EUROPEAN COOPERATION IN SCIENCE & TECHNOLOGY

Brussels, 4 June 2019

COST 033/19

DECISION

Subject: **Memorandum of Understanding for the implementation of the COST Action "Network for Research in Vascular Ageing" (VascAgeNet) CA18216**

The COST Member Countries and/or the COST Cooperating State will find attached the Memorandum of Understanding for the COST Action Network for Research in Vascular Ageing approved by the Committee of Senior Officials through written procedure on 4 June 2019.

MEMORANDUM OF UNDERSTANDING

For the implementation of a COST Action designated as

COST Action CA18216
NETWORK FOR RESEARCH IN VASCULAR AGEING (VascAgeNet)

The COST Member Countries and/or the COST Cooperating State, accepting the present Memorandum of Understanding (MoU) wish to undertake joint activities of mutual interest and declare their common intention to participate in the COST Action (the Action), referred to above and described in the Technical Annex of this MoU.

The Action will be carried out in accordance with the set of COST Implementation Rules approved by the Committee of Senior Officials (CSO), or any new document amending or replacing them:

a. “Rules for Participation in and Implementation of COST Activities” (COST 132/14 REV2);
b. “COST Action Proposal Submission, Evaluation, Selection and Approval” (COST 133/14 REV);
c. “COST Action Management, Monitoring and Final Assessment” (COST 134/14 REV2);
d. “COST International Cooperation and Specific Organisations Participation” (COST 135/14 REV).

The main aim and objective of the Action is to The main aim and objective of the Action is to establish a network which will work to refine, harmonise and promote the use of vascular ageing biomarkers, in order to improve clinical practice and to reduce the burden of cardiovascular diseases globally.. This will be achieved through the specific objectives detailed in the Technical Annex.

The economic dimension of the activities carried out under the Action has been estimated, on the basis of information available during the planning of the Action, at EUR 92 million in 2018.

The MoU will enter into force once at least seven (7) COST Member Countries and/or COST Cooperating State have accepted it, and the corresponding Management Committee Members have been appointed, as described in the CSO Decision COST 134/14 REV2.

The COST Action will start from the date of the first Management Committee meeting and shall be implemented for a period of four (4) years, unless an extension is approved by the CSO following the procedure described in the CSO Decision COST 134/14 REV2.

OVERVIEW

Summary
Cardiovascular disease (CVD) is the leading cause of morbidity and mortality worldwide, regardless of gender, ethnicity or income. The concept that vascular age, as opposed to chronological age, is better related to the prognosis of CVD is rapidly evolving. Arterial stiffness is an important component of vascular ageing and a potent CVD risk predictor, and as such is emerging as an appealing therapeutic target. Despite recent technological advances for the measurement of vascular ageing in clinical practice, unmet needs remain including: complexity of use and heterogeneity of approaches, insufficient validation in clinical settings, fragmentation of expertise, and lack of research driven studies regarding treatment and head-to-head comparisons between different techniques.

Therefore, the aim of the COST action is:

To establish a network which will work to refine, harmonise and promote the use of vascular ageing measures, in order to improve clinical practice and to reduce the burden of CVD globally.

This will be achieved by:

- **Refining** the development of novel, easy-to-use technologies for the diagnosis, prevention, treatment and monitoring of vascular aging by cross-talk between industry and scientists using a translational approach and establishing protocols for validation of new technologies.
- **Harmonising** knowledge by initiating a registry to complete clinical validation of the most established surrogate endpoints, including comparisons of techniques, and by initiating peer network driven intervention studies to utilize the multiplicative effect of the network.
- **Promoting** a vascular ageing culture and to propagate the use of technologies and preventative strategies, fostering solutions feasible in low income countries.

Areas of Expertise Relevant for the Action	**Keywords**
● Clinical medicine: Cardiovascular diseases ● Medical engineering: Medical engineering and technology	● Vascular ageing ● Arterial stiffness ● Cardiovascular diseases ● Medical device

Specific Objectives
To achieve the main objective described in this MoU, the following specific objectives shall be accomplished:

Research Coordination
● Identify and refine new technologies for the assessment of vascular ageing.
● Achieve better understanding of the underlying mechanisms of vascular ageing and, thus, advance its clinical relevance.
● Provide new evidence about the pathophysiological mechanisms leading to the development of vascular ageing to be employed for the study on new therapeutic strategies.
● Create a consensus document on existing vascular ageing measurement methods to be used in clinical practice and on identified gaps.
● Create a consensus document on mathematical models to describe cardiovascular hemodynamics.
● Design and implement a concept for a data registry to enable multi-centre research.
● Define innovative big data approaches for the identification of vascular ageing risk factors to be employed for the implementation of prevention and screening programs.
● Facilitate the development of new techniques/devices via validation (e.g., head-to-head comparison)

● Establish priorities for future translational research via the identification and promotion of basic and pre-clinical experimental protocols.
● Promote vascular ageing prevention with a particular focus on end-users (patients), those who interact with them (e.g., specialists working in medical practices, general practitioners, nurses, pharmacists, patient-organisations, journalists), low-income countries and various health care systems.

Capacity Building
● Develop an interdisciplinary collaborative network covering excellence in science and technology across Europe to foster joint research concerning arterial structure, function and physiology to enhance and exchange knowledge and expertise.
● Combine different research fields with start-ups/industry to create a multidisciplinary and translational approach for the achievement of important breakthroughs.
● Offer interdisciplinary opportunities for cooperation between scientists and physicians/clinicians.
● Bring basic research, applied research and industry together, to translate research from bench to bedside.
● Attract the next generation of Early Career Investigators (ECIs) to research in arterial structure and physiology and support their interdisciplinary education through training schools, workshops, conferences, etc.
● Disseminate knowledge and experience resulting from this network by publications (reports and papers), workshops, seminars, a final conference, public awareness days, an easily accessible user-friendly website and social media.
● Proactively involve specific target groups (e.g., ECIs, students from Inclusiveness Target Countries (ITCs)), women, and teams from countries/regions with less capacity in the field of this COST Action.
● Enlarge the network by involving external experts (outside the network) in network activities, i.e., invitation to present talks, lectures and webinars.

TECHNICAL ANNEX

1 S&T EXCELLENCE

1.1 SOUNDNESS OF THE CHALLENGE

1.1.1 DESCRIPTION OF THE STATE-OF-THE-ART

The European Commission has identified demographic change and population aging as one of the grand challenges Europe is facing. Indeed, the number of Europeans aged 65 years and more will almost double over the next 50 years, from 85 million in 2008 to 151 million in 2060. The European Union's healthcare bill for chronic diseases is over 700 Billion Euro, representing 70% of total healthcare costs [1]. Indeed, the gain in life expectancy has been at least until now coupled with a greater number of years lived with disability, contradicting the general hope of "more years - better life".

In 2015, more than 85 million people in Europe were living with a cardiovascular disease (CVD) [2] and global CVD prevalence was approximately 469.5 million [3]. CVD is the leading cause of morbidity and mortality worldwide, regardless of gender, ethnicity or income [4]. It was responsible for an estimated 17.9 million deaths in 2016, representing 31% of all global deaths [5]. In Europe, CVD is responsible for the loss of more than 64 million disability adjusted life years (DALYs) (23% of all DALYs lost) [2].

The concept that vascular age, as opposed to chronological age, is better related to the prognosis of CVD is rapidly evolving, leading to the introduction of "Early Vascular Ageing" (EVA) as an encompassing paradigm [6]. EVA is genetically determined but it is also influenced by CVD risk factors, such as hypertension, diabetes and hypercholesterolaemia, and is modified by several pharmacological and non-pharmacological means, such as nutrition and lifestyle habits [6]. Exposure to cardiovascular risk factors as early as during childhood or even during fetal life promotes the development and accumulation of subclinical vascular changes that directs the individual towards the trajectory of EVA [7].

Arterial stiffness is an important component of vascular ageing and a potent CVD risk predictor and is currently emerging as an appealing therapeutic target. Large artery elasticity (i.e., the inverse of arterial stiffness) is key in an optimally functioning cardiovascular system: the beating heart generates intermittent propulsion of blood and the large elastic arteries convert this into a continuous blood flow to organs according to their needs. As a consequence of the mechanical wear-and-tear of the wall constituents (and in particular the degradation of elastic lamellae) due to the permanent exposure to the oscillating stress of blood pressure, the cushioning (elastic) properties of the aorta are progressively lost over years, resulting in large artery stiffness [8]. Furthermore, on a molecular level, the paradigm of age-related arterial stiffness has been recently shifting from elastin/collagen content to cell- extracellular matrix interactions and vascular smooth muscle cell tone and stiffness as key molecular/cellular determinants of arterial wall stiffness [9]. Additionally to arterial stiffness, the independent prognostic value of central haemodynamics – beyond the traditional brachial blood pressure measurement – has recently been demonstrated in large studies [10]. Therefore, methods for assessing arterial stiffness and central haemodynamics are important in the modern management of CVD, both in terms of risk assessment and definition of therapeutic strategies.

Large artery stiffness is accelerated in the presence of hypertension, as well as other CVD risk factors, and **may represent an integrated marker of their overall burden on the vasculature over time.** Furthermore, arterial stiffness per se is a mechanism inducing cardiac, renal and brain microcirculatory damage, favouring CVD events [11]. Vascular ageing predisposes people to simultaneous damage in multiple organ systems, thus synergistically increasing the risk of multimorbidity and the progression to functional impairment and disability. Associations between arterial stiffness and organ damage have been shown, e.g., for the systemic hemodynamic atherosclerotic syndrome [12], left ventricular hypertrophy [13], cognitive impairment [14,15,16], frailty [17] and chronic kidney disease progression [18].

Many approaches are available to evaluate the different components of vascular ageing in humans. Among these, the most robust and promising biomarkers are those evaluating arterial stiffness and central hemodynamics, but none of them fulfil all of the criteria to be considered a surrogate endpoint as yet [19]. Carotid-to-femoral pulse wave velocity (cfPWV) is currently the gold standard measure for large artery stiffness in a clinical setting. cfPWV, a measure of regional stiffness, is obtained typically

via applanation tonometry by measuring the transit time between arrival of the blood pressure wave at the carotid and femoral arteries. Other transit time-based techniques include Doppler ultrasound, magnetic resonance imaging (MRI), photoplethysmography, ballistocardiography and others. It is also possible to measure stiffness in different arterial segments (i.e., brachial-to-ankle, finger-to-toe, etc.) via a number of different methods or to estimate it at a single site (via oscillometric recording of brachial artery waveform from a brachial pressure cuff). Arterial stiffness can also be quantified locally (e.g., at the carotid artery) using ultrasound echo tracking or MRI [20]. Central haemodynamics can be estimated non-invasively by tonometry or oscillometry, and guidelines for the non-invasive measurement of central haemodynamics have recently been published [10].

With advances in technology, the number of techniques available for evaluating regional and local arterial stiffness and central haemodynamics is increasing. Despite this, only for cfPWV a standardized methodology is available. Unfortunately, cfPWV is a rather complex, user-dependent and expensive measure, thus so far limited to skilled research settings and expert operators. The concordance between different techniques to measure cfPWV and central haemodynamics are poorly understood and validation studies are limited. **Thus, there is an urgent need to refine the methods for measuring vascular ageing.**

Most of the available evidence on the clinical significance of the aforementioned arterial stiffness measurements is related to cfPWV. There is substantial evidence from epidemiological research regarding the predictive value of cfPWV for cardiovascular morbidity and mortality, and also for reclassifying those at intermediate risk [21]. However, most of these studies have used a single method to determine arterial stiffness and thus it is not possible to determine which technique is superior or ready for routine clinical use. In an attempt to harmonise the various techniques, reference values for cfPWV and central blood pressure have been determined in European populations [22,23] but urgently need to be expanded worldwide, in order to appropriately take ethnical differences into account. Furthermore, it is unclear whether improving arterial stiffness and central haemodynamics leads to lower CVD risk. To achieve this, **either large clinical trials or harmonisation of data from observational cohorts through a "big data" approach are needed.** Until this is achieved, the measurement of arterial stiffness and central haemodynamics will not be included in clinical practice or in current guidelines for cardiovascular risk stratification [24].

Detection of early vascular ageing may be useful at all chronological ages, but particularly in young individuals, in order to identify those at elevated CVD risk and in whom more intense preventive strategies may be recommended and implemented [25]. Furthermore, as CVD is more prevalent in low-income countries or ethnic minorities, the use of low-cost, easy-to-use and effective methods for assessing arterial stiffness and haemodynamics in such populations is advisable for reducing CVD risk [26]. **The promotion of arterial stiffness and haemodynamic measures within routine clinical care as well as the use of such measures in low-income countries or in populations with difficult access to health care, may significantly improve the quality of life for many while, at the same time, reducing the financial burden on healthcare systems worldwide.**

1.1.2 DESCRIPTION OF THE CHALLENGE (MAIN AIM)

Despite the technological and scientific advances over the last decades in the utility of arterial stiffness and haemodynamics for routine clinical practice, a number of unmet needs are still present:

- The complexity and heterogeneity of techniques/devices, lack of easy-to-use and cheap techniques/devices to be used in large numbers of subjects, including low-income countries;
- Insufficient validation in clinical settings: while a large body of evidence on vascular biomarkers has been accumulated in the last 30 years, no biomarker fulfils all of the criteria to be considered a surrogate endpoint;
- Fragmentation of expertise in few research labs globally and lack of penetration of new concepts within the wider clinical audience;
- Lack of investigator/research driven intervention studies, especially concerning: 1) the impact of treatment on vascular biomarkers, 2) head-to-head comparisons between different techniques.

Therefore, the main aim of the COST Action VascAgeNet is:

To establish a network which will work to refine, harmonise and promote the use of vascular ageing biomarkers, in order to improve clinical practice and to reduce the burden of CVD globally.

This will be achieved by:

- **Refining (R)** and advancing the development of novel, easy-to-use technologies for the diagnosis, prevention, treatment and monitoring of vascular ageing by cross-talk between applied scientists, start-ups / industry and basic scientists using a translational approach and establishing standardised protocols for validation of new technologies.
- Identifying gaps in, and **harmonising (H)** knowledge by initiating a large registry to complete clinical validation of the most established surrogate endpoints, including head-to-head comparisons of different techniques, and peer-network-driven intervention studies on vascular ageing to utilise the multiplicative effect of the collaboration network.
- **Promoting (P)** a vascular ageing culture and propagating the use of technologies and preventative strategies. Additionally, fostering solutions feasible in high- as well as low-income countries and various health care systems.

The COST Action VascAgeNet is in line with current priorities of the European Commission, including inter-sectoral collaboration, networking and optimising the use of population and patient cohorts at the European level, data sharing, the scaling up of evidence-based innovations and best practice in health promotion, prevention and management of chronic diseases, and new concepts in patient stratification towards personalised and efficient healthcare. The European Commission identified CVD as a key research priority. The objective of the European-funded research on CVD is to advance knowledge that will lead to an improvement in the diagnosis, prevention, treatment and monitoring of CVD. An emphasis is placed on translational CVD research - promoting the translation of basic research findings into clinical applications, using broad multidisciplinary approaches. Moreover, the Action plans to develop additional research proposals within the scope of H2020/Horizon Europe and other future European priorities. Recently, several Members of the European Parliament and the European Chronic Disease Alliance launched a manifesto (http://www.alliancechronicdiseases.org/manifesto/) calling on the European Commission to recognise health as an objective in its own right in its 2019-2024 programme and to further invest in chronic disease prevention and management. One of the four outlined priorities is the need for a European Chronic Disease Awareness Day.

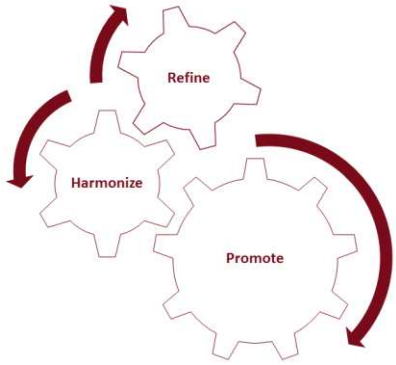

Figure 1: Concept of the COST Action VascAgeNet

1.2 PROGRESS BEYOND THE STATE-OF-THE-ART

1.2.1 APPROACH TO THE CHALLENGE AND PROGRESS BEYOND THE STATE-OF-THE-ART

Table 1 presents the identified challenges and the progress beyond the state-of-the-art of the Action VascAgeNet. The progress to advance the state-of-the-art is related to the specific objectives for refining (R), harmonising (H) and promoting (P) vascular ageing as described in section 1.2.2.

Table 1: Innovation of the VascAgeNet COST Action

State-of-the-Art (SotA)	Unmet needs/identified challenges	How this will be addressed by the COST Action VascAgeNet (Progress beyond SotA)	
The number of techniques for assessing vascular ageing is increasing; however, standard methods are available only for cfPWV, which are complex, user-dependent, limited to skilled research settings and expensive; evidence for other technologies and methods is limited	Complexity of use and heterogeneity of techniques/devices; lack of easy-to-use and cheap techniques/devices to be used in large numbers of subjects, including low-income countries	**Refine**	**Identification and refinement of methods** for measuring vascular ageing by better understanding underlying mechanisms (R1, R2, R3)
Research performed in Europe and worldwide, but mainly independently in specialised research labs	Fragmentation of expertise in research labs in different countries	**Refine/ Harmonise**	Development of an **interdisciplinary network**; combining of research and industry (R4, R5, P6); increase in **cooperation between research and industry** to reach bedside (H8, H9)
Large amount of evidence on vascular biomarkers exists; but none fulfils all the criteria to be considered as a surrogate endpoint	Insufficient validation in clinical settings	**Harmonise**	Development of a **consensus document** on existing methods as a gap analysis and starting point for further developments (H1, H2)
The concordance between different techniques to measure cfPWV is poorly understood; most studies have applied a single method; thus superiority or readiness for routine clinical use cannot be determined	Lack of head-to-head comparisons between different techniques		Design and build a **data registry** to foster big data approaches for **risk prediction models and head-to-head comparisons** (H3, H4, H6)
Currently, evidence of treatment effects on early vascular ageing marker is limited	Lack of investigator/research driven intervention studies		Design a **peer-network-driven intervention study** and establish priorities for further translational research (H5, H7)
Methods for assessing vascular ageing are not yet established in clinical routine practice	Lack of penetration of new concepts within the wider clinical audience	**Promote**	**Spread vascular ageing concepts and methods** to stakeholders, Early Career Investigators (ECIs), and Inclusiveness Target Countries (ITCs) (P3, P4, P5)
CVD is more prevalent in low-income countries and ethnic minorities	Lack of easy-to-use and cheap techniques/devices to be used in large numbers of subjects, including low-income countries		**Promotion of concepts** in low-income countries and various healthcare systems; push **joint funding opportunities** (P1, P2)

This COST Action will build a network that will uniquely bring together stakeholders who have used methods for assessing vascular ageing in various patient groups and studies, with researchers and companies that have developed and can further enhance measurement methods. In general, no cooperation exists in Europe that would be equivalent or similar to this COST Action that entails (i) **formation of an inclusive network of researchers and industry**, and (ii) **systematic collation and interpretation of the largest-ever agglomeration of vascular ageing data** in Europe. These unique and timely resources will enable the most up-to-date, evidence-based consideration of vascular ageing to be included in next generation techniques, screening and treatment guidelines. For the execution of research, the most advanced ICT (Information and Communication Technologies) facilities for sharing and processing of big data will be applied and new media for surveys targeting the most important stakeholders will be used. Artificial intelligence approaches are increasingly employed for big data analysis and represent a valid method for the purpose of the present Action, especially when considering that the era of large clinical trials is moving to an end.

1.2.2 OBJECTIVES

1.2.2.1 Research Coordination Objectives

The main objectives of the COST Action VascAgeNet are to (i) **coordinate European research** on vascular ageing **in an international context**, (ii) **connect and promote knowledge transfer** between the researcher, practitioner and companies, (iii) **coordinate ongoing research in an interdisciplinary** (medical, engineering, business), **inter-country** (more than 20 countries and more than 10 Inclusiveness Target Countries at the time of submission), and **intersectoral** (academic, research, business) **network**, (iv) bring together nationally-funded research projects in a **collaborative pan-European activity**. This COST Action will establish a multidisciplinary network that will:

Refine (R)

- R1. Identify and refine new technologies for the assessment of vascular ageing.
- R2. Achieve better understanding of the underlying mechanisms of vascular ageing and, thus, advance its clinical relevance.
- R3. Provide new evidence about the pathophysiological mechanisms leading to the development of vascular ageing to be employed for the study on new therapeutic strategies.

Harmonise (H)

- H1. Create a consensus document on existing vascular ageing measurement methods to be used in clinical practice and on identified gaps.
- H2. Create a consensus document on mathematical models to describe cardiovascular hemodynamics.
- H3. Design and implement a concept for a data registry to enable multi-centre research.
- H4. Define innovative big data approaches for the identification of vascular ageing risk factors to be employed for the implementation of prevention and screening programs.
- H5. Initiate peer network driven intervention studies on vascular ageing using the multiplicative effect of the network (H5).
- H6. Facilitate the development of new techniques/devices via validation (e.g., head-to-head comparison).
- H7. Establish priorities for future translational research via the identification and promotion of basic and pre-clinical experimental protocols.

Promote (P)

- P1. Promote vascular ageing prevention with a particular focus on end-users (patients), those who interact with them (e.g., specialists working in medical practices, general practitioners, nurses, pharmacists, patient-organisations, journalists), low-income countries and various health care systems.
- P2. Explore the opportunities for coordinated vascular ageing research that corresponds to the Horizon 2020 and FP9 agenda and other under-explored funding schemes.

1.2.2.2 Capacity-building Objectives

The capacity-building objectives of the Action VascAgeNet will help to fulfil the previously reported aims. In particular, they will ensure the **promotion of a vascular ageing culture, spreading the technological advances obtained to all countries**. In order to improve the clinical and social impact

of the vascular ageing concept, the network will foster strategies aiming at scientific societies, governments, health care systems and the research community. This COST Action will, thus, establish a multidisciplinary network that will:

Refine

R4. Develop an interdisciplinary collaborative network covering excellence in science and technology across Europe to foster joint research concerning arterial structure, function and physiology to enhance and exchange knowledge and expertise.
R5. Combine different research fields with start-ups/industry to create a multidisciplinary and translational approach for the achievement of important breakthroughs.

Harmonise

H8. Offer interdisciplinary opportunities for cooperation between scientists and physicians/clinicians.
H9. Bring basic research, applied research and industry together, to translate research from bench to bedside.

Promote

P3. Attract the next generation of Early Career Investigators (ECIs) to research in arterial structure and physiology and support their interdisciplinary education through Training Schools, workshops, conferences, etc.
P4. Disseminate knowledge and experience resulting from this network by publications (reports and papers), workshops, seminars, a final conference, public awareness days, an easily accessible user-friendly website and social media.
P5. Proactively involve specific target groups (e.g., ECIs, students from Inclusiveness Target Countries (ITCs)), women, and teams from countries/regions with less capacity in the field of this COST Action.
P6. Enlarge the network by involving external experts (outside the network) in network activities, i.e., invitation to present talks, lectures and webinars.

ECIs, ITCs and gender under-representation will be addressed through the following mechanisms:

- At least one Working Group (WG) will be led by a participant from an ITC,
- ECIs will hold at least 50% of all management positions; this Action has been initiated by and will mainly be driven by ECIs,
- Network activities such as workshops and seminars, located preferably in ITCs, will specifically include presentations by ECIs (>40%), women (>40%) and colleagues from ITCs with less capacity in the field of this COST Action (>40%),
- ITC Conference Grants for international conferences will be applied for ECIs from ITCs,
- Short-Term Scientific Missions (STSMs): ECIs, researchers from countries/regions with less capacity as well as researchers after parental/career leave will have the opportunity to visit other network groups in STSMs for up to 3 months long,
- Training Schools will be specifically directed at ECIs, teams from countries/regions with less capacity in the field of this Action, students and researchers after parental/career leave,
- This COST Action has the overall aim to ensure significant female participation for the full duration of the Action.

2 NETWORKING EXCELLENCE

2.1 ADDED VALUE OF NETWORKING IN S&T EXCELLENCE

2.1.1 ADDED VALUE IN RELATION TO EXISTING EFFORTS AT EUROPEAN AND/OR INTERNATIONAL LEVEL

Currently, research in the field of vascular ageing (screening, prevention and intervention) is fragmented. Collaborations are investigator-driven and focused on partial aspects of the concept (e.g., physiological background, mathematical models, clinical application). Distinct Working Groups within various societies exist, but they focus on partial aspects (e.g., cardiology or hypertension) and there is no umbrella for joining forces to allow for an effective and widespread implementation of vascular ageing assessment in clinical routine and in the field of public health. Networking opportunities on pan-European level are restricted to an annual conference on arterial structure and physiology and individual initiatives.

The Action VascAgeNet will enable **effective exchange and wider transdisciplinary learning** (both interdisciplinary and intersectoral). Thus, it will open the possibility to exchange knowledge and data from different research studies/projects at European and international level, to jointly develop new ideas and initiatives. This COST Action will connect European and worldwide experts with the next generation of ECIs, actively involved in the development and implementation of technology for vascular ageing assessment. Without the Action, most scientific partners will only have limited funding available for international exchange. Therefore, the Action will enable the exchange of knowledge, joint development of ideas and research projects, data exchange and scientific publications, thereby**, raising research on vascular ageing to a higher level**. Hence, the COST Action VascAgeNet aims to facilitate activities of existing societies in promoting vascular aging by providing an umbrella for joint efforts. As a central goal of the COST framework, the Action VascAgeNet will enable funding to support the inclusion, training, and mobility for exchange of young researchers as well as activities to increase gender equality. The transition of young investigators (women especially) to established researchers will be supported by facilitating their access to leading positions within the COST Action itself. In summary, this COST Action will **foster bottom-up capacity building in Europe, initiate and promote new interdisciplinary and intersectoral research projects in this field and, thus, increase the research communities' access to much-needed funding and state-of-the-art infrastructure.**

2.2 ADDED VALUE OF NETWORKING IN IMPACT

2.2.1 SECURING THE CRITICAL MASS AND EXPERTISE

CVD and vascular ageing are complex disorders, requiring interdisciplinary and intersectoral collaboration to advance understanding. The Action will bring basic and applied research and industry together in an interdisciplinary approach, to translate research from bench to bedside. The required expertise to achieve the defined objectives is accounted for by the **interdisciplinary and intersectoral network** combining medical research and clinical aspects from various disciplines (hypertension, cardiology, nephrology, physiology, etc.), engineering (electrical engineering, mathematics, physics, etc.), hospitals, universities, research organisations and industry (SMEs). Furthermore, the involvement of senior researchers actively driving research in the specific research area for a number of years, will add to the level of expertise. That said, this Action will mainly be driven by ECIs. The balance between senior researchers and next generation ECIs is a promising approach to explore and drive opportunities for coordinated vascular ageing research through excellence in science and technology, transfer of knowledge and high intrinsic motivation to advance the addressed research area. Furthermore, the large network covering at the time of submission **more than 20 countries, more than 60 investigators and multiple representatives from companies will secure the critical mass required for the implementation of the aims of this Action**. The network includes opinion leaders, ECIs, experts from ITCs, as well as experts from international partner countries. In addition, this COST Action will allow for wider promotion of the concept **by involving the main driving forces, by exchanging and pooling most important data sources and by supporting an increase in research activities in ITCs**.

2.2.2 INVOLVEMENT OF STAKEHOLDERS

In the medical domain, the inclusion of concepts and methods in risk management guidelines is of paramount importance for routine clinical practice. Among different available techniques, only cfPWV is mentioned in the European guidelines for the management of arterial hypertension, though not yet recommended for routine practice. This Action provides the opportunity to build further evidence and improve guidelines by bringing fragmented research in this field together to overcome this issue. In the course of this Action, active contribution to different European **guideline committees and societies** (e.g., in the field of cardiology or hypertension) related to vascular ageing and the standardisation of device validation is planned. This can be guaranteed, given that many proposers are actively involved in several concerned committees and societies, and are part of editorial boards of related scientific journals. The COST Action **VascAgeNet** itself will help to promote the concept of vascular ageing further and to pave the way for vascular ageing to be measured in clinical practice.

Industrial partners active in the field of vascular ageing are involved from the very beginning of this Action (i.e., proposal phase) as active participants. Their role will not only be to present their technologies at workshops and Training Schools, but also to discuss these with other investigators in the WGs. Furthermore, their active involvement will help to translate newly created knowledge from bench to bedside in a smooth transition process.

Within the network, more than half of the secondary proposers work in hospitals, indicating that the integration of vascular ageing within national health care systems is already partly occurring, however, there is room for improvement. This will ease the translation of vascular ageing measurement from clinical research into clinical practice. Representatives from various **health care systems and insurers** will be actively involved in workshops and a final conference, especially focusing on the prevention of vascular ageing. Collaboration with such representatives will be one of the main goals of WG5 focused on dissemination and education (described below).

Finally, end-users, **patients**, and the **general public** will be directly involved during public awareness days, which will be held across Europe with special focus on ITCs, and through **patient organisations**, such as the World Stroke Organization and its local counterparts. The events will be synchronised with local and European initiatives, such as the prioritised and outlined European Chronic Disease Awareness Day from the earlier mentioned manifesto of the European Chronic Disease Alliance. Furthermore, direct links to already running awareness activities in **pharmacies** are already established in several European countries, and will be further intensified to ensure the expected outreach.

2.2.3 MUTUAL BENEFITS OF THE INVOLVEMENT OF SECONDARY PROPOSERS FROM NEAR NEIGHBOUR OR INTERNATIONAL PARTNER COUNTRIES OR INTERNATIONAL ORGANISATIONS

CVD and early vascular ageing as well as research thereupon are not restricted to the pan-European area, but are worldwide phenomena. Thus, this COST Action will connect European and international research and excellence for their mutual benefit. Dr. Bart Spronck at Yale University (United States) is one of the leading experts in biomedical engineering focusing on cardiovascular modelling in preclinical as well as clinical research and, thus, will help to translate knowledge from bench to bedside. Prof. James Sharman and Dr. Martin Schultz from the University of Tasmania, Menzies Institute for Medical Research (Australia) have published prominent research articles in this area in the last years and are experts especially regarding validation and accuracy of measurement devices and methods. Prof. Alberto Avolio from Macquarie University (Australia) has extensive experience in cardiovascular dynamics and is expert in bridging the gap between basic science and implementation of methods for clinical use. AtCor Medical (Australia) develops and markets products for the early detection of target organ damage and management of CVD and its technology allows clinical researchers to noninvasively measure central haemodynamics and arterial stiffness. AtCor is market leader for non-invasive assessment of central haemodynamics and arterial stiffness and, thus, an important part of this COST Action.

3 IMPACT

3.1 IMPACT TO SCIENCE, SOCIETY AND COMPETITIVENESS, AND POTENTIAL FOR INNOVATION/BREAK-THROUGHS

3.1.1 SCIENTIFIC, TECHNOLOGICAL, AND/OR SOCIOECONOMIC IMPACTS (INCLUDING POTENTIAL INNOVATIONS AND/OR BREAKTHROUGHS)

Short-term impact

- The development of an interdisciplinary network consisting of members from research and industry that will drive scientific and technological advances and generate breakthroughs (R4, R5).
- The identification of gaps in the current scientific knowledge regarding the measurement of vascular ageing which will allow for scientific developments over the longer-term that will address these gaps (H1, H2).
- In the short-term, participants will extend their knowledge on vascular ageing and multiply it by incorporating it in their teaching and training activities, which could lead, in the near future, to inclusion of the new knowledge in curricula and continuous education in medicine. This may potentially lead longer-term to international master and PhD programs focusing on vascular ageing (P1, P3).

Long-term impact

- Spreading knowledge about early vascular ageing concepts and methods to various stakeholders, ECIs and ITCs, and harmonising knowledge by initiating a large registry to complete clinical validation will have a short-to-long-term impact on the uptake of these technologies and, thus, strengthen (European) medical industry (P3, P4, P5, P6).
- Through enhanced cooperation between research and industry, the increased cross-talk between researchers/clinicians trialling new technologies and industry will create new technologies and efficient translation of knowledge from bench to bedside. This will aid scientific and technological breakthroughs (H8, H9).
- Building a data registry and fostering big data approaches will allow reliable risk prediction models to be created, in order to identify those at increased risk due to early vascular ageing. This will have significant societal impact in terms of reducing the burden of vascular ageing and thereby reducing health care costs. This will also allow for head-to-head comparisons between different techniques measuring vascular ageing and to identify the most reliable techniques which can be applied in routine clinical practice (H3, H4, H6).
- It is currently unknown which biomarker tracks most effectively drug-induced improvements in vascular health. Therefore, by planning a peer network-driven intervention study to assess the effect of different therapies on vascular ageing, this COST Action will have long-term impact in terms of the design of targeted therapies, thus, reducing the burden of early vascular ageing and establishing priorities for further translational research (H3, H5, H7).
- By harmonising and refining techniques for vascular ageing assessment, currently available techniques will be directly comparable in terms of effectiveness, simplicity/complexity of use, accuracy, costs, etc., which allows for a differentiation of applicability at different stages of prevention, diagnosis and therapy. For example, in early screening, less accuracy is needed and focus can be on wide-spread and easy use, whereas in detailed diagnosis (specialist use), high accuracy is required; for therapy monitoring, trends over time might be sufficient but low cost is of importance. These steps will help to spread the techniques in the long-term, lower costs and finally lead to wider routine clinical use (R1, R2, R3, H1, H6, P1).
- By promoting concepts relevant to vascular ageing in low-income countries, this Action will help to reduce the risk related to arterial stiffening and (premature) CVD over the long-term, and will have significant societal impact on the population health as well as the healthcare systems in low-income countries (P1, P2).

3.2 MEASURES TO MAXIMISE IMPACT

3.2.1 KNOWLEDGE CREATION, TRANSFER OF KNOWLEDGE AND CAREER DEVELOPMENT

Knowledge creation

Knowledge creation will be assured by collaboration between the leading experts on vascular ageing. Since research in this area is rather fragmented, **the most important step for promoting the concept of vascular ageing and translating it into clinical practice is the consensus on physiological and technical mechanisms and on techniques for the measurement for vascular ageing.** This will not only help to improve the understanding of the underlying vascular ageing mechanisms, but will be a stepping stone for new innovations. In medicine, robust evidence from research studies is of vital importance to translate concepts and innovation from clinical research into guidelines and clinical practice. As the current evidence is based on different techniques to measure vascular ageing and research settings, one of the main aims of this Action is to harmonise the available knowledge and data. This will be achieved by initiating a common data registry for reusing existing data and strengthening the impact of the evidence for and against specific measurement techniques.

Transfer of knowledge

In the Action VascAgeNet, there will be several ways for transfer of knowledge. Firstly, WG meetings will be scheduled on a regular basis (face-to-face twice a year and monthly using online tele-conferencing tools). Other means for knowledge transfer within, but not restricted to, the network are Short Term Scientific Missions (STSMs; two per year up to 3 months long) and annual Training Schools. This will not only intensify the exchange among ECIs, but also with senior researchers and company representatives. Workshops, seminars, the final conference and the public awareness events will be used for promoting the concept of vascular ageing and the results of this COST Action, **not only to the participants of the COST Action VascAgeNet but also to external stakeholders and the general public**. Preferably, ITCs will host these events to create even more impact by attracting even more ECIs from the host countries.

Career development

The Action will be of great advantage to ECIs' careers. As already mentioned, the Action has been initiated by and will be mainly driven by ECIs. Thus, ECIs will be adequately represented within the network, heavily involved in Working Groups and decision-making (e.g., Action Chair, Scientific Representative, WG Leader, STSM Coordinator, Science Communication Manager). A criterion for taking on leadership positions will be experience in coordination of and/or participation in national and international projects. The active involvement will not only help ECIs to create new connections and joint research proposals/ideas and learn from (senior) experts in the field, but will provide an opportunity for experience in international collaboration and management.

3.2.2 PLAN FOR DISSEMINATION AND/OR EXPLOITATION AND DIALOGUE WITH THE GENERAL PUBLIC OR POLICY

Dissemination for the previously mentioned stakeholders will take place as follows (for details see WG descriptions in section 4.1.1. and Gantt chart in section 4.1.4):

1. For **researchers**, the Action results will be disseminated through:
   - organisation of, and presentation during, conferences and workshops, that will be particularly open to ECIs, practitioners and policy-making communities,
   - workshops and seminars,
   - at least five (open-access) articles in peer-reviewed scientific journals based on the outcomes of WG2-4,
   - one special issue of an international peer-reviewed journal focused on vascular ageing,
   - a minimum of ten scientific publications to be presented at conferences and non-academic briefs/reports based on the outcomes of WG2-4,
   - dedicated pages on the Action website.
2. For **Early Career Investigators**, the Action results will be disseminated through:
   - organisation of Training Schools, STSMs, and thematic/scientific conferences and workshops,
   - a minimum of four (open-access) publications in special journal series, edited volumes, scientific publications and non-academic briefs and reports. These will be based on papers developed in the framework of WGs and Training Schools,
   - contributions of the Action members to national research platforms and graduate schools,
   - involvement and participation in an extended European research network,
   - dedicated pages on the Action website.
3. For **medical doctors, representatives of health care systems and patient organisations/associations** results will be disseminated through:
   - organisation of, and presentation at specific conferences, workshops and the final conference,
   - distribution of research results through a mailing list,
   - publication of information sheets in jargon-free language,
   - teaching material to be used in curricula at universities or continuous education in medicine,
   - dedicated non-specialist pages on the website.
4. For **companies**, the Action results will be disseminated through:
   - participation in WGs,
   - participation in Training Schools,
   - organising specific panels on vascular ageing, during conferences,
   - dedicated pages on the Action website and social media (e.g., Twitter, Facebook, Instagram, blog).
5. For the **general public**, the Action results will be disseminated through:
   - flyers and posters especially addressing non-professionals,
   - two public awareness events,
   - dedicated pages on the Action website and social media (e.g., Twitter, Facebook, Instagram, blog).
6. For general purposes:
   - specific COST Action website with descriptions of research activities, publications and pages as indicated at items 1 to 5 above,
   - a quarterly newsletter of the COST Action Group distributed by email and available on the website and as hard copy,
   - a poster describing this Action for display by all participants.

Exploitation and Intellectual Property Rights

The Action not only aims to harmonise and promote currently available methods and techniques, but also to identify and refine new technologies for the measurement of vascular ageing. This approach will lead to new developments for vascular ageing assessment and thus help to grow the (European) medical industry. The involvement of industry from the very start of the Action will allow for an early uptake of exploitation activities.

A consortium agreement will be put in place that will protect foreground and background knowledge of the partners. A key tool for the knowledge management will be an intellectual property rights directory, which is intended to give an overview of all used background and all results, i.e., foreground, developed within the project. It will be maintained throughout the lifetime of the Action based on an initial version created at the start of the Action and will serve as a basis to prevent conflicts and to facilitate business planning.

4 IMPLEMENTATION

4.1 COHERENCE AND EFFECTIVENESS OF THE WORK PLAN

4.1.1 DESCRIPTION OF WORKING GROUPS, TASKS AND ACTIVITIES

Immediately after the Action starts, the Project Coordinator (Grant Holder) will ensure that a suitable knowledge management system, such as a Microsoft SharePoint, is put in place for ensuring smooth project work. The system will hold all relevant and systematically identified administrative documents (including project meeting minutes, deliverable lists, implementation plan updates) and results. It is the responsibility of the Project Coordinator to ensure all partners are able to access and use this system effectively. The Project Coordinator will also ensure that data protection legislation is followed. Working Group (WG) and joint Management Committee (MC) meetings are scheduled twice a year with intermediate monthly tele-conferences. The WGs and their interactions are graphically illustrated in Figure 2. The WGs and their tasks (T), deliverables (D) and milestones (MS) are detailed in the following sections.

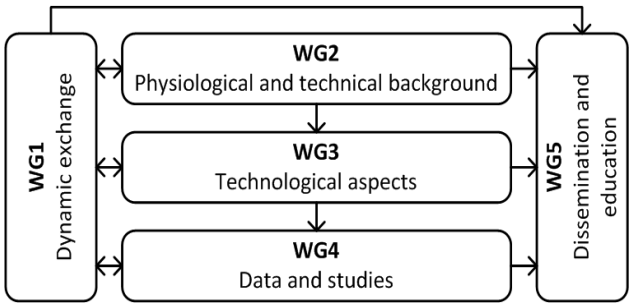

Figure 2: Interactions between Working Groups (WGs)

Working Group 1: Dynamic exchange

Objectives: The objectives of WG1 are (1) to ensure the interdisciplinary collaboration within the network to enhance and exchange knowledge and expertise (R4); (2) to enlarge the network during the course of the COST Action and to build collaborations with external experts (P6); (3) to proactively involve ECIs, ITCs, under-represented gender, etc. (P5); (4) to create a multidisciplinary and translational approach for the achievement of important breakthroughs especially by linking research and industry (R5) and finally; (5) to explore and promote subsequent funding possibilities based on the COST Action's content (P2).

Tasks and deliverables:

T1.1 Coordination of intersectoral and interdisciplinary cross-WG activities (two meetings per year) to ensure knowledge exchange and stimulate inter-topic crosstalk (D1.1 Plan and report on activities; MS1: Action started, MS2: First WGs interim reports done, MS4: Halfway reached, MS9: Final report finished and Action terminated).

T1.2 Activities focused on the enlargement of the Action and involvement of ECIs, ITCs, etc. in close collaboration with WG5, e.g., two STSMs per year for up to 3 months long with focus on ECIs in ITCs (D1.2 Report on activities).
T1.3 Exploration of funding opportunities for coordinated and interdisciplinary vascular ageing research (D1.3 Report on identified opportunities and proposal activities).

Working Group 2: Physiological and technical background – from bench to bedside

Objectives: The activities of WG2 are mainly aimed at **refining** the understanding of the underlying mechanisms of vascular ageing (R2) and the mathematical models used for their assessment (H2), thus advancing their clinical relevance. It will focus on the provision of new evidence concerning the pathophysiological mechanisms leading to the development of (early) vascular ageing (R3), thus enabling the translation of basic and pre-clinical research from bench to bedside (H7, H9).

Tasks and deliverables:

T2.1 To summarise current knowledge on mechanisms of vascular ageing, derived from basic research, and on genetics of vascular ageing, and establish research priorities for integration of novel pathways into the framework of integrative physiology and translation into clinical research (D2.1 Call-for-action document).
T2.2 To reach consensus on the application, differences, interplay, limitations and potential complementarity of different mathematical models and techniques (e.g., wave separation analysis, wave intensity analysis, etc.) used for vascular ageing assessment advancing their potential clinical application (D2.2 Consensus document on mathematical models).
T2.3 To accelerate the translation from bench to bedside by implementing cross-domain activities (involving basic scientists, vascular physiologists, clinical researchers pharmacologists, pharmaceutical companies) to identify future targets for treatments concerning vascular ageing (D2.3 Report on activities).

Working Group 3: Technological aspects – supporting technology breakthroughs

Objectives: The activities of WG3 are mainly aimed at performing technological breakthroughs in standardizing, **refining** and **harmonising** (R1, H1) of existing and new technological approaches for the assessment of vascular ageing. An important aspect will be the validation and head-to-head comparison of new techniques and devices (H6).

Tasks and deliverables:

T3.1 Harmonisation and standardisation of existing techniques for vascular ageing assessment in order to propose a consensus document to be used in clinical practice and for the validation of new techniques (D3.1 Consensus document on vascular ageing technologies).
T3.2 Creation of a framework to support the development and validation of innovative techniques (D3.2 Report on framework; MS5: Framework created).
T3.3 Translation of vascular ageing approaches from research to industry (D3.3 Report on translational activities).
T3.4 Identify gaps for application in routine clinical practice of techniques evaluating vascular ageing, by launching a large-scale survey among clinicians, both specialists (especially in cardiology, nephrology, internal medicine, vascular medicine, neurology) and general practitioners (D3.4 Report summarizing survey results and implications).
T3.5 Provide an effectiveness analysis for the preventative strategies based on vascular ageing assessment compared to already establised care (D3.5 Effectiveness analysis).

Working Group 4: Data and research studies – big data approaches

Objectives: The activities of WG4 are mainly aimed at creating a big data registry for **harmonising** available data and studies for enabling multicentre research initiatives (H3). The work will also be aimed at identifying new risk factors for vascular ageing by means of big data approaches (H4) and at promoting interventional studies using the networking and data power obtained creating the big data registry (H5).

Tasks and deliverables:

T4.1 Design and implement a concept for the creation of a large and comprehensive data registry identifying appropriate strategies for data collection and management, as well as methods for assuring high data quality and including clearance from an ethical committee (D4.1 Concept for data registry; MS6: Registry set up).
T4.2 Define and implement big data approaches to be deployed in the registry for providing new interpretation of the data (D4.2 Overview on big data approaches for the registry, D4.3 Report on newly identified vascular ageing risk factors to be employed in screening).
T4.3 Strengthen the collaborative nature of the network to facilitate shared initiatives which can take advantage from the multiplication effect of the network (D4.4 Concept for a peer network driven intervention study).

Working Group 5: Dissemination and education – promoting vascular ageing

Objectives: The main objective of WG5 is to **promote** a vascular ageing culture (P1) and to propagate the use of technologies and preventative strategies. It will focus on combining the technical WGs 2-4 and fostering joint dissemination and education:

- Dissemination of results addressing various stakeholders, e.g., scientists, doctors, nurses, patients, patient associations, representatives from health care systems, guideline committees (P4).
- Education for clinicians, especially focusing on ECIs, ITCs and women (P3, P5).

Tasks and deliverables:

T5.1 Preparation of dissemination plan and material with special focus on health care representatives (D5.1 Dissemination plan and material).
T5.2 Scientific dissemination via (open-access) publications, e.g. consensus documents from WG2 and WG3, conference presentations, special issue of an international peer-reviewed journal, non-academic briefs/reports, etc. (D5.2 Consensus documents; MS3: Consensus statements published and gaps identified; MS7: Analysis finalized and published).
T5.3 General dissemination via easily accessible, user-friendly website, social media, information sheets, posters and a newsletter (D5.3 Report on activities).
T5.4 Targeted dissemination via annual 2-day workshops at the location of a COST Action participant (preferably in an ITC), annual 1-day seminars connected to large conferences, webinars, a final conference and two public awareness events in different countries (D5.4 Report on activities; MS8: Final conference conducted).
T5.5 Preparation of education plan and material (D5.5 Education plan and material).
T5.6 Organisation and accomplishment of annual Training Schools (D5.6 Annual Training Schools and report thereupon).

4.1.2 DESCRIPTION OF DELIVERABLES AND TIMEFRAME

All deliverables are described in the WG descriptions in section 4.1.1 and their timing illustrated in the Gantt chart in section 4.1.4. The Action's major deliverables are as follows and are based on the Action's most important activities:

- D1.2, D5.5 and D5.6: These deliverables include the activities especially targeting ITCs and ECIs, thus covering the planning, organisation, implementation and reporting of **education activities**, such as STSM and Trainings Schools. They are evenly distributed over the course of the Action to promote a vascular ageing culture and especially targeting ECIs in ITCs.
- D1.1, D1.3 and D5.1-D5.4: These cover all activities related to dissemination and planning of follow-up research activities. These deliverables form the foundations of the COST Action including the planning, preparation, implementation and reporting on **dissemination material and activities**.
- D2.1, D2.2, D3.1 and D3.4: These deliverables will describe the consensus reached by this COST Action on underlying mechanisms of vascular ageing (T2.1), mathematical models for their assessment (T2.2) and existing technologies (T3.1), and summarise identified gaps for their routine clinical use (T3.4). They will form the basis for scientific publications (T5.2) **and all**

harmonisation and refinement efforts, thus being scheduled for the first two years of the Action (see Gantt chart in section 4.1.4).

- D3.2 and D3.3: These will include the framework for the validation of refined assessment approaches and report on the **translation from research to industry**. Thus, these deliverables are based on the consensus documents and planned thereafter.
- D4.1, D4.2 and D4.3: WG 4 and its deliverables will be dedicated to developing a **big data registry for harmonising available data and studies** to enable multicentre research initiatives and to create new evidence. Registry conception, implementation and data collection including ethics will take up a large amount of the Action's time period (envisaged 3 years). Big data approaches will be evaluated in the meantime and applied after data submission is closed, thus in the last year of the COST Action.

4.1.3 RISK ANALYSIS AND CONTINGENCY PLANS

Risk	Chance	Impact	Mitigation measure
Low attendance at the Action networking activities	Medium	High	Delegation of responsibilities to different Action Members in order to enhance commitment among Action Members. A broad variety of activities, able to address the needs of the various target groups and a dissemination plan that will be tuned according to the feedback of each activity.
Incapability to involve a wider audience in WGs activities	Medium	High	The partners have recognised expertise in the field and are involved in networks that allow raising the interest of experts and professionals, outside the initial COST network. Thus, one measure to address this risk is to specifically target experts during the Action and invite them to join either ad hoc or permanently WGs, Conferences and other COST Networking Activities.
Possible delay in the deliverable release	Low	Medium	These risks will be addressed by appointing a publications coordinator, regular meetings of WG leaders, and delegating responsibilities to different Action members to enhance commitment.
Legal issues considering the data registry	Low	High	Many proposers already run large datasets and have experience in coping with these issues. However, legal and ethical issues regarding privacy of data could become a barrier. The leader of WG4 will ensure: 1) to get ethical approval for the registry, and 2) to only include data collected in research projects approved by a local ethics committee or institutional review board in the registry. Furthermore, an expert on legal issues will be involved.
Fragmentation and overlap between WGs.	Low	High	WG 1 and 5 are coordinating technical WGs. Joint publications and dissemination/education activities are envisaged.
Lack of research resources limiting the achievement of the objectives.	Low	High	While networking and dissemination is mostly not covered, many investigators receive funding through their institution or have access to national grants for research activities.

4.1.4 GANTT DIAGRAM

The GANTT diagram below displays the timing of the tasks of the Action VascAgeNet. Whilst the chart provides the general planning of the workshops and seminars, the detailed timing will depend on the possibilities of co-location with appropriate conferences and workshops, so as to achieve the maximum dissemination impact. It is intended to complete this Action with a final conference.

	Year 1				Year 2				Year 3				Year 4			
	Q1	Q2	Q3	Q4	Q5	Q6	Q7	Q8	Q9	Q10	Q11	Q12	Q13	Q14	Q15	Q16
WG1: Dynamic exchange																
T1.1 Coordination of cross-WG activities																
T1.2 Enlargement and involvement		STSM		STSM		STSM		STSM		STSM		STSM		STSM		STSM
T1.3 Funding opportunities																
WG2: Physiological and technical background																
T2.1 Current knowledge on mechanisms																
T2.2 Consensus on mathematical models																
T2.3 Translation from bench to bedside																
WG3: Technological aspects																
T3.1 Harmonisation and standardisation																
T3.2 Framework creation																
T3.3 Translation from research to industry																
T3.4 Gap identification																
T3.5 Effectiveness analysis																
WG4: Data and studies																
T4.1 Concept for data registry																
T4.2 Big data approaches																
T4.3 Peer network driven intervention study																
WG5: Dissemination and education																
T5.1 Dissemination plan and material																
T5.2 Scientific dissemination																
T5.3 General dissemination										Public Awareness Event			Public Awareness Event			
T5.4 Dissemination via workshops/seminars			Workshop		Seminar		Workshop		Satellite Meeting		Workshop		Seminar		Workshop	Conferenc
T5.5 Education plan and material																
T5.6 Education via training schools					Training School			Training School			Training School			Training School		
Meetings	WG Meeting MC Meeting		WG Meeting MC Meeting		WG Meeting MC Meeting		WG Meeting MC Meeting		WG Meeting MC Meeting		WG Meeting MC Meeting		WG Meeting MC Meeting		WG Meeting MC Meeting	
Deliverables				D5.1, D5.5		D2.1, D3.1, D3.4, D5.2		D5.3, D5.4, D5.6		D1.1, D5.5		D2.2, D3.2, D4.1, D4.2				D1.1, D1.2, D1.3, D2.3, D3.3, D3.5, D4.3, D4.4, D5.3, D5.4, D5.6
Milestones	MS1			MS2			MS3		MS4			MS5	MS6			MS7-9

REFERENCES

[1] European Commission. The European Union explained – Public Health. 2014

[2] European Heart Network. European Cardiovascular Disease Statistics. 2017.

[3] GBD 2016 Disease and Injury Incidence and Prevalence Collaborators. Lancet. 2017 Sep 16; 390(10100): 1211–1259.

[4] GBD 2013 Risk Factors Collaborators. Lancet. 2015;386(10010):2287-323.

[5] GBD 2015 Mortality and Causes of Death Collaborators. Lancet. 2016;388(10053): 1459–1544.

[6] Nilsson PM, et al. Hypertension. 2009;54(1):3-10.

[7] Olsen MH, et al. Lancet. 2016;388(10060):2665-2712.

[8] O'Rourke MF, Hashimoto J. J Am Coll Cardiol. 2007;3;50(1):1-13.

[9] Lacolley P, et al. Physiol Rev. 2017;97(4):1555-1617.

[10] Sharman JE, et al. Eur Heart J. 2017;38(37):2805-2812.

[11] Laurent S, et al. Hypertension. 2009;54(2):388-92.

[12] Scuteri A, et al. Int J Cardiol. 2018;263:132-137.

[13] Chung CM, et al. Am J Med Sci. 2012;344(3):190-3.

[14] Angermann S, et al. Clin Sci. 2017;131(13):1483-1493.

[15] Nilsson ED, et al. J Hypertens. 2014;32(11):2152-7.

[16] Rabkin SW. J Alzheimers Dis. 2012;32(3):541-9.

[17] Orkaby AR. J Gerontol A Biol Sci Med Sci. 2018 (early online)

[18] Townsend RR. Hypertension. 2018 Jun;71(6):1101-1107.

[19] Vlachopoulos C, et al. Atherosclerosis. 2015;241(2):507-32.

[20] Laurent S. J Hypertens Res. 2018;4(2):39-52

[21] Ben-Shlomo Y, et al. J Am Coll Cardiol. 2014;25;63(7):636-646.

[22] Reference Values for Arterial Stiffness' Collaboration. Eur Heart J. 2010;31(19):2338-50.

[23] Herbert A, et al. Eur Heart J. 2014;35(44):3122-33.

[24] Piepoli MF, et al. Eur Heart J. 2016;37(29):2315-2381.

[25] Koivistoinen T, et al. Hypertension. 2018;71(3):451-456.

[26] Faconti L, et al. J Hypertens. 2016;34(11):2220-6.