

Strategic Research and Innovation Agenda

Candidate European Partnership:

Fostering a European Research Area for Health

(ERA4Health)

Draft version (21.01.2022)

This draft has been prepared by the informal Working Group of SRIA of ERA4Health following the roadmap adopted in the plenary meeting with interested funding organisations held on 17th of June 2021. The drafting process includes the involvement of experts, public consultation and revision by interested organisations to participate in ERA4Health. This draft SRIA has been revised by Commission services for checking compliance with EU priorities and Strategic Orientations.

Final version of this document shall be adopted by future ERA4Health partners. If you would like to provide any feedback or share your thoughts/reflections/opinions on this document, please leave a comment by email to: ERA4Health@isciii.es

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Abbreviations

AI	Artificial Intelligence
AMR	Antimicrobial Resistance
BBMRI-ERIC	The Biobanking and BioMolecular Resources Research Infrastructure
CVD	Cardiovascular Diseases
EATRIS-ERIC	European Infrastructure for Translational medicine
EC	European Commission
ECRIN-ERIC	The European Clinical Research Infrastructure
ECS	Early Career Scientist
ELIXIR	Life-Science Infrastructure for Biological Information
ENM	EuroNanoMed
ERA	European Research Area
ERA-NET Cofund	Public to public Partnership scheme under Horizon 2020 Framework Programme
ERI	European research Infrastructure
ERDF	European Regional Development Fund
ESF+	European Social Fund Plus
ETPN	European Technology Platform on Nanomedicine
EU	European Union
EU-Openscreen-ERIC	European Infrastructure of Open Screening Platforms for Chemical Biology
ETPN	European Technology Platform on Nanomedicine
FAIR	Findability, accessibility, interoperability, and reusability
HDHL	Healthy Diet for Healthy Life
HE	Horizon Europe
HPC	Health Configuration of the Horizon Europe Programme Committee
IHI	Innovative Health Initiative
IICS	Investigator-Initiated Clinical Study
JPI	Joint Programming Initiative
JTC	Joint Transnational Call
KET	Key Enabling Technology
KPI	Key Performance Indicators
KSO	Key Strategic Orientations
OA	Open Access
RRI	Responsible Research and Innovation
SDG	Sustainable Development Goal of United Nations
SHAFE	Smart Healthy Age-Friendly Environments
SRIA	Strategic Research and Innovation Agenda
SSH	Social Sciences and Humanities
TRL	Technology Readiness Level
UMN	Unmet medical need
UN	United Nations

1. Executive Summary

All future European Partnerships under Horizon Europe have to develop a Strategic Research and Innovation Agenda (SRIA) or a Roadmap before their launch in order to ensure that the long-term vision is translated into concrete roadmaps with smart and measurable objectives.

In order to reflect openness and inclusiveness, the development of ERA4Health's SRIA has involved a broad set of stakeholders and relevant experts and it has been designed to be open and participatory, using methods that emphasize co-creation and collaboration. It has mainly included: (1) Establishment of a core team in charge of the SRIA process, (2) Contextualization of the partnership, (3) Identification and elaboration of R&I priority areas and (4) validation. During the elaboration of this SRIA, it underwent experts' consultation, public consultation and high level consultation according with its level of advance and particular needs. During its elaboration, the EC representatives joined internal and external activities.

European Partnership under Horizon Europe Fostering a European Research Area for Health Research (ERA4Health) will be a leading European initiative for the flexible joint programming of health related research and innovation programmes, effectively involving European funding organizations.

This European Partnership will further strengthen and expand this eco-system to potentially target many more, smaller research funders across the EU so as to identify the areas in which to launch Joint Calls as well as calls for investigator-initiated clinical studies.

The general objective of ERA4Health is to reach, through the creation of a comprehensive network aimed at strengthening and expanding the existing conducive eco-system, an effective joint approach and generate knowledge and products (e.g. preventive guidelines, medical protocols) for identified research areas. In **section 3**, a list of specific objectives is associated with their expected outcomes and the expected impact is well described.

The Partnership will cover 2022-28 and will integrate research and innovation areas covered by previous ERANET and Joint Programming Initiatives (JPIs), as well as investigator-initiated clinical studies (IICs). It will be composed of two phases. ERA4Health will be based on the consolidated networks that are about to finish [ERA-NET cofunds under the framework of JPI HDHL (ERA-HDHL and HDHL-INTIMIC), ERA-CVD and EuroNanoMed].

This SRIA is the strategic document that provides the framework for selecting the call topics that will be included in the Annual Work Plans. The type of research subject to the selected calls will cover basic, translational to applied and clinical research. The main funding instruments in ERA4Health are the Joint Transnational Calls (JTC) for Projects but other instruments could be implemented (call for networks/knowledge hubs, mobility grants, etc.). **Section 5** describes the definition of our priority areas. ERA4Health will support the development of Research and Innovation through the implementation of two well differentiated but complementary phases according to the level of maturity of the Partnership: Phase 1 will integrate joint calls focused on prevention and public health, nutrition- and lifestyle-related diseases, cardiovascular diseases and nanomedicine (**section 5.1**). In parallel, it will establish a supporting framework to tackle hurdles in the execution of IICs and overcome the challenges in launching international joint calls effectively on IICs, which would take place in Phase 2 (**section 5.2**).

However, the focus of ERA4Health will not be limited to the thematic areas of the ERA-NET cofunds mentioned above as new research priorities may be identified (these include but are not limited to infectious diseases and other emerging health threats, cancer or others). It provides a great scope to this partnership.

Besides the scientific areas studied during the SRIA elaboration, Responsible Research and Innovation (RRI) as an approach that anticipates and assesses potential implications and societal expectations with regard to research and innovation was highly considered to be properly included. Its implementation mode and expected impact can be read in **section 6**.

As established in the partnership description, developing a framework for implementation of IICS is an important task corresponding to the Phase 1 and key for the implementation of Phase 2, so areas that might need attention when designing a clinical study are defined in **section 7**.

Finally, links with other Partnerships and relevant EU programmes to avoid the overlapping and duplication of national and EU research funding and complement each other to cover all the needs and demands as well as the Key Performance Indicators (KPIs) to measure the Partnership progress were analysed and included.

2. Introduction

Public research and innovation funders in Europe have been successfully working together in different initiatives since 2003 with the main goal of coordinating research investments through research programmes in specific priority areas and the implementation of Joint Transnational Calls (JTCs). Currently, several ERA-NET Cofunds in the biomedical and health research field are running in parallel with similar structures, activities, processes and actors: some 80% of all investment is made by 19 funding organisations from 10 countries, including the European Commission.

The level of national and regional investment in JTCs has been constantly increasing since 2004, and is almost Euro 8.9 billion (excluding EU contribution) in 2020.

The Partnership “Fostering a European Research Area for Health Research”, named ERA4Health, aims at establishing a flexible and much more effective coordination between most funding organisations in the ERA for Health and Well-being. With this wide scope, ERA4Health will allow to centralize common and similar activities duplicated in different ERA-NET Cofunds, while keeping the diversity needed for the scientific development in each of the thematic fields. ERA4Health will take advantage of the consolidated networks that are about to finish (ERA-NET cofunds under the framework of JPI HDHL¹ (ERA-HDHL and HDHL-INTIMIC), ERA-CVD² and EuroNanoMed³). Their activities will be the pulling force that moves the wheel towards the consolidation of ERA4Health. These ERA-NETs have been launching yearly calls for many years (i.e. EuroNanoMed first call was launched in 2009, JPI HDHL funding activities started in 2013 and ERA-CVD first co-funded call was launched in 2015) so the procedures for transnational research funding and the related activities (e.g. linking different types of stakeholders, dissemination of the funding outcomes) are well established. In addition, both the funding organisations involved and the scientific and technological community and businesses in the respective fields expect the continuation of funding instruments to pursue and initiate new collaborations and activities.

However, the focus of ERA4Health will not be limited to the thematic areas of the ERA-NET cofunds mentioned above as new research priorities may be identified (these include but are not limited to infectious diseases and other emerging health threats, cancer or others). In addition, ERA4Health will bring novelty by expanding its funding to transnational **Investigator-Initiated Clinical Studies (IICS)**. It will identify bottlenecks, which hinder transnational clinical studies and propose ways to overcome them by establishing a supporting framework and new funding procedures.

The Partnership will cover 2022-28 and is open to public research and innovation funders at both national and regional level in the EU and those from Associated Countries to Horizon Europe, from Third Countries as well as other funders sharing the ERA4Health objectives (e.g. Philanthropic organisations and industry). ERA4Health will make a special effort to engage with and to include different EU research funders, funding a wide or limited scope of research and innovation type of beneficiaries in its actions. New funders will be enrolled in the Partnership to develop the capacity of ERA4Health to fund IICSs.

¹ <https://www.healthydietforhealthylife.eu/>

² <https://www.era-cvd.eu/>

³ <https://euronanomed.net/>

The implementation will be done in two phases. **Phase 1** will integrate previous European initiatives and implement joint calls in those areas and identify the funding needs in other areas of biomedical research. In parallel, it will develop a framework to carry out joint transnational calls on IICs. Phase 1 will last 2 years. At the end of this period, the Health Configuration of the Horizon Europe Programme Committee (HPC) will decide whether to extend and intensify the focus on IICs, based on pre-agreed criteria. This decision will only affect the focus area of the partnership, not its existence over the 7 years. According to the HPC decision, transnational calls for IICs and joint calls for other priority areas will be launched during the **Phase 2**.

Investments done by ERA4Health during those phases will contribute to address key strategic orientation (KSO)⁴ of the Cluster Health of Horizon Europe and, in particular, in a direct way impact areas on (1) staying healthy in a rapidly changing society and (2) tackling diseases and reducing disease burden and in an indirect way (3) ensuring access to innovative, sustainable and high-quality health care and (4) unlocking the full potential of new tools, technologies and digital solutions for a healthy society. Furthermore, ERA4Health will also contribute to UN Sustainable Development Goals (SDG), in particular, SDG 3 “Good Health and Well-being for People” with its nine health-specific targets aiming for universal health coverage for all at all ages by 2030, leaving no one behind, and ending preventable deaths.

Consistently with the impact-driven approach adopted by Horizon Europe, before its launch all future European Partnerships must develop a Strategic Research and Innovation Agenda (SRIA) to be adopted by the Partnership Consortium in order to ensure that the long-term vision is translated into a concrete roadmap with measurable objectives. This SRIA is the result of a structured process undertaken and agreed in order to link the mission and vision of the partnership with a planning that provides the basis for an Annual Workplan.

As the first step in its preparation, a Working Group (WG) was formed, composed by potential partner’s representatives some of them linked to predecessor ERA-Nets and Joint Programmes. The process for the development of the SRIA involved:

- Sept 2021. First draft of SRIA developed by the WG and a selected group of 22 experts (**Draft 1.0**).
- Oct 2021. The WG developed an online survey to get results from Public consultation. It was highly disseminated to around 230 stakeholders from different related areas. As a result of the original document and the inputs received through 53 entries from 15 different countries, the second version was produced (**Draft 2.0**).
- 16 Nov 2021. A Workshop was organized in order to discuss the results of the Public Consultation with relevant stakeholders and interest groups. In consequence of the participation of 66 attendees distributed among subgroups, the WG included the agreed contributions and comments and generated a new document (**Draft 3.0**).
- December 2021. As a last step in the elaboration of the SRIA, it was taken to a High Level consultation of National ministries and national/regional funding agencies of health (both acting as potential partners/beneficiaries of ERA4Health), approved its content and was moved to the Management Board of ERA4Health for its proper adoption (**Final Draft**).

⁴ Creating a more resilient, inclusive and democratic European society

3. Objectives & Expected Impact

3.1. Objectives

The general objective of ERA4Health is to reach, through the creation of a comprehensive network aiming at strengthening and expanding the existing conducive eco-system, an effective joint approach and generate knowledge and products (e.g. preventive guidelines, medical protocols) for identified research areas.

In this light, ERA4Health gathers public funders of health research in the European Research Area that jointly identify and implement a common funding strategy in priority areas to advance health research and develop innovation

Indeed, the ERA4Health Partnership will tackle the following challenges: (1) the increasing demand for a better quality of life of citizens and a better care of patients which lies in having access to and use evidences of the benefit and drawback of health interventions, (2) the need to transform public health care systems in order to make them more effective, efficient, equitable, accessible, and resilient and (3) the need to strengthen disease prevention and health promotion. In this view, ERA4Health network will contribute to a better economy by supporting the development or the optimisation of new prevention strategies, medical intervention, early diagnostic, or treatment modalities more effective and less costly.

The Partnership will work towards the following **Specific Objectives** to be achieved by 2028:

SO1. Support relevant biomedical and public health research including clinical fields and intervention areas (prevention, diagnosis and treatment)

ERA4Health will support the generation of knowledge, which can provide the evidence base to inform interventions and disease prevention and, thanks to the use of appropriate tools, contribute to more effective translation of pre-clinical results and decrease the time required for new product development (e.g. complex in vitro setups models, relevant animal models). Taking into account the experiences made in the four quality Horizon 2020 ERA-NET addressing Cardiovascular Diseases (ERA-CVD), Nano Medical Technologies (EuroNanoMed) and Diet related diseases/Healthy Diets (related to the JPI "A Healthy Diet for a Healthy Life"), it will expand other priority areas addressing important public health needs. ERA4Health will have access to and make use of the evidence on the benefits and drawbacks of health interventions, in particular for optimising prevention strategies at an individual and societal level, clinical management, personalised medicine and nutrition considering the patient from a holistic point of view (including socio-economical contexts), optimizing the decision-making processes especially considering concomitant treatment modalities and avoiding overtreatment.

ERA4Health will rely on an effective governance mechanism for co-designing and jointly implementing co-funding strategies for key Joint Transnational Calls in health research and innovation on selected priority areas of common interest.

Expected outcomes:

- Research funders, policy-makers and the research and innovation community work together in an effective joint approach, including for identifying and prioritising topics of common

interest and European benefit, thanks to a trusted governance and effective working modalities.

- Generation of new knowledge and use of research results to develop evidence-based strategies and policies, and deploy good practices to European countries and regions.

SO2. Improve the utilisation of existing health technologies in clinical practice

ERA4Health will bring novelty in public to public partnership by establishing **streamlined processes to conduct multinational investigator initiated clinical studies (IICSs) on health interventions**. Hence, ERA4Health will support the conduct of large, non-commercial but pragmatic clinical trials within the new regulatory framework for clinical trials⁵ and for which a multinational dimension is key for their design and success. IICSs will address important public health needs for Europeans benefit, which are not adequately covered yet. It will involve a critical number of the European Research Area (ERA) funding actors in health research by especially engaging funding organisations that have had, until now, limited involvement in public to public partnerships, as well as, enhancing the participation of partners already involved in such initiatives supported by previous EC framework programmes by mobilizing more resources. ERA4Health takes up the challenge to overcome the main obstacles to test health interventions at European level and support large-scale IICS conducted by the research community independently from private interests.

Expected outcomes:

- Access to and use evidences of the benefit and drawback of health interventions, in particular for optimising clinical management, repurposing, comparative effectiveness, treatment combination or optimisation studies, personalised medicine and nutrition and avoiding overtreatment.
- Countries cooperate better and use context-specific knowledge and evidence to make their health and care systems more sustainable and resilient with respect to upcoming needs and crises.

SO3. Build capacity, in particular in conducting IICSs at European scale

Europe is running out of well-trained physician-scientists (physicians who have trained in basic scientific research, “MD-PhDs”) who are capable of working together and with other clinical trial professions. At the same time patient-oriented research is becoming increasingly multidisciplinary, with new technologies constantly appearing. In many cases young investigators are not being sufficiently well trained to cope with this multidisciplinary environment. In a worst-case scenario this situation leads to a real and damaging decline of patient-oriented research and related studies in Europe and greatly reduces the competitiveness of Europe in the field of clinical research and related research on drug development and diagnostics.

ERA4Health will connect clinical research capacities, primary health care settings, regulators, clinically-based European networks and alliances, research infrastructures and European- based service providers of high public health interest, and patient associations. European Research infrastructures help to structure the scientific community and play a key role in the construction of an efficient

⁵ <https://eur-lex.europa.eu/legal-content/EN/TXT/?uri=celex%3A32014R0536>; 31/01/2022, date of entry into application

research and innovation environment⁶. The transition towards customised health care is data knowledge-driven. By promoting interdisciplinary collaboration among Biomedicine Researchers, the Partnership ERA4Health will seek the use and harmonization of the scientific equipment, knowledge-based resources, scientific data and any other infrastructure to achieve excellence in research and innovation.

Expected outcomes:

- ERA4Health identify the main barriers to test health interventions at European level and facilitate the research community to conduct large-scale investigator-initiated clinical studies of various health interventions addressing important public health needs in a seamless way.
- ERA4Health partners and relevant stakeholders build a more effective and integrated public health research system. Utilization of health services, preventative measures, technologies, tools and digital solutions are more cost-effective.

SO4. Implementation of Responsible Research and Innovation principles

ERA4Health will **implement and develop Responsible Research & Innovation (RRI)** and other cross cutting objectives in multiple ways from the Partnership operationalization to the implementation of calls or the project evaluation and will self-assure that research performed under the frame of ERA4Health respects RRI principles.

- ERA4Health will promote **research that anticipates and assesses potential implications and societal expectations** with regard to research and innovation, with the aim to foster the design of inclusive and sustainable research and innovation to ensure a true societal impact.
- ERA4Health will **engage with the society through citizens and patients** by giving a voice in the definition of ERA4Health scope and activities but also by communicating to them the major discoveries in the produced research. In addition, supported research will be citizens and patients, including children, centred.
- ERA4Health will **increase capacity building**, in particular in transnational IICS by providing a platform and tools to connect all stakeholders and by promoting formal and informal science education at a wide range of levels (from students to early career researchers)
- ERA4Health will support **gender equality** in all ERA4Health activities meaning an equal gender distribution in its different governance bodies and consultative groups, funded principal investigators. ERA4Health will also support the inclusion of gender dimension in the funded research content.
- ERA4Health will **support research ethically conducted** with an ethic committee embedded in its governance bodies.
- **Promote open access and data sharing** including by adhering to the FAIR (findability, accessibility, interoperability, and reusability) data principles and supporting the development of adequate data governance structures. It will also support the establishment of the modalities of data sharing and exploration of health data (e.g., from health care records, disease and patient's registries, genomic banks) for new digital health technologies and tools.
- **Communicate and disseminate**, in particular to decision makers, **research and innovation outcomes** and citizen's and patients need for preventing, diagnosing and treating diseases.

⁶ European research infrastructures (including e-Infrastructures), Work Programme 2018-2020.

Communication activities aim at promoting the Partnership activities towards the broad public. Thus they will necessarily focus on the scope and impacts of the project for society, transforming the more complex jargon into contents addressing less technical audiences with the objective to guarantee outreach and enhance its visibility.

The Communication, Dissemination and Exploitation activities are rather transversal and instrumental to support ERA4Health objectives. They comprise activities for a proactive communications effort, which include maintaining a strategic calendar to prepare for important events, working with a network of communication contacts and strengthening the messaging both in terms of content and in the mode of communicating. Active promotion and communication activities will include online and non-electronic communication methods and tools as appropriate, special events as well as publications are core activities.

Expected outcomes:

- Citizens are more knowledgeable to make better decisions for their own health and well-being, monitor their health, and trust in knowledge-based health interventions launched by health authorities.
- Health policies and actions for health promotion and disease prevention are knowledge-based, people-centred and thus targeted and tailored to citizens' needs and designed to reduce health inequalities.

3.2. Expected impact

The aforementioned objectives mainly contribute to the impact area '*Good health and high-quality accessible healthcare*' which on top of that contributes to the Sustainable Development Goal 3 (Ensure healthy lives and promote well-being for all at all ages).

The activities of ERA4Health will support health care providers to better tackle, manage diseases and reduce the disease burden on patients effectively thanks to better understanding of prevention and treatment of diseases, more effective and innovative health technologies. In addition, a well-established collaboration in ERA4Health reinforces a European Research Area on health and brings better ability and preparedness to manage epidemic outbreaks and improved patient safety, thus contributing to an increased preparedness of EU health care systems for disease outbreaks.

In more details ERA4Health will lead to achieve the following impacts:

- improve the quality of research programming in the European Research and Innovation Area by building on best practices through networking European public funders of health research and will increase the outputs of the research and innovation discoveries for the benefit of society and economy.
- contribute to the transformation of healthcare systems in their efforts towards better health promotion and disease prevention while ensuring fair access for everyone to innovative, more patient oriented, sustainable (including from a fiscal point of view) and high-quality health care.

- contribute to living conditions that safeguard and promote health by positively impacting determinants of population health in relevant settings and on a variety of levels, including the local, regional, national and international level.
- increase knowledge on disease development and disease treatment that will lead to better prevention strategies, improved patient management and ultimately better health.
- contribute to effective, efficient, equitable, accessible, and resilient public health care systems that will be fiscally sustainable in the medium and long term. For example, the utilization of health services, preventative measures, technologies, tools and digital solutions will be more cost-effective.
- support the generation of findable, accessible, interoperable and reusable data, which at the same time will ensure appropriate protection of patients' safety and rights, and data-driven approaches to confirm previous study or to respond to other research challenges and determine the effectiveness of other health interventions will reduce the research cost by avoiding effort duplication.
- improve the development of health strategies and innovations oriented towards public health needs in real-world settings. They will be more transferable and potentially useful as well as better accepted by end-users and will increase the scientific quality and societal relevance of produced knowledge, technologies and innovations, as for example by integrating an in-depth understanding of both genders' needs, behaviours and attitudes. In addition, health strategies and innovations will be easier implemented in other regions/countries, in particular in the countries with the poorest specific health indicators.
- support citizens' empowerment to make them more knowledgeable of disease threats and be able to make more conscious decisions for their health.
- facilitate more patient-oriented clinical research make citizens adhere to knowledge-based disease management strategies and policies (especially for controlling outbreaks and emergencies).
- contribute to breaking the glass ceiling in the long term by increasing the participation of women in research and by making women have a voice by achieving gender balance in decision making.
- contribute to the production of goods and services better suited to potential markets and will thereby contribute to the European economy.
- offer rapid and coordinated responses to cross border health emergencies once the network integrates the whole research and innovation actors.

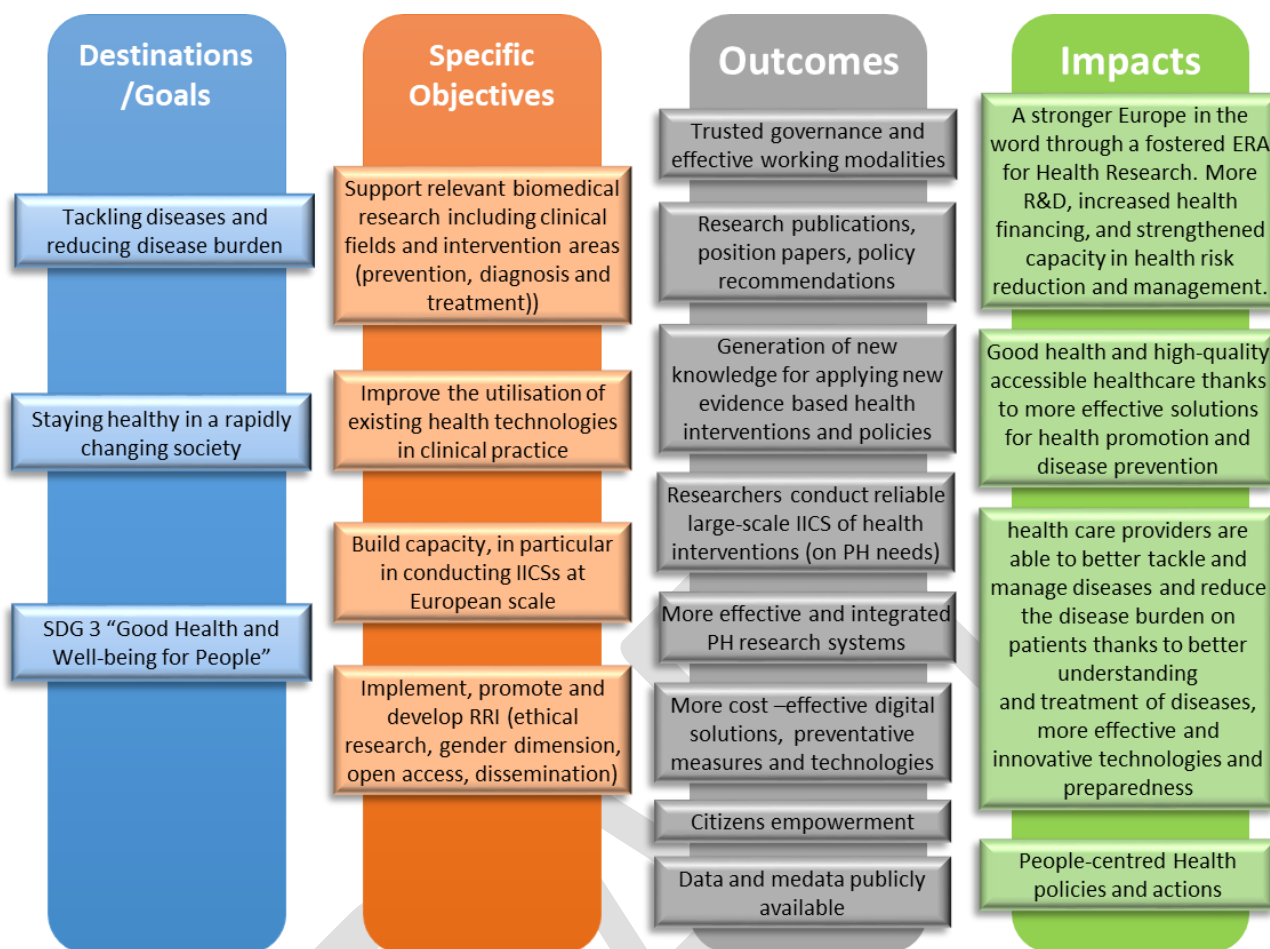


Fig 1. Impact pathway of ERA4Health including specific objectives, expected outcomes and impacts

4. Purpose of the research and possible funding instruments

As previously mentioned, the overarching aim of the funding activities of ERA4Health is to support the generation of knowledge, which can provide the evidence base to inform health interventions and disease prevention and, thanks to the use of appropriate tools, contribute to more effective translation of pre-clinical results, make health services, preventative measures, technologies, tools and digital solutions more cost-effective and health care systems more sustainable and resilient to new and existing threats. ERA4Health promotes effective working procedures in order that research funders, health policy-makers and the research community work together to identify and prioritise topics of common interest and European benefit that are not fully covered by other existing European programmes and initiatives.

This SRIA is the strategic document that provides the framework for selecting the call topics that will be included in the Annual Work Plans. The type of research subject to the selected calls will cover basic, translational to applied and clinical research.

In addition, during the Phase 2 of ERA4Health the implementation of large-scale multinational calls for Investigator Initiated Clinical Studies of various health interventions addressing important public

health needs is envisaged as an additional focus of the partnership; notwithstanding the approval of Phase 2 is conditional to the readiness to implement IICS. The final scope of the clinical studies will be identified during the Phase 1 although some indications are given in chapter 5.2.

The main funding instruments in ERA4Health are the **Joint Transnational Calls (JTC)** for projects. However, other instruments could be implemented (call for networks/knowledge hubs, mobility grants, etc.) according to the specific needs of the respective research field. JTCs enable scientists in different countries to build an effective collaboration on a common interdisciplinary research project based on complementarities and sharing of expertise, with expected impact to use the results in the future for the benefit of patients. The flexibility of ERA4Health to target new areas will also allow the participating countries and EU, to quickly launch a JTC to address an identified health societal challenge in times of need such as in case of health emergencies or other urgent research needs.

This collaboration enables not only transnational collaboration but also collaboration between public and private Partners from academia (research teams from universities, higher education institutions, public research institutions) and clinical/public health research (research teams from hospital/ public health, healthcare settings and other healthcare organisations) or research teams from industrial enterprises (all sizes). The eligibility of the participants shall depend on the conditions applied by the corresponding national/regional funding organisation participating in the call and can vary depending on the outline of the calls.

5. Definition of different Research Areas

In order to promote and protect human health and well-being, prevent diseases and decrease the burden of diseases and disabilities on people and communities, support the transformation of health care systems as pursued by cluster Health, ERA4Health will support the development of Research and Innovation through the implementation of two well differentiated but complementary phases according to the level of maturity of the Partnership.

A common vision based on a European Health Research Strategy and collaboration among countries and regions in Europe will be key in the leading role of EU in health research to make Science and Innovation community stronger and more efficient to tackle the existing and future challenges. It includes the definition of Research Areas. Phase 1 will integrate selected European initiatives and implement joint calls focused on **prevention and public health, nutrition- and lifestyle-related diseases, cardiovascular diseases and nanomedicine (section 5.1)**. In parallel, it will establish a supporting framework to tackle hurdles in the execution of IICSs and overcome the challenges in launching international joint calls effectively on IICSs, which would take place in Phase 2 (**section 5.2**). Our below **Priority Areas** have been mainly chosen because:

- Public health value and burden of disease (e.g. CVDs are the leading cause of death globally, direct costs of nutrition and lifestyle related diseases in terms of health care expenditure in the Member States is enormous, in the order of billions of Euros⁷). The improvement in these research areas will positively affect the global results of the partnership and its expected

⁷ [Nutrition & Diet for Healthy Lifestyles in Europe. EURODIET core report](#)

impact. A better prevention, earlier diagnosis and better treatments through innovative and efficient methods will contribute to the achievement of the expected impact set out in the Strategic Plan for the health cluster: 'health care providers are able to better tackle and manage diseases (infectious diseases, including poverty-related and neglected diseases, non-communicable and rare diseases) and reduce the disease burden on patients effectively thanks to better understanding and treatment of diseases, better benefiting from the prevention by nutrition more effective and innovative health technologies, better ability and preparedness to manage epidemic outbreaks and improved patient safety'.

- Evolving from a predecessor framework on these areas, will enable the European Research Area to have major possibilities of strengthening and growth. Biomedical and Health research at EU level needs to be more efficient to deliver better and of higher-quality solutions for prevention, diagnosis and treatment as well as providing better and equal access and affordable Health Care Systems to the citizens. Common inputs such as national and regional cash funding, in kind contributions, consolidated databases, experts and advisory boards' support and mainly their multidisciplinary expertise, will serve as a basis for the development of ERA4Health.

However, these priorities do not exclude the addition of new, not mentioned priorities addressing emerging health public issues (see **section 5.3**) without duplicating research areas which are/will be the scope of other European Partnerships in Horizon Europe (see **section 8**).

5.1 Selected high priority research areas

5.1.1 Prevention and Public Health strategies

Around the world, countries are struggling with an alarming rise in lifestyle-related diseases, with continuing increases in incidences of obesity, cardiovascular diseases, diabetes, cancer and other chronic diseases, with huge societal and economic consequences. Therefore, efficient prevention and public health strategies are crucial to enable people to stay healthy as long as possible and to reduce the economic and societal burden of disease. However, there are still significant knowledge gaps on how to these could look like and how they can be implemented best. Research implemented within ERA4Health aims to enable citizens including patients to healthier lifestyles and behaviours and to facilitate improved evidence-based health policies and more effective solutions for health promotion and disease prevention.

Assessing and understanding determinants of health behaviours

In order to develop effective measures to maintain or improve public health it is vital to gain a better understanding of citizens' health behaviour, the underlying determinants and interconnectivity of these behaviours and how to influence and permanently improve them. These insights will help policymakers and health professionals to develop targeted public policies and interventions that are tailored to the citizens' needs and thus reduce health inequalities and truly improve public health.

- a) Defining elements of the choice architecture and understand the interdependency of the determinants of health literacy, diets, food choice, purchase drivers, tobacco and alcohol consumption, physical activity, sedentary and sleep behaviour considering the possible impact of age, sex and gender, ethnic differences or other demographic features.
- b) Overweight and obesity prevention and prevention of (related) cardiometabolic diseases, better understanding of the role of the exposome throughout life including early environmental exposure to an unhealthy diet, certain dietary beliefs and behaviours and/or low levels of physical activity or critical life events.
- c) Predicting health-related behaviours and intervening on modifiable determinants by accurately calculating health effects and effective countermeasures, among others with the assistance of computer models, to change behaviours in different target groups.
- d) Quantification of health inequalities and variations in health determinants across different geographic and socio-economic or vulnerable groups and explore potentials of targeted prevention strategies.
- e) Identification of distal and proximal life-course drivers of health-related behaviours starting from before conception to old age (Developmental Origins of Health and Diseases – DoHAD approach).
- f) Further understanding the connections between the life-course living environments in public health and healthy behaviours, fostering the implementation of Smart Healthy Age-Friendly Environments (SHAFE).
- g) Promoting the data-driven decision making and planning through surveillance and epidemiological studies integrated systems to provide always updated information basis to unlock the potential of using digitalization, big data obtained from wearables or community-centered studies and the internet of things to gather knowledge and monitor patients (e.g. for prevention of hospital-linked infectious and malnutrition).

Assessing and understanding the effects of public health interventions

To be effective and widely accepted policy measures and interventions for health promotion and prevention need to be evidence-based and people-centred. Therefore, more research efforts are needed that aim to understand the full pathway from research evidence, intervention and policy design to behavioural change and health impact. In addition to the generation of new knowledge about the efficacy of public health strategies and interventions, cost-effectiveness calculations are important to convince policy makers also about the economic benefits of such measures.

- a) Effectiveness of health literacy approaches (e.g. shift from individual level to population level) covering the whole lifespan focusing at specific vulnerable population groups/windows of opportunities
- b) Public policies and targeted health-promoting interventions to create awareness for and enable healthy and sustainable choices, to support healthy and sustainable diets (considering the whole food chain from production to consumption) as well as health-enhancing physical activity on a population level and change health behaviours by using multi-stakeholder co-creation and citizen science approaches including the development of an evidence framework to assess their effectiveness.

- c) Real-world research (e.g. natural experiments involving local stakeholders) and addressing the analytical challenge of big data as well as digitalization in public health.

Implementation and scale-up of effective prevention and public health strategies

Across Europe and beyond, several public health measures are continuously developed, pilot-tested for a specific target group or small community. Some of those prove as effective, whereas a lot of them are not able to provide enough evidence for their efficacy. Following from that there is a great need to investigate the different implementation strategies and factors that hinder or facilitate the successful implementation of such measures. In addition, there is great interest in further research into those strategies that have a strong evidence base to scale them up to larger target groups or adapt and transfer them to other communities, regions or countries.

- a) Factors influencing the implementation of public policies with an expected positive impact on citizens' health (e.g., costs, political and administrative feasibility, digital backlog, acceptability among stakeholders including the public and the market sector) with a particular focus on the cost-effectiveness of public health management approaches (e.g. differences by member states) in synergy with Partnership "Transforming Health and Care Systems"⁸.
- b) Scaled- up, population-level adoption and implementation of public health measures known to be effective including insight into factors influencing policy adoption and implementation, e.g.:
 - i. The scientific, societal, political and administrative processes that have led to the adoption or rejection of evidence-informed policies in some, but not other European countries and regions, or on the EU level.
 - ii. Transferability and adaption of interventions and public policies to new contexts, target groups, regions/countries.
 - iii. Factors influencing the acceptability of evidence-informed policies among stakeholders (including the public and the market sector).
 - iv. Participatory research involving stakeholders (including policy-makers and the public) to identify promising strategies for implementation / to overcome implementation bottlenecks.
 - v. Communication and collaboration between healthcare professionals and patients and citizens

System-level dynamics, interactions, and links between public health and other key societal challenges

With the current COVID-19 pandemic, the emerging climate crisis as well as the ongoing demographic change to name only a few examples it becomes obvious that public health related research questions have interlinkages to many other key societal challenges. These challenges can thus only be tackled with the appreciation that health related questions are usually part of complex systems with their own dynamics. Research implemented within ERA4Health aims to also take the bigger picture into account and will investigate synergies and trade-offs between (public) health research and other societal sectors with a specific focus on synergies with other partnerships, e.g. the Partnerships One Health/AMR and Sustainable Food Systems.

⁸ https://ec.europa.eu/info/files/european-partnership-health-and-care-systems-transformation_en

- a) Investigation of synergies and trade-offs between obesity prevention and other societal goals (e.g., environmental sustainability), as well as complex systems approaches to obesity prevention particularly during childhood to adulthood transition.
- b) Interdisciplinary research on systems-level dynamics influencing food systems, population and planetary health, the effectiveness of relevant interventions, and their implementation. Participatory research (including informal careers) to develop strategies for systems-level change (should include relevant stakeholders, including patient associations and the public).
- c) Interactions (including synergies and trade-offs) between public health goals and interventions and other sectors and societal goals (e.g. environmental sustainability; social inclusion; political and social cohesion / the avoidance of the polarization and fracturing of societies and political systems; economic stability; human rights; quality of live; animal welfare).
- d) Methods for investigating such interactions and dynamics (including methods for integrating systems perspectives into health-related primary research and evidence syntheses).
- e) Human health and the integrity of the earth's natural systems (including the climate system, among others) interact in multiple ways, e.g.
 - i. Influence and relevance of processes of global environmental change (including climate change, biodiversity and habitat loss, air, water and soil pollution, depletion of fresh water resources, land degradation, transfer of human-borne contaminants to food, among others) on human health.
 - ii. Effects of health-related behaviours and interventions on environmental sustainability (e.g. carbon emissions, interventions on food systems to limit human and environment exposure to contaminants).
 - iii. Effects of environmental policies and interventions (e.g. a carbon price) on human health including nutrition.
 - iv. Development of effective strategies to maximize synergies and avoid trade-offs between human health, economic imperatives, and environmental sustainability in the design and implementation of policies.
 - v. Strategies for improving cross-sectoral cooperation and coordination between the health and environmental sectors in priority setting, as well as in policy design, implementation and evaluation (e.g. between different government departments, health care systems, sectors of civil society, and scientific disciplines across the food system until human health and environment) to ultimately improve human and planetary health.
 - vi. Methods for considering environmental sustainability in health research with the support of digital tools such as AI and computer modelling & simulation (both primary research and evidence syntheses).

5.1.2 Nutrition- and lifestyle-related-diseases

To increase the level of understanding and for filling defined existing knowledge gaps in nutrition and lifestyle-related diseases basic biological research (on e.g. biomarkers, metabolism and the physiology of nutrients, microbiome, nutrition influence on immunity and infection) as well as applied research on habitual diets and health care (e.g. precision and chrononutrition, obesity treatment, translation of

research) are needed. In the environmental and sustainability themes, the topic of healthy and sustainable diets and equitable food systems shows also close synergies with the Partnership on Safe and Sustainable Food Systems, but ERA4Health focuses on their impact on health.

Biology and basic science

Research is still needed to provide insights into the biological mechanisms behind malnutrition, physiological factors (and their interaction) involved in food behaviour and effects of physical activity and sedentary behaviour. Sensitive and reliable biomarkers are vital in assessing the long-term health effects of diets and food products. Better understanding of important basic science as metabolism and physiology of nutrients, complex nutrition-gut metabolism interactions as well as the cognitive control of regulation of food choice and food intake will support governments, industry and non-governmental organisations in the development of evidence-based and effective dietary interventions.

- a) Exploration of (new) biomarkers (e.g. blood, urine, faeces, saliva as well as digital biomarkers) of exposure and risk as well as the efficacy of food-based solutions:
 - i. Biomarkers as valid measures of exposure that reflect behaviour- and diet, nutrition and other modifiable behaviours-related health status at both individual and group levels and represent the effects of physical activity and sedentary behaviour, specific ingredients, food additives and/or contaminants, xenobiotics generated during processing, foods and/or dietary patterns.
 - ii. Biomarkers that reflect risk factors and that are predictive to the efficacy of dietary changes food-based solutions are needed that are specifically designed for the different physiological situations of the individual in order to obtain therapeutic targets for personalized strategies.
- b) Better understanding of the metabolism and the physiology of nutrients alone and in combination with other nutrients (as e.g. vitamin E where enzymes and other factors are involved) as well as the physiological functions of their metabolites by making use of bioinformatics for the interpretation of omics data.
- c) Better understanding the complex nutrition-gut-metabolism interactions by the use of artificial intelligence and machine learning models, of big data analytics such as next generation sequencing technologies to study the composition, diversity, and activity of the human microbiome, with a specific emphasis on:
 - i. Research on the synergistic and antagonistic effect of the different components that influence the microbial composition and thereby health including lifestyle, the cardio-metabolic profile and the gut-brain-axis with effects on the development
 - ii. Influence of microbiota on the maintenance and decline of cognitive function throughout life.
 - iii. Knowledge on the role of early exposures and feeding practices on primocolonization by microbiota of GI tract and long-term development of food preferences and habits and how one can benefit from the properties of gut microbiota to improve the efficacy of food-based solutions (biological efficacy of nutrients, bioremediation against pollutants).
 - iv. Development of novel "Nutraceuticals", e. g. food derived factors for modification of the gut microbiome to influence specific nutrition-microbiome-host metabolic axes, to generate highly-effective targeted preventive strategies for metabolic and cardiovascular diseases and testing their effectiveness in IICS nutraceutical intervention studies.

- d) Better understanding of the cognitive control of dietary behaviour and the regulation of food choice and food intake and how it is influenced by nutrients present in the gastrointestinal tract and the central nervous system (nutrient-signalling) including metabolic regulation for the prevention of metabolic disorders and research into the associations between neurological processes, micro- and macronutrient composition of the diet, and health issues such as obesity, metabolic disorders and degenerative diseases.
- e) Nutritional factors influence on the immune response, inflammation and immune impairment across the life course, including nutrition-responsiveness in the immunological interplay of chronic and infectious diseases.
- f) Chrononutrition and the effects of biological rhythms and circadian timing of food intake and potential health outcomes (controlled trials) including the development of standardized and harmonized tools to monitor the change in the different physiological parameters of a subject throughout the day taking into account physical activity and sleep.
- g) Exploration of how certain diseases, disabilities or health conditions originate during critical time periods of development (windows of susceptibility) and the importance of early nutrition and early experiences in the developmental origins of health and disease (DOHaD).

Environments and sustainable diets

Food as well as the environment plays a very important role in dietary, physical activity and sedentary behaviour. Further research on malnutrition is needed but also effects on chrononutrition. The co-benefits of healthy diets and surely the increase of the sustainability of these diets and equitable food systems overlap with the research areas covered by the Partnership on Safe Sustainable Food Systems however ERA4Health focus on the health effects.

- a) Food environments and how these influence dietary behaviours, and how they are shaped by policies, interventions, and other determinants within the framework of global food systems considering competing interests (e.g. the commercial sector vs; public health objectives).
- b) Urban and rural environments and how they influence physical activity and sedentary behaviours, as well as how they are shaped by policies, interventions and other determinants.
- c) Over-, under- and malnutrition as a consequence of physiological (e.g. aging, deviant eating behaviour, physical inactivity, sedentary behaviour), pathophysiological (obesity, chronic disease, cancer, psychiatric impairment and neurocognitive decline), and socioeconomic conditions (low income, populations in transition) as well as the exploration of the concept of malnutrition, obesity and climate change as a syndemic.
- d) Chrononutrition and the effects of biological rhythms and circadian timing of food intake and potential health outcomes (controlled trials) including the development of standardized and harmonized tools to monitor the change in the different physiological parameters of a subject throughout the day taking into account physical activity and sleep.
- e) Co-benefits of healthy diets and relevant interventions for other societal goals (including social cohesion; economic productivity; environmental sustainability; quality of life; animal welfare): Diets and diet-related interventions effect a variety of societal and individual goals besides health e.g. (i) Interdisciplinary primary research and evidence syntheses on relevant interactions, co-benefits and trade-offs applying a holistic or risk-benefit assessment approach. (ii) Development of innovative methods for considering such co-benefits (but also potential trade-offs) in dietary and nutrition research.

- f) Development of healthy sustainable diets (considering the whole food chain, from production to consumption) and equitable food systems and linking (assessing) this with their impact on health and the climate change agenda in a syndemic approach.

Applied science in the field of nutrition related to habitual diets and health care

More applied research but also exploration and translation of research findings will ensure that citizens are better informed and will increase their motivation, ability and opportunity to make healthy choices – whether that means improving diet, increasing physical activity or reducing sedentary behaviour.

- a) Precision nutrition concepts for prevention and treatment of lifestyle-related diseases with a focus on the efficacy in combination with an implementation strategy for the translation.
- b) Exploration of research findings into practice, e.g. translating dietary recommendations/menu plans into evidence-based cookbooks or dietary apps and evaluating their impact.
- c) Improvement of obesity treatment:
 - i. research on how interventions can be implemented effectively and sustainably within healthcare systems by co-creating interventions with patients and relevant stakeholders, from public health, urban planning and the commercial sector
 - ii. impact of bariatric surgery including long-term benefits and harms of bariatric surgery, nutritional complications after bariatric surgery and the effect of bariatric surgery in mothers on the health trajectories of their children.
- d) Chrononutrition and the effects of biological rhythms and circadian timing of food intake and potential health outcomes (controlled trials) including the development of standardized and harmonized tools to monitor the change in the different physiological parameters of a subject throughout the day taking into account physical activity and sleep. In addition to the biological component, the social dimension of this theme is also important.
- e) Metabolic, physiologic and health consequences of alternate living and eating behaviours (including veganism, poor diets and overconsuming of food and drinks more energy-dense than needed leading to undernourishment and obesity) accounting sensitive periods (pregnancy, Youth, Elderly), gender.

5.1.3 Cardiovascular diseases

Cardiovascular diseases are the leading cause of death worldwide and in Europe where over 3.9 million deaths per year, around 45% of total deaths, are attributable to cardiovascular diseases. Cardiovascular diseases are also expected to remain the largest cause of death over the next 20 years. In addition, our understanding of, and ability to prevent or treat, the less common forms of cardiovascular diseases are still very limited. Cardiovascular diseases cover a broad range of conditions affecting the heart and blood vessels. Highly prevalent diseases include not only ischemic heart disease leading to heart attack, but also stroke, heart valve disease, peripheral arterial disease and vascular dementia. In addition, there is a series of less common, but devastating, cardiovascular conditions such

as congenital heart disease, inheritable cardiomyopathies and arrhythmias, any of which can lead to sudden and unexpected death – often in young people⁹.

Based on the work made under ERA-CVD and its strategic research agenda made by the consultation of all relevant stakeholders, ERA4Health has identified different priorities of biomedical research to reduce the burden of cardiovascular diseases.

Promoting cardiovascular Health – Better prevention and risk detection

- a) Specific effort should be made to assess the personal predisposition and environmental determinants for cardiovascular disease and to foster the development of targeting screening (work, diet, stress, sleep, physical activities, gender, genomic, socio-economic factors and other variables) in both healthy and risk populations and patients, notably in segmented and vulnerable populations.
- b) Early diagnosis of vascular and cardiovascular diseases should be improved in sort to predict an acute cardiovascular condition before they actually occur and cost-efficient diagnosis should be developed to manage the disease as early as possible. The diagnostic methods should be non-invasive, personalized and based on different approaches (e.g. omics, *in silico*, wearables and artificial intelligence). A better disease diagnosis, monitoring, and management will be facilitated with the development of rapid detection methods that can be used near to the patient, namely point-of-care technologies (e.g. diagnostic methods for SOS needs or underprivileged locations, deployment of personal diagnostic devices and risk estimation algorithms). Particular focus should also be upon improving treatment for secondary prevention in surviving patients with prior stroke and cardiovascular disease, who are at highest risk of second stroke, vascular dementia, coronary events, and vascular death.

New Concepts for better treatment

- a) Research understanding of molecular and cellular mechanisms governing cardiovascular development as well as physiological and pathological signalling will allow the development of new strategies for the reparation of the heart and blood vessels. 'Further insights are required in how changes at the cellular or subcellular level change impact on arrhythmias and pathologies at the organ scale. The problem at hand is interdisciplinary and there is room for novel concepts, methods and technologies combining several disciplines, including (but not limited to) medical imaging and inversion, bio- engineering, material science, optogenetics, statistics, digital twinning, mathematical modelling, data science.
- b) Development of treatment strategies targeting the responsible pathophysiological mechanisms is necessary for chronic heart failure and atrial fibrillation.
- c) In order to administrate an adequate treatment to a patient with a complex condition i.e. comorbidities, the understanding of the interaction between cardiovascular diseases and other chronic diseases and their translation into combined treatment is essential.

Opportunities for better treatment and care

- a) Particular efforts should be made to advance technological developments to miniaturizing and improving the lifespan and efficiency of implanted and wearable cardiac devices.

⁹[https://www.who.int/news-room/fact-sheets/detail/cardiovascular-diseases-\(cvds\)](https://www.who.int/news-room/fact-sheets/detail/cardiovascular-diseases-(cvds))

- b) It is also necessary to improve patient compliance in specific treatment groups by selecting appropriate interventions, including through the use of digital tools.
- c) Precision treatment and personalized management strategies is required to manage cardiovascular diseases based on comprehensive patient data, including but not limited to molecular profile (metabolome, genome and proteome), functional imaging of the heart, comorbidities, lifestyle etc.
- d) The whole chain of care must be patient-centred to effectively care of stroke, meaning the development of optimal care, management, diagnosis, interventional treatment, secondary prevention and rehabilitation.
- e) Studies from the Real World Evidence (RWE) derived from quality registries, hospital records and national registries and databases should allow performing health-economic analyses for primary and secondary preventive actions, generating hypotheses and designing comparative trials to reduce patient mortality and morbidity and increase quality of life. Building competence and European networks on calibration, standardization and data handling for registries is essential to enable the reuse of data for further IICS. Following the example of successful strategies for the rapid identification of new treatment targets for Covid-19, large international collaborations might be supported to develop randomised platform trials for the treatment and prevention of stroke, vascular dementia, and cardiovascular disease.

Living with chronic cardiovascular diseases

Psychosocial aspects of CVD must be taken into account in order to reduce the burden of disease and negative impact on disease treatment and other disorders. Therefore, collaboration with public health authorities, press and media representatives, nurses, pharmacists, school teachers, sport trainers, urban planning bodies, food industry and patient associations will be an essential part of a future strategy.

- a) Cognitive dysfunction as a result of cardiovascular disease

Prior stroke is a major risk factor for development of vascular cognitive impairment and dementia. In addition, cardiovascular risk factors including diabetes, hyper-tension and obesity, smoking and physical inactivity are key determinants of cognitive dysfunction. In an aging population with increasing prevalence of chronic CVD across Europe new insights are urgently needed to develop multiple optimal strategies targeting the cardiovascular compartment in at risk elderly patients. Tailored interventions to the individual risk profile in some optimal time windows such as intensive blood pressure treatment, diet and vascular health intervention may counteract cognitive decline. Research in this field should provide understanding into the intrinsic crosstalk between cognitive problems and comorbid lifestyle diseases including cardiac as well as large and small vessel dysfunction.

- b) Living with a congenital heart defect

Young patients with a congenital heart defect increasingly experience a hand off in care between the paediatric and adult care environments as their survivability increases. Patients require support beyond their immediate needs relative to their physical wellbeing. Survivorship results in a much greater range of considerations for condition management as patient potential life courses develop. Paediatric cardiologists and adult cardiologists should also work together to better inform patients about their increased risk of further CVD. Research on women's health is expanding knowledge as to the cardiovascular implications of pregnancy, both in the immediate state as well as potential long

terms risks. However, much is yet to be further understood particularly with respect to specific patient sub-populations such as women with congenital heart disease. Similarly, occupational health, safety research and labour legislation principally focus at a population level, and thus provide fewer insights with respect to this same sub-population. Hence, future research should be focused to provide better care and guidance that best suits the patient's personal situation.

c) Psychosocial wellbeing in patients with cardiovascular disease

Cardiovascular diseases are a condition with a lengthy development and become increasingly a chronic condition to be managed across the life course. As a result of improvements in management of acute cardiovascular disease, survivors may face significant changes to their lives in order to manage with disease. Patients with manifest disease may live many years following diagnosis and many patients with cardiovascular disease are anxious of recurrent symptoms, suffer from depression as a result of their illness, or feel extremely tired. Psychological problems such as anxiety and depression can hamper patients and their partner/family, for example, in work and social activities. There is a significant need for knowledge that supports the mental well-being of persons with cardiovascular disease, and for rehabilitative programs to which patients are able to adhere long term. Outcomes can rely heavily on behavioural changes, which are notoriously difficult for patients to maintain long term without ongoing support and to find their way in daily life.

d) Guidance and care at the end of life phase of cardiovascular disease patients

Over 10,000 patients die of cardiovascular disease in Europe every day. Some die suddenly, however many are sick over a long period of time. Indeed, as management and treatment of cardiovascular disease has advanced, the burden of disease is concentrating in elderly population, who have much co-morbidity. Serious consideration will need to be taken in future to consider the manner in which care is provided to persons nearing the end of their lives. Research should provide insight into what patients and their caregivers need and expect from doctors and other health care providers in the last phase of life. It also shines light onto whether or not current health care practice takes this into account.

5.1.4 Nano and advanced technologies for disease prevention, diagnostic and therapy

Nanomedicine is a branch of medicine that applies the knowledge and tools of nanotechnology to the prevention and treatment of disease¹⁰. Novel approaches are urgently needed to address unmet medical needs (UMN) meaning conditions for which there exists no satisfactory method of diagnosis, prevention or treatment or, even if such a method exists, in relation to which the medicinal product concerned will be of major advantage to those affected¹¹.

Nanomedicine is understood to be a key enabling instrument for personalized, targeted and regenerative medicine by delivering the next level of new diagnosis tests, drugs, treatments and implantable devices to clinicians and patients, for real breakthroughs in healthcare.

¹⁰ <https://www.nature.com/subjects/nanomedicine>

¹¹ Article 4 paragraph 2 of Commission Regulation (EC) No. 507/2006)

Therefore, the objectives of the SRIA of ERA4Health for Nanomedicine are:

- a. focus on unmet medical needs where advanced technologies and methodologies can make a difference by preventing illness, more quickly diagnose, control disease and treat disease with fewer side effects, and create better medical aids such as more compatible prosthetics,
- b. facilitate the matching of nanotechnology features with other Key Enabling Technologies (KETs) such as Advanced Materials, Micro- and Nano-Electronics, Photonics, Biotechnology, Advanced Manufacturing Systems, Artificial Intelligence and other digital KETs, to deliver new and radically innovative cross KETs medical solutions to patients at affordable cost,
- c. optimise the implementation of medical innovations into the healthcare systems.

Based on the work made under EuroNanoMed and the European Technology Platform for Nanomedicine (ETPN)¹² for the elaboration of the Nanomedicine SRIA¹³, an extensive survey was launched in order to compile a list of shared unmet clinical needs felt by clinical experts, potentially profiting from nanotechnology-enabled products or processes. From the survey it appears that the largest group of diseases for which unmet needs were identified are cancer, neurology, infectious and auto-immune diseases, rehabilitation/aging-related diseases and cardiovascular diseases, which constitute together about 70% of the total number of topics. This is well in line with the Horizon Europe Programme¹⁴ towards major social challenges in healthcare, both in terms of big killers, like cancer and cardiovascular disorders, and of highly disabling diseases bringing very heavy social burden, like infectious diseases, neurological/degenerative disorders and chronic aging-related conditions.

Considering the groups of prevalent applications, it appears that most of the unmet needs are still in the treatment area (60%), with a still relevant number in diagnostics/monitoring (26%), while theranostic applications – unless considered as precious – are still considered less close to reality than the two previous ones. In several cases, anyway, the monitoring applications are aimed at providing not only a better diagnosis or screening but also the basis for personalised treatments, providing higher quality of life and more efficient use of healthcare resources.

Diagnosics/Imaging

The use of nanotechnology in the field of Health Sciences has triggered novel and very promising applications in diagnostics and invasive therapy of human diseases. The development of novel tools with improved imaging characteristics would lead to an early identification of the diseases. Imaging nanotools make it possible to visualize tumours using non-invasive as well as intraoperative imaging approaches.

Relevant topics identified in this area are:

- a) *In vitro* diagnostics, conception of nanoparticles with advanced properties allowing a gain in sensitivity, improved detection or increased specificity towards biomolecules, biomarkers, cells.
- b) *In vivo* imaging, companion diagnostics to develop novel nanomedicine, develop novel contrast-agents based on nanomedicine to increase the sensitivity as regard to current agents,

¹² <https://etp-nanomedicine.eu/>

¹³ [Nanomedicine SRIA 2016-2030 \(etp-nanomedicine.eu\)](#)

¹⁴ [Cluster 1: Health | European Commission \(europa.eu\)](#)

innovate towards nanomedicine for in vivo imaging for preclinical studies aiming at understanding clinically relevant diseases, and helping conceiving future therapies.

- i. Nanoparticle based rapid and simple tests for prevention, diagnostics, and therapy monitoring, including new medical devices and implantable nano-devices.
- ii. Nano-enabled biomarkers, vectors and contrast agents with high-sensitivity and specificity: functionalised nanoparticles for diagnostics and therapy / Molecular monitoring of markers / Multifunctional contrast agents.
- iii. High throughput systems for multiplexed detection of biomarkers of diseases, for optimization of therapy and sensing interfaces.
- iv. Nanostructured surfaces for biosensors tailored to work within the body, on the body, or out of body.
- v. Non-invasive, painless and/or long-term monitoring (such as diabetes and endocrine disorders)

Therapeutics

The merging of nanotechnology and medicine has resulted in new approaches to designing specialized pharmaceutical formulations. While nanomedicine encompasses a diverse array of research fields, the focus of this review is on its therapeutic applications, specifically its impact on drug delivery and those products in clinical development.

Relevant topics identified in this area are:

- a) Vaccines and implantable (long-lasting) nano-devices.
- b) Nanoparticles as nanomedicine or -carriers potentializing radiotherapy and photodynamic therapy, or other physical means relevant to clinical applications.
- c) Nanoparticles and immunotherapy: nanoparticles to target specific immune cells, to impact or modulate the tumour microenvironment, or as adjuvants to increase or modulate the immune response in all types of diseases.
- d) Nanoparticles addressing the limitation of existing nanoparticles as delivery systems of non-soluble and soluble drugs or macromolecules (i.e. proteins, DNA-editing or nucleic acids), providing a higher drug delivery intracellularly.
- e) Nanoparticles to provide combination therapies, combining therapeutic and imaging tools, or hybrids to provide novel properties transferable to novel solutions, including deformable materials under internal or external stimuli.
- f) Novel drug delivery systems and advanced therapies (including cell-based therapies), to improve therapeutic index. Consider the passive or active targeting capacities of nano-vehicles and drug carriers, addressing specific cells or tissues at the cellular and global level, the elimination pathways and the reduction of side effects and address the questions of alternative administration pathways as intra-articular, intra-auricular and intraocular.
- g) Extracellular vesicles: exosomes/extracellular vesicles as delivery vehicles to cross biological barriers, exosome diagnostics/therapeutics, hybrids with synthetic systems development expertise (linking out to businesses).
- h) Nanotechnology-based solutions for crossing biological barriers, to address some of the big challenges in targeted drug delivery.
- i) Solving scale-up production, sterility and storage issues of nanomedicines, cell-based therapies and advanced therapies to promote IICS implementation.

- j) Artificial intelligence to select novel drug delivery systems transferable to larger scale and pilot's production, understand the supramolecular mechanisms of nanomedicine synthesis and favour reproducible lots.

Regenerative medicine

Nanotechnology has considerably accelerated the growth of regenerative medicine in recent years and appears to be a promising approach in restoring function and regeneration of diseased tissues and organs. Application of nanotechnology in regenerative medicine has revolutionized the designing of grafts and scaffolds which has resulted in new grafts/scaffold systems having significantly enhanced cellular and tissue regenerative properties. Since the cell–cell and cell-matrix interaction in biological systems takes place at the nanoscale level, the application of nanotechnology gives an edge in modifying the cellular function and/or matrix function in a more desired way to mimic the native tissue/organ.

Relevant topics identified in this area are:

- a) Tissue engineering for the improvement, repair or replacement of tissue/organ function.
- b) Cell-based therapies, including their uses in 3D-bioprinting strategies and organ transplantation.
- c) “Smart” nanostructured and functionalised surfaces: functionalisation of 2D-3D materials.
- d) Scaffolds and nanoparticles for new and advanced therapeutic treatments.
- e) 3D printing of cells and biomaterials for implants and/or reconstruction.
- f) Intelligent biomaterials/bioactive materials: site specific delivery of active molecules / nanoparticles with spatial and temporal control over the release of biochemical molecules and/or in vivo activation of stem cells / mimic the morphological, mechanical and biochemical environment of tissues / Biomimetic, biocompatible, biocompetent biomaterials.
- g) Nanofunctionalisation for increased biocompatibility of implants: polymer coated medical implants to improve biocompatibility.

Matching with other emerging technologies for healthcare

To exploit the full potential of nanotechnologies for healthcare its special features need to be integrated with other enabling technologies. Economic analyses of market trends and their contribution to solving societal challenges, Advanced Materials, Micro- and Nano-Electronics, Photonics, Biotechnology, Advanced Manufacturing Systems, Artificial Intelligence and other digital technologies, have been identified as the EU's Key Enabling Technologies.

Whilst each of the KETs individually already has huge potential for innovation, their cross-fertilisation is particularly important as combinations of KETs offer even greater possibilities to foster innovation and create new markets. The concept of 'cross-cutting KETs' refers to the integration of different key enabling technologies in a way that creates value beyond the sum of the individual technologies. 'Cross-cutting KETs have therefore the potential to lead to unforeseen advances and new markets, and are important contributors to new technological components or products. The integration of nanotechnology with other KETs is deemed to be of highest benefit to the following healthcare fields:

- Devices and systems for targeted diagnostics and personalised medicine.
- More efficient and less invasive therapies.
- Smart systems and robots for healthcare services.

5.2 Identified research areas to be addressed with IICS

The continuously growing arsenal of health interventions, whether it is a new pharmaceutical product, a medical device, a surgical intervention, or other measures utilised during health and care provision, all reflecting the increasing demand for better quality of care by citizens, force decision makers of public health systems to optimally allocate their limited resources in a well-informed manner. Investigator-initiated clinical studies generate data on safety and effectiveness of a health intervention in real-world settings and thus provide evidence to answer questions that clinicians face in their day-to-day practice in order to optimise the clinical management of patients. Such studies deal with potential diagnostic and therapeutic innovations that traditionally do not attract the private sector but are crucial for optimised clinical management and the sustainability of healthcare systems.

Therefore, the overall scope of the calls for large-scale multinational IICS is the public health value. This partnership shall provide the funding of Investigator Initiated Clinical Studies that are transnational (at least 3 countries involved) academic- but not industry-driven. The support of industry is, however, anticipated as these entities may serve as partners of the funded projects.

Studies of various objectives shall be considered eligible for funding as academics-driven repurposing trials. The objective of the trials can also cover comparing effectiveness and assessment of combination as well as optimization of existing treatment options. Observational studies together with interventional studies of different nature (prevention, diagnostic and treatment) could be funded, including medicinal products, biotherapy, advanced therapy, medical devices and MedTech solutions and procedural interventions. Trials in primary care as well as nurse initiated trials could be also covered by IICS calls.

A broad scope of target morbidities is foreseen, however some medical areas might be excluded from funding if IICS funding is already covered by other European programmes or collaborative funding activities could be pursued (including but not limited to rare diseases, personalized medicine, antimicrobial resistance, cancer or neurodegenerative diseases). For instance, both the observational stratification cohorts and the subsequent interventional clinical trials could be as part of the aim for future calls under the personalized medicine research programs. Phase I clinical trials in any setting are not considered as eligible, as these are, by nature, single site and cannot be implemented with a transnational clinical trials.

Main expectation facing IICS funded within this partnership is to generate the highest level of clinical evidence in response to specific scientific questions. The aforementioned should contribute to support public healthcare systems. The involvement of patients and their families in trial design, as co-applicants (through patient organizations) or in the decision taking processes will be vital for ERA4Health.

5.3 Room for flexible funding topics

Next to the jointly agreed research gaps and prioritized research areas, the anticipation of future problems that may not be obvious today but can be tackled with research and innovation efforts is

also important. The relevance of the R&I process should be ensured by continued reflection and opportunities for a flexible approach in the definition of new crucial funding topics.

Therefore, responsiveness and adaptive changes from the research and health care communities as well as the respective funding bodies are mandatory. Scientists, clinicians and innovators should be able and willing to adapt the research approaches and expected outcomes of their R&I activities to the ongoing societal developments in order to make sure that they are relevant, timely and valued by the society. To ensure a high impact of the funded R&I activities the participating funding bodies agreed to implement a flexible and open approach for identifying and selecting call topics not yet prioritized in this SRIA to be able to respond to emerging health-related challenges.

The main driver for priority settings in biomedical and health research shall be the **public health need** which is determined by the Number of people with a specific disease, Number of deaths a specific disease causes, Degree of disability a specific disease produces, how much a specific disease shortens the average human lifespan and reduces the quality of life of patients, a specific disease's financial and social costs and Threats posed to others by contagious disease. Therefore, the **unmet public health need** shall be defined as a health need currently not addressed by the **healthcare** systems for availability, affordability or accessibility reasons, for example where there is no **effective and efficient** satisfactory method of prevention, diagnosis or treatment for a given public health challenge (both communicable and non-communicable diseases) or health condition.

This may include but are not limited to:

- a) Transversal approaches towards a better disease prevention, diagnostics and treatments such as Predictive medicine (*in silico* medicine), Systems medicine and Regenerative medicine
- b) Development and pilot experiments of technologies to make healthcare systems more efficient, affordable and sustainable such as Artificial Intelligence (e.g. machine learning in diagnostics and decision support tools) and other health related (bio)technologies (e.g. digital, laser, monitoring, diagnostics, images, signals, medical information processing technologies), treatments at home (e.g. adaptation of routes of administration, e-health systems).
- c) Intervention areas focused on target groups not effectively covered by existing research results such as women, paediatric population or elderly health
- d) Biomedical research areas not well-covered by existing European programmes such as immunology, infectiology research or environmental health (effects of climate change on health)
- e) Or research and innovation areas covered by existing European Partnerships that might finish and could continue under the framework of ERA4Health or other European Partnerships whose combination with ERA4Health would give an added value to the pursued results (e.g. higher TRL levels for projects thematically related to other partnerships) or because of the urgency of response (e.g. to new health threats).

6. Responsible Research & Innovation and other cross-cutting issues

Responsible research and innovation (RRI) is an approach that anticipates and assesses potential implications and societal expectations with regard to research and innovation, with the aim to foster the design of inclusive and sustainable research and innovation to ensure a true societal impact.

RRI implies that societal actors (researchers, health care systems, citizens, policy makers, industry, third sector organisations, etc.) work together during the whole research and innovation process in order to better align both the process and its outcomes with the values, needs and expectations of society.

As the involvement of societal groups is essential in RRI it is often connected to co-creation, co-design and co-production – methodologies in which R&I projects are structured to include stakeholders from the outset (e.g. users or interest groups) – and is related to the general Open Science agenda. RRI can also involve interdisciplinarity, with the inclusion of expertise from the social sciences and humanities (SSH). Being inclusive also implies taking diversity seriously.

Implementation of RRI in ERA4Health:

Taking an RRI approach implies to take actions that may include to:

- a) Anticipate the future known and unknown risks associated with a science or technology;
- b) Include a broad range of stakeholders in the development of science and technologies;
- c) Reflect on the underlying assumptions and values driving a scientific research project; and
- d) Respond to these processes by incorporating their outcomes into the design of research projects and funding programmes.

Implementing and developing RRI is a key action of the ERA4Health Partnership objectives. RRI actions will be promoted via integrated actions that for example promote cross-cutting training of relevant stakeholders and institutional change, to foster the uptake of the RRI approach by stakeholders and institutions. In many cases, inter- and transdisciplinary solutions will have to be developed, which cut across the multiple specific objectives of ERA4Health. RRI is closely related to other cross-cutting issues mentioned below, and actions can be taken that address both RRI and other important values, such as public/user engagement, open science or ethical assessments.

6.1 Foster citizen and patient involvement – engage society more broadly in research and innovation activities

One of the main aims of the ERA4Health partnership is the inclusion and strengthening of the patients' and end-users' perspectives during the drafting of this SRIA in a co-creation process and beyond that when drafting annual work plan, scoping call topics, implementing research and other additional activities.

Implementation of citizen and patient involvement in ERA4Health:

- a) The broad involvement of the society in the research and innovation activities of ERA4Health include: Representatives of previously identified relevant stakeholder groups and societal

actors have been consulted during the drafting process of this SRIA to support the identification and prioritization of the most relevant research questions

- b) Citizens, patients and patients' associations will also be consulted and engaged during the implementation of this SRIA via the annual work plan so that the partnership can better respond to societal needs and policy needs.

This might foster more innovative research ideas and will improve the "fit to purpose" of research. Continuous citizen and patient involvement will lead to more evidence-based policy making through better societal acceptance and thus create a higher impact of research. Also, from the economic perspective the engagement of relevant societal actors will help more research outcomes to be taken up and this will ultimately lead to a better value for money of the invested funding budgets.

6.2 Increase capacity building – promote formal and informal science education

Building capacities within the research community and clinical hospitals, in particular in conducting IICS at European scale, and developing innovative ways of connecting science to society is a priority in ERA4Health. This will help to make science more attractive to young people, increase society's appetite for innovation, improve science and technology-literacy in our society and open up further research and innovation activities. In addition, promoting capacity building is key in improving the perspectives of young women and men for a professional scientific career all over Europe and to improve the competitiveness of the European Research Area and its scientific community.

Implementation of capacity building in ERA4Health:

Investing in health research and capacity building is key for the success of ERA4Health and will be targeted by:

- a) Providing a platform that coordinates all relevant stakeholders at national and regional level, the promotion of biomedical research and its application in health and care, enhancing the networking and connection of (clinical) research capacities.
- b) Promotion of tools and organization of networking events to help building connection between research communities (e.g. through Partner Search Tool for calls, etc.).
- c) Research consortia to be funded under ERA4Health will be encouraged to include capacity Building programmes in their research proposals/work plans.
- d) Providing training to the research stakeholders on crossed section issues as for example data management, patient engagement or regulatory affairs.
- e) Developing formal and informal science education teaching and learning to raise children's and youth's awareness of and interest in the different aspects encompassing science and technology in today's society.

6.3 Ensure gender equality

The ERA4Health Partnership is committed to promoting gender equality in research and innovation and will tackle this on two levels – during the research process for those conducting the research and also when defining research objectives and investigating gender differences in the study subjects.

It is part of the European Commission Gender Equality Strategy¹⁵ for 2020-2025, which sets out the Commission's broader commitment to equality across all EU policies.

Because of the peculiarities of the research sector, many structural barriers to gender equality in research and innovation persist, and specific action is needed to overcome persisting gender gaps.

Implementation of gender balance in ERA4HEALTH:

In alignment with Horizon Europe, three objectives underpin the strategy on gender equality in ERA4Health:

- a) Fostering gender balance in research teams, in order to close the gaps in the participation of women and to make sure that all relevant voices are being heard during the entire R&I process.
- b) Ensuring gender balance in decision-making and advisory groups.
- c) Integrating the gender dimension in research and innovation (R&I) content, helps improve the scientific quality and societal relevance of the produced knowledge, technology and/or innovation.
- d) A broader spectrum of gender diversity will be considered.

Expected impact:

- Increase the participation of women in research, improve their careers and achieve gender balance in decision making,
- Increase the scientific quality and societal relevance of produced knowledge, technologies and innovations by integrating an in-depth understanding of both genders' needs, behaviours and attitudes. It also contributes to the production of goods and services better suited to potential markets.

6.4 Conduct ethical research

Ethical research conduct implies the application of fundamental ethical principles and legislation to scientific research in all possible domains of research.

For all activities funded by ERA4Health Partnership, aligned with the European Union objectives¹⁶, ethics will be an integral part of research from beginning to end, and ethical compliance is seen as pivotal to achieve real research excellence. There is a clear need to make a thorough ethical evaluation from the conceptual stage of the proposal not only to respect the legal framework but also to enhance the quality of the research. An Ethical Assessment procedure will be implemented to ensure that all project funded will comply with all concerned ethical requirements.

Implementation of Ethics issues in ERA4Health:

In addition to the scientific evaluation focusing on the scientific merit, the quality of the management and the potential impact, the Ethics Assessment will ensure that all research activities carried out under the ERA4Health are conducted in compliance with fundamental ethical principles.

There are two types of ethics requirements that will be considered for the Ethical Assessment:

¹⁵ https://ec.europa.eu/info/policies/justice-and-fundamental-rights/gender-equality/gender-equality-strategy_en

¹⁶ <https://ec.europa.eu/programmes/horizon2020/en/h2020-section/ethics>

- during grant preparation
- during the ongoing project

6.5 Promote open access and data management & sharing – increase access to scientific results

Open Access (OA) can be defined as the practice of providing on-line access to scientific information that is free of charge to the user and that is re-usable. It is now widely recognised that making research results more accessible to all contributes to better and more efficient science, and to innovation in the public and private sectors.

The Open Science Policy¹⁷ of the European Commission defined two high level ambitions for OA:

- all peer reviewed scientific publications are freely accessible.
- FAIR data sharing is the default for scientific research.

Implementation of Open Access and Data Management in ERA4Health:

ERA4Health is aligned with the European Commission objectives and will promote and increase open access research, specifically in its funding programmes, and will guide researchers on how to implement it properly.

Open access to scientific information in research and innovation refers to two main categories:

- Peer-reviewed scientific publications (primarily research articles published in academic journals).
- Scientific research data and data management plan: data and metadata underlying publications and/or other data (such as curated but unpublished datasets or raw data). In particular, a commitment will be requested from investigators to share the patient-level clinical trial data in compliance with data protection regulations.

In addition, all information and documents being developed within this partnership, including annual work plans, Standard Operational Procedures and other documents will be made available through the Intranet. Data generated by the Partnership will be stored in a centralized data platform and made available to the public.

6.6 Enlarge communication and dissemination strategies

From the very start, the ERA4Health Partnership will set-up a range of activities to provide high visibility of the activities and impacts of the Partnership. The transparent communication and targeted dissemination of the research outcomes, in particular to decision makers, health professionals and patients, and the general public is an important success factor for this partnership. Therefore, the needs of the different stakeholder groups will be addressed with targeted strategies and communication products to improve the outreach of the partnership. A devoted strategy will be

¹⁷ https://ec.europa.eu/info/research-and-innovation/strategy/strategy-2020-2024/our-digital-future/open-science_en#the-eus-open-science-policy

developed at the level of the Partnership itself to ensure that its main outputs and impacts are known, widely disseminated, and easily accessible.

Implementation of communication and dissemination strategies in ERA4Health:

Communication and information sharing is a key success factor in achieving the goals of the Partnership and will be promoted as follows:

- a) One part of the communication and dissemination strategy is to foster the policy science-dialogue. This could be facilitated by developing specific materials, or to support activities to promote interactions between the funded projects and relevant stakeholders and policy makers to disseminate the academic or societally relevant outputs of the funded projects.
- b) Another important ambition of ERA4Health is to provide the citizens with comprehensive insights and information and educating them about science and innovation.
- c) The research projects funded along with the Third Parties and the stakeholders engaged will be asked to actively contribute to result dissemination.
- d) A web platform acting as a “ERA lighthouse” for Biomedical and Health Research will be put in place to highlight the positive results and impacts of the Partnership for researchers and research performance organisations, health and care systems, private sector, policy makers, media and citizens.

Communication with policy makers, stakeholders, the scientific community and the general public will be two-way, with partners both providing and requesting information. The Partnership will provide support and advice to the projects it will fund to improve their capacity to engage stakeholders, to produce policy briefs, to develop data management plans, etc.

6.7 Facilitate uptake of research results and translation of research results into praxis

The translation of research results, from bench to bedside, to foster innovation and smart specialization is vital to deliver the vision of ERA4Health and to ensure the industrial competitiveness of all countries in Europe. In Health, there is a strong need to improve the implementation of existing services, technologies and digital solutions in clinical practices and point of care as well as developing new ones in a cost-effective way. It is necessary to make and maintain the bridge between the triad of researchers, enterprises and end-users including professional care and citizens. However, new regulatory requirements and changing framework conditions as well as non-regulatory barriers, the consequences of globalization and financial crises are major challenges for enterprises in particular SMEs being particularly vulnerable to these challenges due to their limited resources. In addition, the lack of end-users' inclusion into the strategic orientation and the development of the innovation is also limiting the uptake of research results.

Aligned with the EU priority “A Europe fit for the digital age” ERA4Health pretends to encourage and develop new technologies, while at the same time making sure end-users trust.

Implementation of translation of research results in ERA4Health:

In order to facilitate the uptake of research results and translation of research results into praxis ERA4Health will:

- a) gain a better understanding of system's needs by spinoffs, start-ups, SMEs and end-users/patients.
- b) seek to guide and exchange with health actors and patients on the use of new digital management and technologies.
- c) strengthen and better involve health administrations and local/regional ecosystems to facilitate uptake of innovation and generate innovation-based growth.
- d) put an increased focus and understanding of intellectual property and regulatory requirements in research as foundation for realizing innovations.

With these measures the mutual understanding between industry, academia and regulatory bodies will be facilitated to improve the collaboration between the three domains, overcome innovation hurdles and thus to achieve more impact of research investments within ERA4Health.

7. Develop a framework for implementation of IICS

The new EU Clinical Trials Regulation¹⁸ that is already in force and will be applied from 31 January 2022 promotes important changes to make Europe more attractive for clinical trials. As a new concept, it also introduces low-intervention clinical trials (e.g. pragmatic trials to optimise treatment) with risk-proportionate regulatory requirements that needs public support since no commercial interest exist.

Phase 1 of ERA4Health will pilot the possibility to carry out joint calls on multinational IICS and establish procedures to implement IISC transnational calls allowing the funding of IISCs taking into account the above description criteria.

Designing a robust, feasible and successful clinical study affront a number of hurdles and challenges that ERA4health aims to address.

ERA4Health will provide support and advice for an adequate level of site management and monitoring in order to facilitate the effective recruitment, treatment, and retention of patients while maintaining regulatory compliance, protocol adherence, subject rights protection, subject safety, and general management of assessed and recruited individuals. Support for grantees including best trial design and implementation plan will be applied.

The following areas might need attention when designing a clinical study:

- a. budget optimisation
- b. compliance with Good Clinical Practice and national / EU regulations
- c. Quality management system development
- d. patient involvement
- e. compliance with timelines for approval by competent authorities and ethics committees

¹⁸ https://ec.europa.eu/health/sites/default/files/files/eudralex/vol-1/reg_2014_536/reg_2014_536_en.pdf

- f. trial monitoring strategy
- g. vigilance reporting
- h. data capture, data management and data sharing
- i. GMP manufacturing, placebo, blinding
- j. country selection strategy
- k. site and investigator selection strategy, use of objective decision-supporting tools, mitigation measures (closure or activation of sites)
- l. capacity for contracting with investigation sites, and for contracting with service providers - provisions for insurance / indemnification
- m. cost evaluation and financial management of the study

The support should confer to generation of the highest level of scientific evidence in response to specific scientific questions that should contribute to support of the public healthcare systems.

8. Link with other Partnerships and relevant EU programmes

Creating synergies with other related initiatives is essential to avoid the overlapping and duplication of national and EU research funding and complement each other to cover all the needs and demands currently existing in the society in the health area. At the same time, harmonisation of good practices on the cross-section issues should be also pursued.

ERA4Health Partnership will actively promote synergies and collaboration with other key initiatives at European level, namely other EU Funding Programmes, Clusters, Missions and other Partnerships.

The areas for collaboration have been identified according to the nature and aim of each specific initiative:

- **EU funding programmes:** based on EU policies that will help define a relevant approach within each specific area and research priorities.
- **ERANETs/Joint Programming Initiatives (JPI)/European Joint Programme (EJP)/Partnerships:** close collaboration will be promoted with these initiatives in terms of peer-learning and research priorities selection. For each annual programme elaborated by ERA4Health, a deep analysis and exchange of information will be carried out to avoid doubled funding. Besides that, an analysis of complementarities among funded projects will be carried out to foster connections among the consortia funded.
- **Other EU funding instruments:** information on complementarities with research priorities will be exchange to avoid duplications.
- **EU co-funding instruments:** promotion of regional/national complementarities with EU co-funding instruments to leverage EU funding.
- **European Research Infrastructures:** the existing EU Health research infrastructures are a key element for building a European Research Area for Health research offering facilities that provide resources and services for the research communities to conduct research and foster innovation in their fields.

A deep analysis to assess potential similarities with the research agendas of the EU initiatives listed below, and others new, and to avoid double funding, will be carried out by ERA4Health at the time of the elaboration of each Annual Work Plan. The synergies and potential joint activities below have been identified with the information available at the time of publication of ERA4Health SRIA and may be revised as for example to incorporate the actions of the future Horizon Europe work programmes and of new initiatives or instruments.

List of key European initiatives identified

Type of Initiative	EU Initiative	Synergies and potential joint activities identified
EU Funding Programmes	EU4HEALTH	<p>Topics within the work programme related to ERA4Health priority areas are:</p> <ul style="list-style-type: none"> ● Support to coordinated and expedited assessment of clinical trials for COVID-19 therapeutics. ● Implementation of best practices and research results on prevention of non-communicable diseases and risk factors. ● Action grants for the initiative ‘HealthyLifestyle4All’: promotion of healthy lifestyles. ● Improving access to healthcare and effectiveness of health coverage, taking into account vulnerabilities of specific groups and targeted intervention. ● Substances of human origin (SoHO) - Increase resilience, ensure continuity of supply and access to safe and high quality therapies, in particular in times of crisis. ● Safety assessment cooperation and facilitated conduct of clinical trials.
	Horizon Europe - Cluster 1	<p>Topics within work programme 2021-2022 related to ERA4Health priority areas are included in Challenges 1, 3, 4 and 5:</p> <ul style="list-style-type: none"> ● Healthy Citizens 2.0 - Supporting digital empowerment and health literacy of citizens. ● A roadmap for personalised prevention. ● Trustworthy artificial intelligence (AI) tools to predict the risk of chronic non-communicable diseases and/or their progression. ● Prevention of obesity throughout the life course. ● Personalised blueprint of chronic inflammation in health-to-disease transition ● Clinical validation of artificial intelligence (AI) solutions for treatment and care. ● Pre-clinical development of the next generation of immunotherapies for diseases or disorders with unmet medical needs. ● Development of new effective therapies for rare diseases.

		<ul style="list-style-type: none"> ● Non-communicable diseases risk reduction in adolescence and youth (Global Alliance for Chronic Diseases - GACD). ● Enhancing quality of care and patient safety ● Data-driven decision-support tools for better health care delivery and policy-making ● Smart medical devices and their surgical implantation for use in resource-constrained settings. ● Next generation advanced therapies to treat highly prevalent and high burden diseases with unmet medical needs. ● Optimising effectiveness in patients of existing prescription drugs for major diseases (except cancer) with the use of biomarkers. ● Computational models for new patient stratification strategies.
	Horizon Europe - Cluster 6	<p>Topics within work programme 2021-2022 related to ERA4Health priority areas:</p> <ul style="list-style-type: none"> ● Filling knowledge gaps on the nutritional, safety, allergenicity and environmental assessment of alternative proteins and dietary shift. ● Microbes for healthy and sustainable food and diets. ● Transition to healthy and sustainable dietary behaviour. ● Increasing the transparency of EU food systems to boost health, sustainability and safety of products, processes and diets. ● Developing nature-based therapy for health and well-being. ● Food and health nexus in the context of transformative change.
ERANETs/Joint Programming Initiatives	ERA-CVD	<ul style="list-style-type: none"> ● Supporting of actions based on cardiovascular disease prevention strategies: new ways to sustain a healthy lifestyle in the long term, earlier recognition of cardiovascular disease, better assessment of the personal risk of cardiovascular disease. ● Supporting of actions based on disease treatment and management: personalised treatment and management of cardiovascular disease, effective treatment of stroke, treatment of chronic heart failure and atrial fibrillation, improved application of implantable devices, the interaction between CVD and other disorders, repair of the heart and blood vessels, cardiovascular disease in segmented, yet underrepresented populations. ● Living with chronic cardiovascular diseases: living with a congenital heart defect, psychosocial wellbeing in patients with cardiovascular disease, guidance and care at the

		<p>end of life phase of cardiovascular disease patients.</p> <ul style="list-style-type: none"> ●Peer-learning on management and implementation of the governance of the ERANET.
	JPI-HDHL	<ul style="list-style-type: none"> ●The continuation of the JPI-HDHL will be carried out partly throughout ERA4Health and potential call topics have already been identified in the JPI HDHL Strategic Research Agenda covering all three research areas: ●Peer-learning on management and implementation of the governance of the ERANET ●Sharing best practice examples for the implementation of Knowledge Hubs as an alternative funding instrument ●Topics already funded will be considered and ERA4Health will continue its priorities. ●JPI HDHL can act as a bridge to connect societal challenges related to nutrition and health (covered by ERA4Health) and the environmental effects of diets (covered by Food Systems Partnership).
	EuroNanoMed/ETP on Nanomedicine	<ul style="list-style-type: none"> ●The SRIA elaborated on nanomedicine (2016-2030) by the ETP on Nanomedicine (and the ERANET EuroNanoMed has been included in the SRIA of ERA4Health in order to take advantage of the valuable input gathered from international experts. ●Topics from previous years will be considered to avoid funding the same research lines or repeat any topic if duly justified. ●Peer-learning on management and implementation of the governance implemented within the ERANET. ●Organisation of training activities on nanomedicine regulatory affairs
	TRANSCAN-3	<ul style="list-style-type: none"> ●Analysis of research priorities already funded by the ERANET. ●Sharing expertise in clinical trials. ●Peer-learning on management and implementation of the governance of the ERANET.
Partnerships	Rare Diseases (as well as EJP Rare Diseases)	<ul style="list-style-type: none"> ●Objectives related to ERA4Health: develop the ecosystem for discovery research and development of new diagnostic tools and therapies for rare diseases providing an efficient and effective "pipeline" from research to healthcare to ensure that research and innovation results are reaching the patients as quickly as possible and that healthcare needs can better feed into research prioritisation.

	<ul style="list-style-type: none"> ● Analysis of research priorities for IICS. ● SRIA of this Partnership will be reviewed to align the topics included in each ERA4Health work plan.
Sustainable Food Systems	<ul style="list-style-type: none"> ● Synergies regarding the societal transition towards healthy and sustainable diets for all and tackling all forms of malnutrition as well as Food preferences ● Broader perspective on the Food System, connecting the health aspects of nutrition to environmental sustainability aspects ● Health implications of Food processing and technology
Transforming Health Care Systems Partnership	<ul style="list-style-type: none"> ● Review of common research priorities to complement and create connections among projects funded. ● Peer-learning on management and implementation of the governance of the Partnership.
Personalised Medicine	<ul style="list-style-type: none"> ● Objectives related to ERA4Health: it concentrates on diagnostics, patient stratification and personalised treatment, to move towards disease prediction and prevention. ● Areas related to ERA4Health: public health, data science, clinical, biomedical and regulatory science. ● Analysis of research priorities for IICS. ● SRIA of this Partnership will be reviewed to align the topics included in each ERA4Health work plan.
One Health/AMR	<ul style="list-style-type: none"> ● Review of common research priorities to complement and create synergies between calls and funded Projects. ● Areas related to ERA4Health: public health, foodborne diseases, linking food systems, population and planetary Health. ● Analysis of research priorities for IICS.
Pandemic Preparedness	<ul style="list-style-type: none"> ● ERA4Health funded projects will contribute to more resilient healthcare interventions for the society to get better grounds in case of new pandemics. ● ERA4Health will provide peer-learning on the management and implementation of the government of the Partnership.
Innovative Health Initiative	<p>Objectives already identified in the SRIA of IHI:</p> <ul style="list-style-type: none"> ● Contribute towards a better understanding of the determinants of health and priority disease areas. ● Integrate fragmented health R&I efforts bringing together health industry sectors and other stakeholders, focusing on unmet public health

		<p>needs, to enable the development of tools, data, platforms, technologies and processes for improved prediction, prevention, interception, diagnosis, treatment and management of diseases, meeting the needs of end-users.</p> <ul style="list-style-type: none"> ● Demonstrate the feasibility of people-centred, integrated health care solutions. ● Enable the development of new and improved methodologies and models for a comprehensive assessment of the added value of innovative and integrated health care solutions. ● Sharing knowledge on the private sector. ● Sharing knowledge on medical regulatory affairs.
Other EU Funding Instruments	Global Alliance for Chronic Diseases	<ul style="list-style-type: none"> ● Analysis of related research priorities and sharing of research strategy to avoid duplicities. ● Analysis of funded projects to search for synergies among them.
	INTERREG	<ul style="list-style-type: none"> ● Linked priorities are: Axis 1-Research and Innovation. Objective 1B1-Strengthen the synergic and networked operation on R&D&i at a transnational level in the specific sectors of the South East from Smart Specialization. Sector-Biotechnology and Health. ● Strategic projects addressed to: development of collaborative platforms among regions, enhancing European Innovation Associations and European Technology Platforms, development of technology transfer models. ● Analysis of projects related to the research priority areas of ERA4Health to assess regional initiatives that can may contribute to ERA4Health sustainability and continuation of funded projects.
	Cancer Mission	<ul style="list-style-type: none"> ● Sharing of policy strategies identified in the Mission to be aligned.
EU Co-funding Instruments	European Regional Development Fund (ERDF)	<ul style="list-style-type: none"> ● Supporting of the deployment of initiatives aimed at strengthening research, technological development and innovation in health-related areas. ● Co-funding of ERA4Health projects within the regions with linked areas in S3.
	European Social Fund Plus (ESF+)	<ul style="list-style-type: none"> ● Investing in the implementation of education, training and lifelong learning initiatives addressed to young researchers and capacity building.
EU Research Infrastructures	European Clinical Research Infrastructure Network (ECRIN-ERIC)	<p>Links scientific partners and networks across Europe to facilitate multinational clinical research Provide sponsors and investigators with advice, management services and tools to overcome hurdles to multinational trials and enhance collaboration.</p>

		<ul style="list-style-type: none"> ● Collaboration with ECRIN has been initiated for the elaboration of the ERA4Health SRIA. Active part in the actions related to clinical trials will be kept during the execution of ERA4Health. ● Joint workshops will be promoted to promote ECRIN throughout the research community and to improve actions related to clinical trials.
	European Research Infrastructure for Biobanking and Biomolecular Resources (BBMRI-ERIC)	<p>Offers biobanking human biosamples and manage linked to clinical data. Bring together all the main players from the biobanking field – researchers, biobankers, industry, and patients – to boost biomedical research.</p> <ul style="list-style-type: none"> ● BBMRI-ERIC will be promoted among the research community to receive: quality management services, support with ethical, legal and societal issues, and a number of online tools and software solutions for new treatments.
	Life-Science Infrastructure for Biological Information (ELIXIR)	<p>Holds life science data archives and bioinformatics tools</p> <ul style="list-style-type: none"> ● The use of ELIXIR will be promoted by ERA4Health to enable users in academia and industry to access services and bioinformatics resources that are vital for their research.
	European Infrastructure of Open Screening Platforms for Chemical Biology (EU-Openscreen-ERIC)	<p>Offers high-throughput screening of biochemical compounds for medical use.</p> <ul style="list-style-type: none"> ● EU-Openscreen-ERIC will be promoted for the researchers to use its facilities and get access to cutting-edge technologies to develop their own tool compounds.
	European Infrastructure for Translational medicine (EATRIS-ERIC)	<p>Facilitates advancing medical innovations to the market and into the clinics.</p> <ul style="list-style-type: none"> ● It will be promoted by ERA4Health for the researchers to have access to resources and services to translate scientific discoveries into benefits for patients by means of clinical, biological and technological expertise.

And finally other projects and initiatives, especially the ones that support clinical studies:

- a) EU funded Coordination and Support Action STARS¹⁹ - Strengthening Training of Academia - which is an ongoing Program aiming to develop capacities of Academia Regulatory Science (CSA STARS) to conduct IICS.
- b) The European University Hospital Alliance (EUHA)²⁰.
- c) ECRAID²¹ offers a single point of access to a pan-European clinical research network of infectious diseases

¹⁹ <https://www.csa-stars.eu/>

²⁰ <https://www.euhalliance.eu/>

²¹ <https://www.ecraid.eu/>

- d) PedCRIN, The Paediatric Clinical Research Infrastructure Network²².
- e) Connect 4 Children²³, is a large collaborative European network that aims to facilitate the development of new drugs and other therapies for the entire paediatric population.
- f) PERMIT, develop recommendations for robust and reproducible personalised medicine research including clinical research²⁴.
- g) EU-PEARL, Patient- cEntric clinicAl tRial pLatform²⁵.

9. Measuring progress – Key Performance Indicators

The progress of the European Partnership “Fostering an ERA for Health” towards reaching the specific objectives presented in this SRIA will be monitored by the Partnership members and the European Commission, along with the Health Configuration of the Horizon Europe Programme Committee and Strategic Advisory Board, in order to implement the necessary adjustments to our activities and to the SRIA itself. The proposed indicators follow the recommendations of the EC. They are quantitative, qualitative and some would include anecdotal evidence.

Indicators of performance that might be used to assess Partnership objectives, activities and outputs:

Specific Objectives	Activities	Outputs	KPI
Support biomedical research including clinical fields and intervention areas	<p>Robust Governance and decision making process</p> <p>Facilitate the interaction of stakeholders, knowledge exchange, open access and sharing research results</p> <p>Launching joint call for projects</p>	<p>Identification of priorities</p> <p>Alignment of research priorities</p> <p>Joint Transnational research projects portfolio</p> <p>National funding devoted to collaborative research</p>	<p>1. Adoption of AWP</p> <p>2. Number of projects funded</p> <p>3. Financial contributions, committed and actual</p>

²² <https://ecrin.org/projects/pedcrin>

²³ <https://connect4children.org/>

²⁴ <https://permit-eu.org/>

²⁵ <https://eu-pearl.eu/>

Improve the utilisation of existing health technologies in clinical practice	Build the supporting framework to overcome challenges in implementing IICS Launching calls for IICS	Adequate framework and capacities for performing multinational IICS Multinational IICS portfolio	4. Number of Investigators receiving support 5. Number of IICS funded 6. Financial contribution
Build capacity, in particular in conducting IICS at European scale	Share information and best practices Establish links with relevant stakeholders (European Research Infrastructures and others) Support to Early Career Scientists (ECS)	Reduce fragmentation and create synergies with stakeholders ECS involvement in transnational projects and IICS	7. Activities with stakeholders 8. Number of ECS schemes implemented 9. Number of ECS in funded projects
Implement, promote and develop RRI and other cross-cutting issues	Include inclusive and anticipatory assessment of societal or environmental issues Implement ethical assessment Involve citizens (including patients) in E4H activities Promote gender balance at all levels Promote Science education initiatives Include open science measures in calls for projects and IICS Training activities on OA and data sharing	Researchers and Stakeholders are able to respond to socially or environmentally relevant impacts of the research Visibility of the Partnership Research publications, position papers, policy recommendations	10. Number of projects including concrete anticipation of societal or environmental issues with stakeholders 10. % of positive ethical assessments 11. Number of citizens involved in committees/projects/consultations 12. % of women that are Pis/coordinators 13. % of women in review panels/committees 14. % of women as first authors in publications 15. % of projects with educational resource activities 16. % of projects delivering high quality DMP 17. use of existing/common shared databases and repositories 18. No of hits/members in contact lists, press releases, references in media, events, policy conferences, etc.