

Topic 1: Cardiovascular diseases - Improved prediction, prevention, diagnosis and monitoring

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.

Expected impacts to be achieved by this topic

Cardiovascular disease (CVD) remains one of the leading causes of death globally and, as such, has a major impact at a personal, societal, and economic scale. Over 60 million people in the EU live with CVDs, at an economic cost of EUR 210 billion annually.

CVD risk assessment is not fully implemented in many clinical practices across Europe¹ and treatment of CVD is commonly practiced as with a “one size fits all” approach, meaning that all patients are treated with a standard medical regimen regardless of risk level. The prevalence of well established CVD risk factors such as obesity, diabetes, and chronic kidney disease increases, and combined with an ageing population in Europe, the urgency for a more personalised approach and cardiovascular risk assessment becomes evident.

The generation of a personalised risk-benefit approach, based on data derived from transcriptomic, proteomic and multimodality imaging studies, combined with data from wearables will contribute to the following impacts:

- Accuracy of diagnosis and efficacy of treatment will increase by the individualised sub-phenotype-risk approach which will allow for a risk-focused targeted therapy.
- Patients will be empowered and encouraged to take control over their health by accessing an integrated overview, including biometric data derived by wearables, of their health information, which can also be used for a more informed dialogue with their health care provider(s).
- Early diagnosis of CVDs combined with better understanding of the mechanisms involved, will lead to the development of more cost-effective strategies, and identify new care pathways.

¹ Rossello X, Dorresteijn JA, Janssen A, Lambrinou E, Scherrenberg M, Bonnefoy-Cudraz E, Cobain M, Piepoli MF, Visseren FL, Dendale P, This Paper Is A Co-Publication Between European Journal Of Preventive Cardiology European Heart Journal Acute Cardiovascular Care And European Journal Of Cardiovascular Nursing. Risk prediction tools in cardiovascular disease prevention: A report from the ESC Prevention of CVD Programme led by the European Association of Preventive Cardiology (EAPC) in collaboration with the Acute Cardiovascular Care Association (ACCA) and the Association of Cardiovascular Nursing and Allied Professions (ACNAP). Eur J Prev Cardiol. 2019 Sep;26(14):1534-1544. doi: 10.1177/2047487319846715. Epub 2019 Jun 24. PMID: 31234648.

Expected outcomes

The results of the selected project will provide the basis for better primary and secondary prevention of CVD. The goal is to identify existing comprehensive CVD and heart failure (HF) patient datasets (with contextual parameters e.g., behavioural, socioeconomic, gender, ethnicity) and integrate them with data from diagnostic tools (e.g., wearables, imaging devices, bio samples/ biopsies) to provide the basis for prediction models to improve stratification of patients, reveal insights to achieving earlier intervention.

This topic expects the following outcomes:

- Identification of relevant data sets, for instance derived by classical diagnostic screening, in-vitro-diagnostics, 'multi-omic' platforms (comprising genomic, transcriptomic, proteomic and multimodality imaging data, most preferably with multiple timepoint assessments to ascertain directionality and dynamics of relevant changes), continuous glucose monitoring (CGM) data, continuous electrocardiogram (ECG) from wearable, HF and activity data, wearable devices and digital health applications.
- Leverage data in currently available IMI federated databases (open access at the end of the project) in compliance with GDPR (General Data Protection Regulations), such as results/data/biomarkers/electronic health records provided by project participants, adding to the knowledge base.
- Demonstration of the utility of biomarker-combinations including data from different modalities e.g., wearables, smart acute care setting devices, imaging/screening for the diseases and comorbidities.
- Based on existing biomarker combinations, determination of whether new biomarkers are needed for detecting patients at risk.
- Developed and/or evaluated artificial intelligence (AI) models that, using data from various sources, can identify patients who require and respond differently to prevention and/or treatment of atherosclerotic cardiovascular disease (ASCVD) and HF in clinical practice.
- Identification of previously undiagnosed subgroups of ASCVD and HF patients, for instance insulin resistance, diabetes, and obesity into clinically meaningful subgroups.
- Documentation and analysis of patient preferences regarding information, diagnosis and treatment of CVD, as well as requirements and preferences of individuals to share their data.
- Integration of patient data (e.g., federated database concept) to enable a holistic overview of specific patient groups to enable more effective and efficient disease management and execution of screening programmes and individual treatment tailoring.
- Inclusion of validated patient reported outcome and experience measure (PROMs and PREMs) data including biophysical, mental and psychosocial parameters with the aim to use in a clinical setting. This may include, but not limited to, measures on quality of life, sleep quality, physical activity, emotional stress, satisfaction with treatment, healthcare service experience.

- Development/validation/recommendation of decision trees/algorithms to be used in the health care pathway (including referrals, e.g., from general practitioner to specialist) and disease management.
- Sustainability of relevant results and data repositories.
- Identification of incentives that reward positive health behaviour and motivate consistent and continuous data generation especially when health status has changed.
- Utilisation of the knowledge gained from the project to facilitate and guide better prevention considering the patient perspective.
- Pilot study in the type 1 diabetes population that historically has been excluded from clinical trials.

Scope

The overall aim of the project is to provide tools for earlier diagnosis of atherosclerosis and heart failure as well as earlier identification of patients at risk including biomarker tools to assess changes in risk and measure response to therapeutic intervention. Currently, patient data from various sources such as devices, intake forms, and diagnostic and exploratory tests are not integrated or monitored to give a complete understanding of the patient's disease state. Integration of these data sets, e.g., by a federated database, and its accessibility to health care providers and researchers will provide better understanding to help detect, monitor, and treat ASCVD and HF. The selected project should clearly outline their approach for data capture, storage and sharing, for instance data federation, or an open centralised database architecture. The proposed data management strategy should be sustainable, and align with the FAIR principles. To fulfil this aim, the selected project should:

- 1 Increase our understanding of the initial hallmarks of disease, which will allow for a better identification of individuals at risk for ASCVD and HF at young age, also to create a clinical risk profile based a multi-omic approach (genetic markers, transcriptomics, proteomics, and in depth multimodality imaging data) in adolescents who have either genetic and/or enrichment of specific endpoint associated risk factors (obesity, chronic kidney disease, type 1 diabetes, type 2 diabetes, genetic preponderance for HF and increased atherosclerosis).
- 2 Generate a better risk model by evaluating whether and to which extent risk factors identified in large prospective CVD primary prevention cohorts are predictive in a secondary prevention setting. The data from surrogate markers (imaging), predictive markers (plasma based multi-omics), and data from wearables will generate a more refined risk engine.
- 3 Quantify the social, ethical and regulatory implications of the new risk estimation models and gauge the potential additive value of data generated by wearable devices in current healthcare systems, and to which extent regional and legal issues have an impact. Moreover, the risk-benefit of wearable derived data will be ascertained in individuals who are likely to be frontrunners in the adoption (i.e., people with type 1 diabetes and people with a (genetic) risk for premature atherosclerosis and/or HF).
- 4 Model short- and long-term economic and public health morbidity and mortality benefit/risk assessments of therapeutic intervention in people at risk with the new estimation models to prevent or delay onset of CVDs.

- 5 Develop a decision tool that will allow a physician to select the intervention to best address ASCVD and HF in an individual patient. The tool will provide a risk-benefit profile, helping the physician and the patient in a decision-making process, integrating also patient reported outcome and experience measure (PROMs and PREMs) data
- 6 Explore possibilities for novel methods of clinical development and trial execution. Based on learnings about risk prediction and pathophysiological modelling, novel surrogate endpoints may be considered for a risk based Cardiovascular Outcome Trial approach. The project could provide an exploratory and interactive platform to discuss the validity of novel methods of evidence generation, such as the use of data from wearable devices. The project should pave the way to transform the rather static phase 3 clinical trial approach into a more agile (more inclusive/enriched patient population, faster, costs-effective etc.) and sustainable part of clinical development. The Covid-19 pandemic has highlighted the need to invest in infrastructure, adaptive clinical trial designs, integration of AI approaches and faster regulatory approval. During the pandemic, the world has experienced a transition to virtual and remote care as more and more patients connect with their health care teams online. This presents an enormous opportunity and benefits to patients. A pathway forward could be to through use of real world evidence (RWE) data address sex, ethnicity and race disparities in Cardiovascular Outcome Trials and better promote CV management across.

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

The data deemed useful in redefining and reclassifying the CVD risk profile are stored in a multitude of databases of clinical academic institutions (large cohorts of patients with multimodality imaging for example), research institutes (data about genetic risk markers; genome wide variation (for example UK biobank), large pharma (intervention studies with well documented parameters over time, in conjunction with plasma and genetic biobanks), other data owners (large numbers of datasets using the specific focus of the company: proteomics data, specific novel biomarker tests for example), healthcare wearables (large datasets on biometrics).

To allocate the data into a centralised system, a concerted action is needed, and the subsequent analysis should be performed by the different stakeholders with a multitude of areas of expertise working in aggregated task forces. The subsequent question on whether and to which extent the data derived can and should be used in clinical care and/or clinical trials should be answered in close collaboration with payers, patients, and regulators.

Additionally, to change behaviours in a clinical practice setting where patients are empowered and encouraged to take control over their health and to secure a patient participatory research approach (e.g., through PROMs and PREMs), supported by interest organisations within the area of public health, a combined effort is needed under a Public-Private Partnership that promotes the interchange of knowledge and experience. Additionally, through a cross-sectorial collaboration focused on clinical research and public health, we can learn to recognize and appropriately address sex², race and cultural biases and disparities in the health care delivery process of CVD management, whilst enabling novel ways to deliver people-centred, safe, effective, cost-effective, and affordable health solutions.

² Sex differences in quality indicator attainment for myocardial infarction: a nationwide cohort study | Heart (bmj.com)

Pre-identified industry consortium and contributing partners

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

Indicative budget

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

Indicative duration of the action

The indicative duration of the action is 48 months.

This duration is indicative only. At stage 2, the consortium selected at stage 1 and the predefined industry consortium and contributing partner may jointly agree on a different duration when submitting the full proposal.

Contribution of the pre-identified industry consortium and contributing partners

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

- Data: data from clinical trials, biobank data, real world data, wearables and other smart devices, algorithms, identification of risk, sensor technology, telecommunication, AI, mobile technology
- Expertise: medical expertise, bioinformatics, data science, public health, patient input, clinical and regulatory expertise, early identification from wearables
- Technology: such as wearable devices, mobile technology, telecommunication technology and other smart devices that will enable the recording of new data.

<The allocation of the EUR xxx financial contribution will be decided by the full consortium at stage 2 when preparing the full proposal.>

Applicant consortium

The stage 1 applicant consortium is expected, in the submitted short proposal, to address scope and deliver on the expected outcomes of the topic, considering the expected contribution from the pre-identified industry consortium and contributing partner.

The applicant consortium is expected to address all the research objectives and make key contributions to the defined deliverables in synergy with the industry consortium. Applicants must ensure that the relevant results and data repositories will be sustainable after the end of the project(s)

and made public. Potential spin offs from the project should be identified. The focus of this project is not target identification but leveraging currently available data for risk and outcome prediction tools, generated by artificial intelligence approaches, as brought in by the various project participants.

This will require mobilising the following expertise and/or resources:

- Access to cohorts and databases of cardiovascular disease including data on people with atherosclerosis and heart failure
- Access to cohorts of young adults and adults who have type 1 diabetes, type 2 diabetes, obesity or genetic preponderance for HF and increased atherosclerosis with early CVD risk markers such as Inflammatory and Mitochondrial Biomarkers, aortic and cardiac structure and function, carotid atherosclerosis and arterial stiffness
- Access to pre-existing clinical cohorts with as broad and detailed relevant phenotyping as possible and access to biobanked specimens for selected biomarker analysis wherever available (including documented informed consent), ideally including cohorts with when relevant different treatment approaches
- Collect prospective data with new devices such as wearables to support the use of these new technology in medical applications such as the early diagnosis and managing of patients with CVD.
- Expertise in AI and software
- Expertise in devices and digital health
- Economic benefit-risk modelling should engage multidisciplinary teams of patient advocates, health care economists, and health care payers
- Engagement with patient organisations and other interest organisations within the area of public health

At stage 2, the consortium selected at stage 1 and the predefined industry consortium and contributing partners will form the full consortium. The full consortium will develop in partnership the full proposal, including the overall structure of the work plan and the work packages, based upon the selected short proposal at stage 1.

Dissemination and exploitation obligations

To be determined