the detection of joint areas at risk of progression and quantification of structural progression to a more advanced stage
    e. the measures from existing innovative tools such as functional assessments with mobility and activity assessing devices (including algorithms) to reflect independence, gait measures, assessments of muscular strength and function, as well as balance and coordination to subtly measure functional changes.
    f. evaluating differences and commonalities of osteoarthritis (OA) and inflammation-driven joint diseases such as psoriatic arthritis (PsA), rheumatoid arthritis (RA), erosive hand osteoarthritis (eHOA).
- A validation strategy is provided for a selected set of novel endpoints to measure and predict OA disease progression that enables planning of regulatory implementation pathways. This validation strategy supports innovative outcome-based and patient-centred development approaches for medicines and other therapeutic options to be discussed by regulatory authorities, healthcare providers, patients, scientists and industry, shaping new approaches to the development of efficient treatments in OA and respective regulatory frameworks.
- A decision tool is provided that supports shared decision-making for patients and health care providers based on the prediction of disease progression, the most likely associated OA disease drivers and current disease burden.
- A responsible AI framework is established, that enables guidelines or determines any boundaries for predictive modelling at various stages of value generation e.g. biological discovery, patient subgrouping, and clinical trials enrichment.
- Data platform(s) are designed and implemented to allow a workable and efficient collaboration across the participating organisations in their respective geographies, respecting each data contributor's access, privacy and consent approaches, which can be facilitated by federated data

sharing. This outcome may serve as a blueprint for other data collaborations under the umbrella of the EU's newly minted AI act and data policies[1, 2].

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

## Scope

Osteoarthritis (OA) has no cure and affects the lives of more than 500 million people worldwide with widespread individual, societal and economic consequences. OA has long been underestimated in its impact; the disease negatively affects social functioning, daily activities and independence, ranks 7th for years lived with disability in people over 70 years and is associated with increased mortality. Various development efforts over the years have failed to provide a disease-modifying treatment. The epidemiology as well as clinical and biological insights strongly suggest the existence of several pheno- and endotypes of osteoarthritis; failure to account for those differences critically hampers progress in the field. The implementation of innovative approaches to stratify the patient population, predict the course of disease and define patient-relevant endpoints is specifically relevant in an ageing society with a high prevalence of obesity, metabolic syndrome, and multi-morbidity. Furthermore, there is an increasing prevalence of post-traumatic secondary OA in relatively young individuals affected at the prime of their lives.

The overall aim of this topic is to build a public-private partnership able to integrate and leverage the plethora of existing and currently collected data on OA and to use a data driven approach to significantly progress the field in order to:

1) improve the understanding of osteoarthritis as a complex disease,
2) foster progress towards regulatory validation of patient-relevant endpoints to measure and predict OA disease progression as well as alternative endpoints to measure response to treatment
3) allow predictive modelling while actively seeking feedback to incorporate the perception of patients, care givers, primary care physicians and regulators.

The action generated by this topic should pave the way towards transforming the current rather static late-stage development approaches into a more patient-centred and simplified (more inclusive/enriched patient population, faster, cost-effective etc.) as well as sustainable part of clinical development. This aim is supported by increasing the insights into OA as an heterogenous disease with various underlying patient risk profiles, patho-mechanistic pathways and underlying genotypes/ epigenetic/ metabolomic/ transcriptomic phenomena based on big data. Such insights will allow the creation of integrated risk profiles combining clinical and multi-omic approaches (e.g. clinical characteristics, transcriptomics, proteomics, genetic markers, and in-depth multimodal imaging data).

These advances are needed to support the development of cost-efficient integrated health care solutions including focused, individualised treatments for specific patient segments. The use of AI-based approaches is crucial for the integration of the totality of existing patient datasets to better



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

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

understand disease drivers in various tissues of joints thereby upscaling, broadening and/or sharpening current methodology.

The proposed action must:

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

- Provide a flexible federated data lake house with appropriate tools for access, management and governance, data curation, integration, and augmentation for consequent high-performance analytics using e.g. new or contributed AI (foundation) models and modelling workflows. This infrastructure will deploy existing or newly developed approaches or implementations to host and wrangle disparate data assets ranging from public, commercial, and not-for-profit observational and trial clinical data to -omics, images, or data from wearables. Applicants should address in their proposal key challenges around federated data collection, data privacy, data transfer, data storage, data processing, curation, and harmonisation of data, etc. to achieve a comprehensive understanding of OA by upscaled, big data analytics from:
    1) genetic analyses (GWAS),
    2) AI-driven big data analyses for identification of clinical patterns in phenotypes and endotypes,
    3) algorithm-based imaging analyses of whole joints and peri-articular tissues,
    4) the evaluation of performance assessments using novel technologies and devices.
- Generate and validate a risk model for disease progression by evaluating whether and to which extent risk factors identified in the literature and the above-mentioned data sets are predictive for the progression of structural joint changes as evidenced by imaging, pain and functional decline documented by patients and ultimately leading to joint replacement surgery. The combination of surrogate markers such as imaging [1] with medical history and medication, as well as with predictive markers (plasma-based multi-omics, polygenic risk scores) [2][3], patient reported outcome data and data from wearables or performance tests [4], will generate a more refined predictive engine in analogy to e.g., established fracture risk prediction algorithms in osteoporosis.
- Work towards a broad consensus between all stakeholders especially linking patients, caregivers and healthcare providers' perspectives to regulatory and health technology assessment (HTA) bodies. This will enable the elaboration of a set of endpoints relevant to these groups depending on the phase of development of treatments (i.e. early phase trials for medication or devices efficacy, while late-stage development needs to prove effectiveness, which may necessitate different sets of outcomes), incorporating the various domains of assessments, and taking into account the predominant effect (structural or symptomatic) of the evaluated treatment. This will help to shape new regulatory frameworks for accelerated targeted OA treatment development based on big data analyses, in-silico trials, digital twin approaches and similar innovative trial designs.
- Use data analysis and modelling to provide evidence and knowledge that could enable the evaluation of existing innovative tools (such as functional assessments, imaging approaches etc.) and innovative treatment solutions for OA, based on their scientific validity and feasibility as a prerequisite. Design a strategy to progress them towards regulatory validation and implementation. The action should provide an exploratory and interactive platform to evaluate the validity of novel methods of evidence generation, such as the use of data from wearable devices, innovative imaging, and surrogate markers for joint replacement surgery.

- Model short- and long-term economic and public health impact from OA including morbidity and mortality. These new risk models should support benefit/risk assessment as well as quality and efficacy assessments of therapeutic interventions in patients diagnosed with OA to prevent or delay the onset of disease progression, but also avoid overtreatment and thereby optimise the use of health care resources.
- Develop a decision tool that will support shared decision-making between physicians and patients to select the intervention best suited to address the various stages and symptoms of OA in an individual patient, integrating also patient reported outcome and experience measure (PROMs and PREMs) data as well as patient preferences. The diversity of patients at risk or affected by the disease must be considered when discussing patient-relevant outcomes to enable the focused development of treatments and healthcare solutions specific to the needs of individual patients.
- Leverage real-world evidence (RWE) data to address the diversity of patients including sex and gender, ethnicity, and race disparities to develop patient engagement strategies. This should enable, engagement with specific groups for the design of OA outcome trials and better promotion of OA management.

The action should contribute to address the research needs outlined in the Regulatory Science Research Needs initiative[3], launched by the European Medicines Agency (EMA), assessing the utility of real-world healthcare data to improve the quality of randomised controlled trial simulations and patient and public involvement and engagement.

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

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

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

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

## Expected impacts

The project should contribute to all of the following impacts:

- The federated integration of big data from disparate data sources including the use of digital twin and similar methodological approaches will lay the foundation for advanced trial designs that allow more efficient and smaller trials, reduction of patients' burden and exposure to placebo.
- The development of predictive models for disease progression and joint replacement, which are crucial to efficiently discuss treatment strategies, support assessments of quality in health care and

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

equitably plan and allocate health care resources. In addition, such predictive models can revolutionise outcome trial designs, shortening the trial duration and patient burden as well as reducing development costs. The aspired modular flexibility to data availability allows their sustained use in various settings and economic circumstances.

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

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

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

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

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

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

## Pre-identified industry consortium and contributing partners

In the spirit of partnership, and to reflect how IHI JU two-stage call topics are built upon identified scientific priorities agreed together with a number of proposing industry beneficiaries (i.e. beneficiaries who are constituent or affiliated entities of a private member of IHI JU), it is envisaged that IHI JU proposals and actions may allocate a leading role within the consortium to an industry beneficiary.

Within an applicant consortium discussing the full proposal to be submitted for stage 2, it is expected that one of the industry beneficiaries may become the project leader. Therefore, to facilitate the formation of the final consortium, all beneficiaries, affiliated entities, and associated partners are encouraged to discuss the weighting of responsibilities and priorities regarding such leadership roles. Until the role is formalised by execution of the Grant Agreement, one of the proposing industry beneficiaries shall, as project leader, facilitate an efficient drafting and negotiation of project content and required agreements.

## Indicative budget

- The maximum financial contribution from IHI up to EUR 14 000 000. ***NB: this amount is indicative and subject to change, pending approval by the IHI Governing Board.***
- The indicative in-kind contribution from industry partners is EUR 11 166 000. ***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 9 260 000. ***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 and contributing partners, it is anticipated that some elements of the contributions will be in-kind contributions to operational activities (IKOP) from those countries that are neither part of the EU nor associated to the Horizon Europe programme.

The indicative in-kind contribution from industry partners may include in-kind contributions to additional activities (IKAA).

## Indicative duration of the action

The indicative duration of the action is 60 months.

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

## Contribution of the pre-identified industry consortium and contributing partners

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

- Data: data from clinical trials (such as patient profiles, soluble or imaging biomarkers, genetics at baseline and follow up information especially from placebo arms or observational cohorts), biobank data, real world data, biomarker data
- Expertise: medical expertise, bioinformatics, data science, public health, patient input, clinical and regulatory expertise, data & AI experts, technology architects, data privacy experts
- Technology: high performance computing in cloud infrastructure, data lake house infrastructure, GenAI platforms and algorithms, data governance tools, tools to curate enrich and augment the data for AI models readiness

## Applicant consortium

The first stage applicant consortium is expected, in the short proposal, to address the scope and deliver on the expected outcomes of the topic, taking into account the expected contribution from the pre-identified industry consortium and contributing partner(s).

This requires mobilising the following expertise:

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

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

- Timely access to data from registries, cohorts and any other relevant data collection is critical for the success of the action generated by this topic and has to be clearly documented in the proposal.

Moreover, applicants are expected to build on previous activities /consortia on national/EU level such as the Digital Health Catalyst[4] a co-creation from two IMI projects (Mobilise D[5] and IDEA-FAST[6]) aiming to maximise insights from real-world digital measurements and remote monitoring options, or the BigData@Heart[7] [6] initiative (IMI2 call 7) that similarly to this topic aims at leveraging big data to gain insights into phenotypes and pathologic mechanisms or EUROPAIN[8] among others (please see some additional examples listed below, this is however not an exhaustive list).

At the second stage, the consortium selected at the first stage and the predefined industry consortium and contributing partner(s) will form the full consortium. The full consortium will develop the full proposal



[4] Digital Health Catalyst, last accessed March 19th 2024

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

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

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

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

in partnership, including the overall structure of the work plan and the work packages, based upon the short proposal selected at the first stage.

## Dissemination and exploitation obligations

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

## Additional information (examples only)

Links to project related EU programs:

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

https://www.approachproject.eu

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

https://www.ehden.eu

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

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

Links for more information on OA as a serious disease:

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

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

## References


[1] u J. et al. **DeepKOA: a deep-learning model for predicting progression in knee osteoarthritis using multimodal magnetic resonance images from the osteoarthritis initiative**. Quant Imaging Med Surg. 2023 Aug 1;13(8):4852-4866. doi: 10.21037/qims-22-1251. Epub 2023 Jun 2. PMID: 37581080; PMCID: PMC10423358.

[2] Takahashi H. et al. **Prediction model for knee osteoarthritis based on genetic and clinical information**. Arthritis Res Ther 12, R187 (2010). https://doi.org/10.1186/ar3157

[3] Kraus VB, et al. **Serum proteomic panel validated for prediction of knee osteoarthritis progression**. Osteoarthr Cartil Open. 2023 Dec 4;6(1):100425. doi: 10.1016/j.ocarto.2023.100425. PMID: 38116469; PMCID: PMC10726242.

[4] Demanse D. et al. **Unsupervised machine-learning algorithms for the identification of clinical phenotypes in the osteoarthritis initiative database**. Semin Arthritis Rheum. 2023 Feb;58:152140. doi: 10.1016/j.semarthrit.2022.152140. Epub 2022 Nov 19. PMID: 36446256.

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

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

## Glossary

| Acronym | Meaning |
|---|---|
| AI | Artificial Intelligence |
| EMA | European Medicines Agency |
| GWAS | Genome-Wide Association Studies |
| HTA | Health Technology Assessment |
| IKOP | In-Kind Contributions to Operational Activities |
| IHI JU | Innovative Health Initiative Joint Undertaking |
| IMI | Innovative Medicines Initiative |
| OA | Osteoarthritis |