Brussels, 27 May 2022

COST 024/22

DECISION

Subject: Memorandum of Understanding for the implementation of the COST Action “Building an open European Network on OsteoArthritis research” (NetwOArk) CA21110

The COST Member Countries will find attached the Memorandum of Understanding for the COST Action Building an open European Network on OsteoArthritis research approved by the Committee of Senior Officials through written procedure on 27 May 2022.

MEMORANDUM OF UNDERSTANDING

For the implementation of a COST Action designated as

COST Action CA21110
BUILDING AN OPEN EUROPEAN NETWORK ON OSTEOARTHRITIS RESEARCH (NetwOArk)

The COST Members through 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, 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 document amending or replacing them.

The main aim and objective of the Action is to identify risk factors on the prevalence of OA, understanding pathogenesis, phenotypes, end-types and co-morbidities, in order to develop new treatments and delivery of care to reduce the burden of Osteoarthritis for Society.. This will be achieved through the specific objectives detailed in the Technical Annex.

The present MoU enters into force on the date of the approval of the COST Action by the CSO.

OVERVIEW

Summary
Osteoarthritis (OA) is the most common form of arthritis and the single most common cause of pain and physical disability in older adults. An estimated 10% to 15% of all adults aged over 60 have some degree of OA, with prevalence being higher among women than men and likely representing underreporting which is common in many disease prevalence studies. Despite the growing OA epidemic and major socio-economic impact, the population is facing a staggering lack of disease-modifying therapies that can bring symptomatic relief and preserve joint function by preventing cartilage- and joint degeneration and thus delaying OA progression. The research specifically aimed at OA management in Europe is scattered and not strategically coordinated, although several networks have OA partly in focus, it minor part of their agenda en lacks the focus and dedicated commitment to coordinate progress. The main aim of EU-netwOArk is to set up the European Society for Osteoarthritis (ESOA), with three major stakeholder groups, 1) patients, 2) clinicians and 3) researchers, both from academia and industry. The COST Action will allow us to start the process of building such a European Society, with the aim of coordinating and stimulating more interdisciplinary and transdisciplinary research, technological development and translation of the results to the clinic, aimed at improving the quality of life of those affected by OA in Europe. The area's to be addressed in this Action are Primary prevention, Diagnostics, Treatment, Interaction (comorbidities) and Care Management. EU-netwOArk aims to boost new scientific breakthroughs on the five main OA themes.

Areas of Expertise Relevant for the Action	Keywords
● Health Sciences: Health services, health care research	● OsteoArthritis ● Health Sciences ● Translational research ● Patient driven

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

Research Coordination
● 1. Align and coordinate all European research activities on OA and develop a joint pre-clinical and clinical research agenda.
● Stimulate collaborations with, knowledge exchange and translation of research results to relevant stakeholders such are care providers, policy makers, health insurers, patient representative organisations as well as patients, leading to new scientific breakthroughs in terms of innovative therapies and to encourage exchange of early career investigators to accomplish multidisciplinary research.
● Provide standards to set up a European registry of patients with all stages of OA and share a webbased platform for clinical, biomarker and MRI data.
● Define the standards, definitions, and criteria of the most relevant (early stage) OA clinical phenotypes, including models, detection modalities for diagnostics.
● Develop guidelines for the secondary prevention of OA based on the subject phenotype, comorbidities, and lifestyles, and coordinate European action for the prevention of OA.
● Perform a pan-European survey to better understand the beliefs, needs and feelings of patients and health professionals, with a unique emphasis on patients.

Capacity Building

● Training of Early Career Investigators/Researchers in multidisciplinary research on a holistic OA approach covering multiple domains.

● Support and training of researchers & physicians (including PhD students) from participating countries and Inclusiveness Target Countries who may have a need for interdisciplinary knowledge and currently lack other means to achieve such experience, including travel grants to visit international conferences.

● Encouraging researchers working in associated areas of OA, such as health education, patient representation organisations or Self-Management (ICT) tooling companies.

● Development of a new academic curriculum, which approaches OA health from a holistic perspective and includes the different scientific domains that are relevant

● Working with national patient representative organisation to translate the overview of accumulated OA research into information packages and language that is suitable for patients.

● Recruiting and training of influencers who are active on social media, targeting people suffering from OA, to stimulate dialogue between patients, clinicians and researchers.

● Working with policymakers so that current and future risk factors for developing OA are known and addressed properly.

● Working with national and European health professional associations to implement joint R&D agenda and facilitate knowledge exchange.

● Training the network in the funding opportunities in Europe for collaborative research, with the objective to increase ITC participation in research projects and empower them to develop new opportunities

TECHNICAL ANNEX

1. S&T EXCELLENCE

1.1. SOUNDNESS OF THE CHALLENGE

1.1.1. DESCRIPTION OF THE STATE OF THE ART

Osteoarthritis (OA) is the most common form of arthritis and the single most common cause of pain and physical disability in older adults. The 2017 Global Burden of Disease Study has reported that the burden of musculoskeletal disorders is much larger than estimated in previous assessments and accounts for 6.8% of DALYs (Disability Adjusted Life years) worldwide. An estimated 10% to 15% of all adults aged over 60 have some degree of OA, prevalence being higher among women than men. Across the EU Member States, the prevalence of diagnosed OA varies from 2.8% in Romania to 18.3% in Hungary, likely a consequence of underreporting, which is common in many disease prevalence studies. Multiple studies emphasise that OA represents a significant economic burden to patients (loss of income) and society [1] [2]. The annual cost of OA treatment per patient ranges from €1330 to €10 452, depending on the country, the approach taken to disease management and the health care system, which highlights significant health disparities across Europe. The direct and indirect costs of OA were shown to increase with age and with quality of life in several studies.

The prevalence of OA is increasing due to demographic changes, the dramatic increase in the ageing population and an increase in related risk factors such as obesity. According to the United Nations, by 2050 people aged over 60 will account for more than 20% of the world's population [3]. Already today, OA affects 7% of the global population, more than 500 million people worldwide, with women disproportionately affected by the condition [4], and one-third of these people being severely disabled [3]. Furthermore, it has been shown that knee and/or hip OA increases cardiovascular mortality by 50% [5] [6]. This is linked to an increase in sedentary lifestyles and physical inactivity and is related to pain and loss of function. If solutions can be found to reduce inactivity in these patients, it has recently been shown that it has a significant reduction in cancer, diabetes and cardiovascular disease: If 20% of the knee OA population (14 million in the US) who are inactive had more active lifestyles (defined as ≥150 minutes of moderate-to-vigorous activity/week), 871,541 QALYs would potentially be saved, and 95,920 cases of cancer, 222,413 cases of cardiovascular disease, and 214,725 cases of diabetes mellitus would potentially be averted [7].

Therefore, interventions and prevention measures that positively impact on OA are also likely to have a beneficial impact on cardiovascular and metabolic comorbidities that are associated with it. Alarmingly, OA is increasingly affecting the younger population due to rising numbers of overweight individuals, increasing sedentary lifestyles and increasing numbers of sports and trauma related injuries in the physically active part [8]. The number of years during which patients experience pain and disability due to OA is rapidly increasing and one of the underlying causes can be found in the global increase in life expectancy. Despite the growing OA epidemic and major socio-economic impact this brings, the population is facing a staggering lack of disease-modifying therapies that can bring symptomatic relief and preserve joint function by preventing cartilage- and joint degeneration, thereby delaying OA progression. OA has a complex pathogenesis involving multiple cellular and molecular players. Because of the lack of any etiological treatment to stop or slow down the changes in the joint tissues, the current

management of OA patients is based on symptoms and largely based on the use of analgesics and anti-inflammatory drugs. Recently, thanks to our better understanding of this disease, new therapeutic avenues have appeared, some of which have been evaluated in clinical trials. Among them, biological/cell therapies using mesenchymal stem/stromal cells (MSCs) is regarded as having the potential to develop disease modifying therapies. Several clinical trials in which MSCs were intra-articularly injected have reported promising results. In parallel, the identification of new therapeutic targets involving certain signalling pathways, immune cells, and autophagy/senescence processes, have given rise to new hope. Lastly, the advent of biofabrication processes, especially 3D bio-printing, will allow us to manufacture organoids or mini-joints for large-scale screening of OA drug candidates in the not-too-distant future [17]. Non-pharmacological OA therapies are limited by high costs, lack of access, reimbursement and patient compliance. Lack of patient education and compliance result in very low take-up of some of the best combined exercise and weight loss programs [9]. This leaves total joint replacement as the only currently available option to treat the consequences of end-stage OA. However, considering the increase in life expectancy, the demand for an active life-style well into retirement, and an alarming growth in the number of young OA patients, costly and high-risk revision surgery of the primary prosthesis is a major problem that we should be addressing by delaying the need for total joint replacement through innovations from basic research. This is further supported by the fact that 20% of patients undergoing a total knee prosthesis continue to have chronic pain [10].

Molecular interrogation of disease through human ex-vivo tissue analysis, in-vitro organoid studies, preclinical models have radically reshaped the knowledge landscape. Inflammation in OA appears to be distinct from that seen in RA. Genome-wide genetic studies point out that repair pathways are underlying OA onset, which accords well with recent promise using growth factor therapies or Wnt pathway antagonism. Nerve growth factor has emerged as a robust target in OA pain in phase 2–3 trials. These studies, both positive and negative, align well with those in preclinical surgical models of OA, indicating that some of the pathogenic mechanisms identified in rodent models can translate to valid human targets. Several novel candidate pathways are emerging from preclinical studies, offering hope of future translational impact [11]. More recent studies are developing molecular OA biomarkers sensitively marking (aspects of) OA disease pathophysiology such as senescence or hypertrophy and next generation regenerative medicine options for OA with iPSC cell technology such as iPSC derived OA cell-therapy (iMSCs) as well as iPS-cell derived generation of (large scale) neo-cartilage constructs for implantation purposes.

Orthobiologics (hyaluronic acid, platelet rich plasma (PRP), bone marrow concentrate (BMAC) and emerging stem cell therapies and exosomes may extend the pain free interval and improve quality of life, but the clinical trials for these agents are of low quality. Thus, there is an urgent need for better defined and conducted clinical trials to evaluate the true efficiency of these biological approaches for the treatment of OA. Regenerative, biological, and joint resurfacing therapies are slow to progress from bench to bedside due to technological, manufacturing, and regulatory hurdles. There is a need for a concerted pan-European perspective regarding the use of orthobiologics and advanced therapies to streamline basic and translational research in the field. Encouraging knowledge transfer and enhancing trust between industry, basic, and clinical scientists will optimise our collective chance of success. It is also possible that a treatment for OA might come from another disease area. This is not implausible because the current biological treatments for RA originated from cancer research. Therefore, it is entirely conceivable that effective future treatments for OA may derive from cardiovascular and metabolic research areas and it is therefore crucially important that OA researchers are able to network with and connect with those outside their own area. Furthermore, there is a lack of understanding about the biomechanical influence on disease progression. It is unclear what kind of activities create (un)healthy

load and under what (phenotyp3/endotype) circumstances — and the interplay between joint morphology and load — OA progresses.

At the present time, most OA patients do not receive appropriate care and many of them are not served well by underutilising efficacious, evidence-based lifestyle and behavioural management strategies, particularly exercise and weight loss. There are a multitude of reasons as to why this evidence practice gap exists, including perceptions among health care providers that OA is merely a part of normal aging, with limited treatment options and competing demands from other comorbid health conditions in the context of routine visits [12]. Chronic Disease Self-Management Program (CDSMP) has been developed by Stanford University and has also been successfully implemented in Europe (EU founded EFFICHRONIC H2020). It includes action planning and feedback about problem-solving skills and other desired behaviours and competencies, such as the reinterpretation of symptoms and specific training in disease management. Research has shown its effectiveness in improving the health, quality of life, self-care and self-management of the disease, as well as increased physical activity and social relations, improved communication with health systems, fewer health claims, and decreased use of emergency and health services [13].

1.1.2. DESCRIPTION OF THE CHALLENGE (MAIN AIM)

The research specifically aimed at OA management in Europe is scattered and not strategically coordinated. Although several related networks exist (see 2.1), none of them is dedicated focus on interdisciplinary OA research as in this Action. Consequently, coordination of research activities is currently poor and major European organisations working on OA are not actively engaged in a collaborative effort. Individual research projects focusing on limited areas of OA, are being developed in isolation, without interaction or awareness of other related research activities. OA research is primarily developed under the scope of national initiatives, or as side projects in larger European projects, which often focus on other diseases, such as RA. For young researchers there is no clear European platform or network available that oversees and represents OA research, which is also valid for midterm careers that have the ability to train ESR's but often lack the security of a permanent position. This COST Action empowers both groups to pursue and retain a challenging and rewarding career in OA research. By means of this COST Action, further alignment and acceleration of existing research can be achieved, translation to clinicians and patient (representatives) can be implemented, and a platform for young researchers will be established to empower OA research careers.

The research domain of a complex and chronic condition as OA is extremely broad and covers many scientific disciplines. It ranges from fundamental biology of tissues involved, especially cartilage, epidemiological studies and prevalence in different countries, alongside the recognition of gender, ethnic and geo-political influences on surgery as end stage disease treatment. It also includes topics like health equality & psychology and care in individuals with low Social Economical Status (SES) and OA, prevention strategies and (early) diagnostics. Furthermore, behavioural research and social and psychosocial factors of OA are broadly researched, leading to the identification and definition of new risk factors and useful insights into associated comorbidities The main aim of EU-netwOArk is to set up the European Society for Osteoarthritis (ESOA) with three major stakeholder groups, 1) patients, 2) clinicians and 3) researchers from both academia and industry. The COST Action will allow us to start the process of building such a European Society, with the aim of coordinating and stimulating more interdisciplinary and transdisciplinary research, accelerating technological development and translation of the results to the clinic, with the aim of improving the quality of life of those affected by OA in Europe. The new ESOA will develop its own unique mission and vision, strategic priorities, communication channels and dissemination vehicle in the form of a new open access journal. ESOA will collaborate

with all major organisations — such as EULAR, OARSI, ESCEO and EORS — and will bring together members from these organisations that are interested in OA. See paragraph 2.1.1. for further details.

The proposing network has identified the following five key research challenges to be perused first:

1. Primary prevention: identification and management of risk factors to impact the prevalence of the disease in the general population. Strong European networks are an absolute must in this field.
2. Diagnostics: defining and understanding (early) OA pathogenesis, clinical phenotypes and molecular endotypes, which highlights an acute need for stratification of OA. Stratification will lead to better understanding of risk factors and co-morbidities, the ability for early diagnosis and personalised treatments, but more importantly it will set the basis for new personalised and targeted drug discovery and development. Pan European collection and storage of patient tissue samples for generating comprehensive data using omics technologies is crucial for disease stratification, drug discovery and repositioning, and precision medicine.
3. Treatment: Development of new, phenotype-based range of pharmacological and non-pharmacological therapies for retardation of disease progression (phenotype-based medicine) or regeneration of deteriorated cartilage. The aim is to treat early, thus there is a need for "early (surrogate) outcomes" to assess such treatment.
4. Interaction: Understanding comorbidities associated with the different OA phenotypes, leading to new scientific understanding of risk factors and secondary preventions strategies.
5. Care management: The current reactive approach to end-stage OA disease — using palliative treatment options — is both counterintuitive and harmful. Addressing it will go well beyond the development of guidelines, algorithms to facilitate adoption of appropriate evidence-based practice, and assessment of quality indicators. Changing the delivery of care will require complex interventions aimed at improving consumer knowledge, self-management, pychocological programs and health care delivery characterised by integrated, multidisciplinary chronic disease management.

EU-netwOArk aims to boost new scientific breakthroughs on the five main OA themes as mentioned above. Therefore, a multi-disciplinary research and communication network on OA disease management is established, bringing together (academic) research institutes, private research organisation, patient organisations, pharmaceutical organisations, governmental health representation and clinicians and health care workers. Basically, the entire OA value chain, from bench to bedside and vice versa and from legislative to research lab is covered in this action. Stocktaking / incentivisation of research efforts, alignment, (future) collaborations and translation of results enabled by this COST Action will boost the impact of the topics mentioned above.

1.2. PROGRESS BEYOND THE STATE OF THE ART

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

Prevent OA occurrence and progression. There is a large body of literature about the role of modifiable risks factors on OA occurrence and progression. The most investigated are joint trauma (professional and sport), overweight/obesity and diet. Recently, additional risks factors have been suggested like chronic use of some drugs (e.g. anti-vitamin K) or co-morbidities like metabolic syndrome. Further, OA of the lower limbs are associated with increased mortality probably because of sedentary lifestyle, gait speed or contribution to inflammation. Identifying and managing OA risk factors may contribute to improving not only OA but also the general health of patients, with potentially high economic impact.

Understanding of (early) OA phenotypes. Emerging evidence over the last few years suggests that OA is a heterogeneous and multifaceted disease with multiple clinical phenotypes [18]. Identifying early stage OA is an important research priority because it allows us to gain a better understanding of the

molecular pathways and mechanisms (molecular endotypes) that may be involved in each distinct clinical phenotype and target them more effectively using a variety of preventive and treatment strategies. For research in this field to advance, it is important to find consensus on early (surrogate) outcomes while developing biomarkers sensitively marking such early OA disease processes

The concept of endotypes and phenotypes has already paved the way for a comprehensive molecular and cellular and clinical classification of several diseases, such as the example set by the research in field of allergy and asthma. However, in most fields of medical research, the clinical phenotype is defined as the phenotypic presentation of the disease in an individual and is focused on the clinical presentation of the disease, rather than the molecular mechanisms underlying it. A limitation is that the molecular endotype alludes to the pathogenesis at the molecular and/or cellular level, ignoring its clinical presentation. Insights from other fields of medicine, such as the one illustrated here, may be deployed in the future to benefit the OA research community, as efforts to create and disseminate consensus-based definitions in the OA field are currently ongoing. Setting up next generation molecular and cell biological technology such as involving iP-stem cells for sustainable cell sources, 'organ-on-chips' development to study interacting disease processes between bone-cartilage and CRISPR/Cas genome engineering to introduce (therapeutic) gene manipulations. These technological advancements well facilitate in development of next generation regenerative treatment options for OA. Most evidence on the presence of clinical phenotypes and molecular endotypes so far are new, come from a few studies and lack validation. Further research is needed to validate previous findings and to assess their implications for clinically important outcomes and clinical trial design. In this regard, the availability of high-quality data, ideally longitudinal and from different populations, is key for OA phenotyping research. Efforts to combine datasets from existing OA cohorts/previous clinical trials are likely to be helpful by providing large datasets for the identification and validation of phenotypes. In addition, imaging and/or laboratory biomarkers may be useful to better define clinically relevant phenotypes. Existing initiatives in this field need further developing and coordinating, such as the OA trial bank data, building on the European infrastructure BBMRI-ERIC. In this line of action, the establishment of a pan European network of disease specific biobanks for collection, storage and management of tissue samples would represent an important step towards an unified collection of biospecimens to be utilized for both clinical and research-based services

Development of sub-type-based medicine. One reason for the failure of clinical trials testing new therapeutics intended for structure modification in OA, is that it is unclear at present which patients would be most suitable for a specific therapy. For example, the failure of bisphosphonates to slow OA progression might have been due to enrolling any patient with symptomatic OA, rather than selecting symptomatic patients with greater subchondral bone turnover. Equally, the failure of some of the therapeutics targeting inflammatory pathways should have been tested in carefully selected sub populations with inflammatory forms of OA. This concept of stratification is not new in clinical medicine, but it is still emerging in OA research. To address the heterogeneity of OA to improve clinical research and trials, a new model of understanding OA based on a phenotype-guided approach is urgently needed. Recently, a significant research effort has emerged aiming to define a classification of OA phenotypes for the purpose of better identifying individuals at higher risk of progression and to better delineate OA subpopulations caused by distinct risk factors and disease mechanisms that would be suitable for targeted treatment and prevention strategies. Sub-type-based medicine and corresponding clinical trials are needed to address the need for disease-modifying therapies. The development of proper models (i.e. predictive modelling, computational, in vitro, including whole osteochondral explant cultures in loaded bioreactor, in vivo) to develop and test new sub-type based interventions is a prerequisite to advance beyond the current state-of-the-art in this field. For this, we propose to initiate an EU registry, with secured web site accessible to the COST partners to accumulate clinical,

radiological, MRI and blood biomarkers (e.g. bone turnover markers, cytokines, miRNAs, etc.) data of OA patients after informed consent.

Understanding comorbidities. Since the prevalence of OA increases with age, coexistence with other chronic diseases is common, further increasing the impact on the quality of life of those patients. The major comorbidities of OA patients are systemic arterial hypertension (SAH), depression, cardiovascular disease, diabetes, and dyslipidaemia. Metabolic syndrome, defined as the association of SAH, central obesity, glucose intolerance, and hypertriglyceridemia or low HDL levels (at least three of the five criteria) in the same individual also occurs at a higher frequency in OA patients. Despite the clear relationship between OA development and trauma resulting from excessive weight, the occurrence of OA in joints that do not bear load suggest that the chronic low-grade inflammation status existing in patients with metabolic syndrome can alter the metabolism of cartilage, regardless of excessive weight. In addition, glucose intolerance can also contribute to maintaining that persistent inflammation status in obese individuals with metabolic syndrome. Furthermore, overlapping phenotypes in older individuals presents a major challenge for patient phenotyping in the older age groups and for patients' gratification in clinical trials. Further research on the causality of comorbidities, in relation to different phenotypes, and clinical implications is needed.

OA management and patient empowerment. Our current palliative approach, in clinical medicine, of analgesic prescription followed by a long wait before joint replacement for end-stage OA, is not sustainable in the long-term and needs to change. We need to focus care to tailor management to the individual needs of the consumer, targeted toward the central complaints of pain and functional limitation, with a chronic disease multidisciplinary management approach. Modern health care systems are typically reactive and focused on acute care, whereas the management of OA ideally needs to be more efficient, better coordinated, and patient centred to support integration of the best evidence into practice. The pendulum of treatment choices provided for patients by health care professionals needs to swing from drugs and surgery to behavioural management with a focus on exercise, weight loss, and self-management [12]. This focus is emphasised in recently published treatment guidelines [14].

Self-efficacy awareness is one of the pillars of success on which a training action in the health field, aimed to reach the patient empowerment, should be built. In accordance with this project's aims, the patient's empowerment and to provide them with the opportunities and conditions to develop their skills and knowledge to turn their selves into an active agent of their own care and life, is a key objective besides the pair-to-pair education. The meaningful learning often occurs by or from an equal: for example, people suffering from diseases or their informal caregivers or relatives.

The key role of the peers in the self-directed education would be explained by the social determinants of health [15]. Our peers are similar people who often have grown under the same material circumstances (climate, environmental conditions, food available, etc.), and who may even have similar behavioural, biological, and psychosocial factors. Meanwhile, the structural determinants — for instance the cultural background, socioeconomic context, political environment, wealth distribution and race-class-gender status, besides microeconomic issues, job positions or education — together with the material circumstances of life, also have an important impact on equity, access to affordable health services, access to information, well-being or healthy behavioural patterns.

The prevalence of OA in lower social classes is significantly higher. Reaching this group with adequate (written) information remains a huge challenge, calling for improved education, information, and interventions to improve compliance in this group. In addition, patient partners almost always are well educated, thus not fully representing the target population. Setting up a European wide CDSMP dedicated to OA would impact quality of life prevention and as access to health care at an optimal time.

1.2.2. OBJECTIVES

1.2.2.1 Research Coordination Objectives

The main research coordination objectives of the EU-netwOArk action are to:

1. Align and coordinate all European research activities on OA and develop a joint pre-clinical and clinical research agenda.
2. Stimulate collaborations with knowledge exchange and translation of research results to relevant stakeholders such as care providers, policy makers, health insurers, patient representative organisations as well as patients, leading to new scientific breakthroughs in terms of innovative therapies and to encourage exchange of early career investigators to accomplish multidisciplinary research.
3. Provide standards to set up a European registry of patients with all stages of OA and share a web-based platform for clinical, biomarker and MRI data.
4. Define the standards, definitions, and criteria of the most relevant (early stage) OA clinical phenotypes, including models, detection modalities for diagnostics.
5. Develop guidelines for the secondary prevention of OA based on the subject phenotype, co-morbidities, and lifestyles, and coordinate European action for the prevention of OA.
6. Perform a pan-European survey to better understand the beliefs, needs and feelings of patients and health professionals, with a unique emphasis on patients.

Because of the different science domains involved, these research objectives can only be achieved through multi-disciplinary and multi-sector research collaboration. However, this is still quite uncommon in the health science domain. Although some initial collaborations between orthopaedic surgeons, physiotherapists and primary care health practitioners are developing throughout Europe for example, well-coordinated multi-disciplinary research across different science domains involved in OA is non-existent in Europe.

This COST Action is seen as a great opportunity by all founding partners and broadly consulted stakeholders, since it enables the creation of multi-disciplinary network of key stakeholders, including patients and patient groups, basic, translational and clinical academic researchers as well as industrial, entrepreneurial and social researchers overcoming the scientific domain barriers that traditionally exist as impediments to transdisciplinary research. This COST Action will – for the first time – consolidate and extend efforts from national research programs in primary care, rheumatology, orthopaedics, health science, pain medicine, psychology, pharmacy, cell therapy, physiotherapy, nutrition, public health, occupational therapy, epidemiology, health economics, and the lived experience of OA and also translate this scientific knowledge to the OA national patient organisations, clinicians and policy makers in order to generate a solid European research platform.

1.2.2.2 Capacity-building Objectives

EU-netwOArk has been designed to start building the European Society for Osteoarthritis (ESOA). A major backbone of ESOA will be the annual European scientific conference on OA. This COST Action will enable this conference to be organised for the first four years, which will generate momentum and interest from the research field and potentially identify future sponsors, to continue the tradition after the COST funding of the first four years. Placing the patient centrally in the organisation of this COST Action is a key element of the EU-netwOArk approach. The network is convinced that patients and patient organisations should be pro-actively involved in defining the research agenda, as well being more actively involved in raising awareness and dialogue with fellow sufferers. Social media will allow for new audiences and engagement approaches, based on the participation of individuals who can demonstrate the ability to act as spokespersons, ambassadors, and figureheads.

In order to achieve these ambitious but SMART and realistic objectives, the EU-netwOArk Action first needs to build the network with relevant academic disciplines, the pharmaceutical industry, Biotech SMEs, primary health care practitioners, National and European Health care professional associations (e.g. EULAR, EORS, ESCEO), international societies (OARSI, ICRS, ORS), patient organisations (EULAR PARE, OAFi) and research institutions, in order to generate the first ever real-time overview of all research activities related to OA across Europe, and in target COST Inclusiveness Target Countries (ITC). The founding partners have sufficient contacts and networking access to complete the network in the short term, hence boosting the impact of this action with great enthusiasm, momentum, and conviction. This will be implemented in the EU-netwOArk Action by the following concrete measures:

- Training of Young Researchers and Innovators/Researchers in multidisciplinary research on a holistic OA approach covering multiple domains. This means that researchers will develop combined knowledge for example, prevention and non-pharmaceutical interventions, and hence boosting cross-sectoral collaborative research and a more holistic approach to OA. This network already has 10 open PhD positions available and aims to multiply this amount by means of private and public funds (e.g. Marie Curie projects).
- Support and training of researchers & physicians (including PhD students) from participating countries and Inclusiveness Target Countries who may have a need for interdisciplinary knowledge and currently lack other means to achieve such experience, including travel grants to visit international conferences.
- Encouraging researchers working in associated areas of OA, such as health education, patient representation organisations or Self-Management (ICT) tooling companies.
- Development of a new academic curriculum, which approaches OA health from a holistic perspective and includes the different scientific domains that are relevant.
- Working with national patient representative organisation to translate the overview of accumulated OA research into information packages and language that is suitable for patients.
- Recruiting and training of influencers who are active on social media, targeting people suffering from OA, to stimulate dialogue between patients, clinicians and researchers.
- Working with policymakers so that current and future risk factors for developing OA are known and addressed properly.
- Working with national and European health professional associations to implement joint R&D agenda and facilitate knowledge exchange.
- Training the network in the funding opportunities in Europe for collaborative research, with the objective to increase ITC participation in research projects and empower them to develop new opportunities.

In summary, the capacity building objectives of the EU-netwOArk Action are to:

1. Organise an annual European conference on OA with a greater focus on patient engagement.
2. Facilitate trilateral communication between people suffering from OA and clinicians, and researchers developing new treatments for OA by a.o. dedicated workshops & patient panels.
3. Coordinate and improve the clinical and research training on OA throughout Europe, especially by organising summer/winter schools for PhD students, using the Gordon Research Conferences model, and install a student and young researcher section of ESOA, and facilitate actual PhD projects.
4. Improve knowledge exchange between academia, health care organisations, policy makers and industry, to facilitate the development of better treatment and prevention strategies en facilitate new spin-off / start up companies.
5. Coordinate prevention action through (social) media and web-based applications.

Implementation of this COST action would enable not only to cluster and align research efforts, but also translate these efforts to concrete roadmaps and information packages from patient perspectives. The above-mentioned capacity-building objectives will be implemented by Training Schools, workshops, and visits from participants to clinics, laboratories and research facilitated via Short Term Scientific Missions

(STSM). Particular attention and priority will be given to ESR participants and participants from ITC's to generate a well-balanced and pan-European OA network.

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

The growing societal need related to OA, as described in section 1, currently lacks a specific medical and / or scientific organisation in Europe. There are many networks dealing with parts of the OA challenge, but there is no place to date where these aspects are integrated and discussed in their context. EU-netwOArk aims to set up a community of researchers, physicians & patients and a new European society — to urgently bring together all European key players from patient, academic, clinical and industrial and social care organisations involved in improving the prevention and treatment of OA — and implementing them across the European community. Next to that, there is an explicit need to generate a platform for young researchers and innovators in OA to stimulate and empower their careers, offer interesting training positions, and provide an invaluable network to boost their individual ambitions. The European scale is crucially needed to mobilise enough research capacity and funding, to advance in this highly specialised challenge, with inputs needed from a large array of disciplines. The current state-of-the-art demonstrates that research efforts at the national level so far have only elucidated fragments of the knowledge gap. OA is researched in primarily national initiatives or as sidestep in larger European projects that often focus on RA. Several organisations have been identified that (partly) address OA, but as already explained in section 1, OA is poorly represented in these communities and none of these organisations clearly focus on OA. Furthermore, most of these organisations do not critically involve patients, clinicians, researchers, and industries, including innovative SMEs and start-ups. Start-ups and SMEs often do not have the resources to attend the large international conferences and they are frequently left out of networking opportunities. EU-netwOArk will facilitate entry and engagement to the network for SMEs and start-ups. Below, this is further detailed for the most relevant organisations.

The European League Against Rheumatism (EULAR) is the organisation representing the people with arthritis/rheumatism, health professionals and scientific societies of rheumatology across all European nations. However, the strategic focus of this organisation has always been on rheumatic and musculoskeletal diseases of an "inflammatory" nature. With RA as focus, little attention is given to OA. A close collaboration of the novel ESOA with EULAR is foreseen, with for example, the possibility to combine the annual conference, especially in the start-up phase. The Osteoarthritis Research Society International (OARSI) focuses specifically on OA, but the patient perspective is very weakly represented. The EU-netwOArk network is convinced that a patient-centred approach is crucial for the development of improved treatments and prevention of OA. Furthermore, OARSI is strongly US-oriented, leaving less room for the establishment of a specific European approach. The new ESOA will have a strong and deep-rooted European focus.

The strategic focus of the European Society for Clinical and Economic Aspects of Osteoporosis, Osteoarthritis and Musculoskeletal Diseases (ESCEO), is on bone and Osteoporosis in particular, paying too little attention on soft tissues and/or ligaments, which are critically involved in OA.

Furthermore, there is little consideration of the patient's perspective in ESCEO. Within the European Orthopaedic Research Society (EORS), OA is only a small area of interest, with most of its research focused on bone and ligaments, biomechanics, and implants to repair joints. Preventing post traumatic OA is an interest of the International Cartilage Regeneration & Joint Preservation Society (ICRS). The new ESOA will be the reference organisation for OA in Europe, holding regional meetings with a unique international flavour. Most of these organisations mainly organise large international conferences, leaving less room for focused interaction between European researchers working in Europe. Currently, European researchers working on OA, especially early career researchers, do not have an appropriate venue to present their work and network with other relevant scientists. The existing conferences such as https://2021.oarsi.org/ and https://www.wco-iof-esceo.org/ do not provide enough opportunity for presenting European focused OA research. A smaller scale and finer grained organisation in Europe, which also stimulates more personal networking and research collaboration, is an added value to the existing landscape of clinical and academic societies discussed above. For the early stage researchers, the novel GRC style summer/winter schools bring clear added value to the existing opportunities for research training, especially for PhD students and early career investigators, thereby allowing established researchers to mentor them in an informal networking setting.

2.2. ADDED VALUE OF NETWORKING IN IMPACT

2.2.1. SECURING THE CRITICAL MASS AND EXPERTISE

The initiators of EU-netwOArk are convinced that, from the very beginning, the perspective of patients, clinicians, industry, and academics need to be involved in a balanced manner. This Action is the first to bring all scientific, clinical, industrial and patient expertise together, to tackle the challenge of OA in a comprehensive manner and connect (academic) research institutes, private research organisation, patient organisations, pharmaceutical organisations, governmental health representation, clinicians and health care workers. Basically, the entire OA value chain, from bed to lab and from legislative to industry is covered in this Action.

2.2.2. INVOLVEMENT OF STAKEHOLDERS

The network of proposers includes 41 partners (51-49 M/F gender distribution) from 17 countries (9 of them are COST Inclusiveness Target Countries) and is made up of 31 academic institutions, 1 governmental organisation, 4 companies, and 3 associations representing patients. The initiators of EU-netwOArk recognise that patients should be actively involved in the design, conduct and dissemination of research. Unfortunately, research generally continues to be carried out on patients, but not with patient and patient group involvement. Patient participation in research empowers patients, democratises research, and enhances the quality of research and the development of equitable healthcare solutions. The COST Action aims to improve patient involvement in 1) setting priorities, 2) study leadership and design, 3) improved access to clinical trials, 4) preparation and oversight of the information provided to participants, 5) post-study evaluation of the patient experience, and 6) the dissemination and application of results. Further, developing Chronic Disease Self-Management Programmes will empower patients to become active agents of their own care and life.

Currently, the academic and industrial research on OA is dispersed over many disciplinary networks or related disease-oriented societies. There is a eminent and pressing need to create a platform where researchers from these separate networks can meet to discuss research progress, exchange crucial breakthroughs and plan future research. As indicated in paragraph 2.2.1, there are a multitude of societies and related conferences that address fractions of the OA challenge.

Next to patients, health care providers are crucial stakeholders to bring the results of research to the benefit of those suffering from OA. As described in previous sections, current management of OA is inadequate due to limited uptake of key treatments like education, exercise and lifestyle adjustments and the lack of treatments proven to affect disease progression. To date, there is no cure for OA, and the most common treatments only ease the symptoms. Therefore, the initiators of EU-netwOArk underscore the importance of a translational research approach. The goal of this translational research approach is to combine disciplines, resources, expertise, and techniques within the pillars benchside, bedside and community, to promote enhancements in prevention, diagnosis, and therapies. The health care providers include rheumatologists, orthopaedic surgeons, physiotherapists, prevention workers, primary care, pain medicine, pharmacists, and nutritionists. There is a clear lack of entrepreneurial scientists and clinicians capable of translating basic research in clinical applications and products for the health care market. For novel diagnostic methods, drugs, or advanced therapy medicinal products to become available in clinical practice as fast as possible, the early involvement of industry is key. This can either be high-tech start-ups, large pharmaceuticals, or medical technology companies. Improving the interaction between these key players, to accelerate the development from bench to bed, of methods and products that can improve the quality of life of those suffering from OA, is the driving force for organising EU-netwOArk.

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

OA is a global problem, affecting people from all continents. The pursuit of better prevention, diagnosis and treatment is also conducted by researchers, clinicians, companies, and patients from all over the world. Therefore, it is crucial for the European OA network to be well connected to networks in other continents. Already at this initial stage, EU-netwOArk has connected to researchers in Australia and the US. It is the ambition of the network to establish interaction with all relevant initiatives worldwide. Worldwide networks like OARSI and ICRS, are of particular interest in this respect. On a more practical level, EU-netwOArk will actively invite key-representatives from other continents to participate in its activities, such as the training schools and the annual conference, to stimulate the exchange of knowledge and coordinate research efforts worldwide.

3. IMPACT

3.1. IMPACT TO SCIENCE, SOCIETY AND COMPETITIVENESS, AND POTENTIAL FOR INNOVATION/BREAKTHROUGHS

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

As previously described, the changing European and global demographics indicate that new treatment strategies for OA aimed at curing, preventing, or as a baseline to at least halt the further development of OA, are urgently needed. Although significant attention has been focused on the development of costly disease modifying drugs for RA, this is not the case for OA and that is why we need to bring together European researchers who can tackle translational and transdisciplinary aspects of OA and its links beyond orthopaedics and rheumatology to the immunological and metabolic challenges in their broadest sense. There have been tremendous advances in our understanding of the epidemiology,

impact and burden of OA in Europe and globally, and the identification of those at risk of disease progression, but our understanding of the pathogenesis of the condition is limited, hampering drug development. Opportunities for progress now lie in the application of public health interventions to prevent OA, targeting overuse of inappropriate and low-value care, equitable access to existing cost-effective interventions, and identification of low-cost, safe pain relief and prevention of metal health disorders associated. New thinking will be crucial to improve OA prevention, management, and policy [4]. EU-netwOArk will contribute to increasing awareness of OA and advance the agenda of improved OA prevention and care.

OA prevention is feasible and readily within reach now at the primary and secondary levels, but it needs a system redesign to ensure widespread implementation of injury prevention programs and community-based obesity reduction and physical activity. Despite good evidence indicating that, by reducing weight and preventing joint injury, we can significantly reduce the risk of people developing OA, deployment of such programs is slow, inefficient, and poorly taken-up. Direct engagement of patients in these activities will improve these efforts. EU-netwOArk can contribute by bringing together healthcare professionals, policy makers and scientists to stimulate the formulation, dissemination of implementation of such evidence-based modifications of healthcare systems throughout Europe.

Identifying phenotypes of OA is an important research priority because it allows us to treat the disease more effectively, especially in a community setting with poor areas with low resources contexts. This knowledge will also allow us to gain a better understanding of the pathways and mechanisms that may be involved in each distinct phenotype and target them more effectively using a variety of preventive and treatment strategies. Engaging with industry will have significant impact on their drug development efforts. Unfortunately, the OA research and clinical development arena is littered with phase 2 clinical trial failures, and many of the corporate interests have come and gone over the years as a consequence of these failures, branding OA as a “difficult to treat” and insurmountable disease. However, much has been learned from these negative clinical trials, and this knowledge is now being applied in more thoughtful clinical trial designs. EU-netwOArk will contribute to overcoming these limitations, increasing interaction between academics, industry, and regulatory authorities to learn from past mistakes, avoid making them again in future clinical trials, and pave the way to facilitate more efficient, more pragmatic and adaptive trials, raising a real possibility that effective disease modifiers are well within our reach.

EU-netwOArk helps all stakeholders involved in OA to meet, network, learn, exchange ideas, find partners, provide mentoring, and innovate cooperatively. The Action strengthens diversity, the intellectual fuel of scientific enterprise, creating opportunities for researchers in emerging start-ups and scientific disciplines, at an early stage in their careers, and in countries that are still building their scientific capacities. EU-netwOArk helps by cross-pollinating ideas and people to harness the power of hybrid thinking, fresh perspectives, and wider understanding.These networking efforts of EU-netwOArk will have longer term impacts in science, technology and society as summarised below. The network will advance the definition of criteria for endo-/phenotypes, how to classify them, how to measure them, how to treat them, how to follow them up, how to predict them, and how to prevent them. The actual research needed for this, will be funded from other sources than COST.

Scientific (breakthroughs)

- Understanding OA phenotypes, allowing for stratification of patients.
- Understanding comorbidities associated with the different OA phenotypes, leading to new scientific understanding of risk factors.
- Identification of biomarkers for diagnosis (OA sub phenotype), prognosis (treatment success), and disease monitoring.

Technological (potential innovations)

- Development of new, phenotype based therapies for retardation of disease progression (subtype-based medicine) or regeneration of deteriorated cartilage, such as intra-articular injection therapies in combination with slow release of drugs.
- Development of nanotechnology-based solutions for targeted drug delivery, cellular imaging and nano sensor based smart orthotics.
- Development of next generation regenerative medicine options for OA with iPSC cell technology such as iPSC derived OA cell-therapy (iMSCs) as well as iPS-cell derived generation of (large scale) neo-cartilage constructs for implantation purposes
- Development of predictive phenotype-specific pre-clinical in vitro models including organ cultures, bioreactors, and sensors, including micro-biosensors, for drug screening and real-time monitoring.

Socioeconomic

- Awareness of the seriousness of OA as a disease by key European and national policy makers.
- Improved prevention based on to better understanding of risk factors and co-morbidities of OA.
- Decrease DALY's by improved treatments, symptom control, disease management, reduced waiting lists for interventions, and prevention of OA related disability.
- European OA platform for your researchers providing key training opportunities and fellowships
- Increased participation of ITC partners in new OA focused research projects

3.2. MEASURES TO MAXIMISE IMPACT

3.2.1. KNOWLEDGE CREATION, TRANSFER OF KNOWLEDGE AND CAREER DEVELOPMENT

EU-netwOArk will stimulate knowledge creation by setting a research agenda and coordinating (national) research efforts throughout Europe. It will stimulate collaboration of academic and industrial research groups to bring together consortia and to formulate collaborative projects. The network will generate consensus guidelines for the collection of bio samples and clinical data from early OA patients, from all stages OA patients, together with respective electronic medical record (EMR) to create a curated database for basic and clinical research tissue biobank and secure (encrypted) data network. These databases and bio banks will have a large positive impact on the size and the quality of clinical studies. Consensus guidelines for the design of clinical trials, including the cofactors to be measured in each OA trial and surrogate outcomes, will help companies to increase their success rate in phase 2 and 3 clinical trials, thus stimulating new products and services to become available for the people suffering from OA.

Transfer of knowledge: The network will stimulate the development of consensus knowledge and a harmonic synthesis of the available scientific evidence into clinical guidelines with a short-term impact on clinical practice throughout Europe. On the medium term, translating scientific findings into meaningful medical devices, pharmaceutical products and advanced therapy medicinal products is a growing challenge. The Action will facilitate key players in the field of OA to meet and to build the network of experts needed to translate the many recent promising results in life sciences in meaningful clinical applications. The network will pay due attention to improving both the competencies of the researchers involved, as well as the support structures available in the RTD organisations, such as the technology transfer offices (TTOs) to support and stimulate business development and knowledge transfer. These TTOs are tasked to help researchers to manage the process of identifying opportunities for use or commercialisation, the protection of intellectual property, co-innovation-based business development or plain industrial knowledge transfer to an existing or a spin-off company. Sharing of best laboratory and clinical practice within the network will allow for further professionalisation of these support departments.

Career development: Human resources are a critical factor in achieving the challenging goal of alleviating the burden of OA. There is a dire need for researchers that are capable of translating key basic science findings towards meaningful clinically applicable interventions. EU-netwOArk aims to create a new generation of scientists and clinicians, well-rounded individuals who will be capable of combining and translating major innovations in life sciences into meaningful clinical applications and the health care market. This also includes scientists and clinicians with entrepreneurial skills, that can carry the translation of science into novel therapies and products. The Gordon Research Conferences style Training Schools, the Short-Term Scientific Missions and conference grants for researchers from ITCs are the tools to increase the number of young researchers selecting a career in OA research. Furthermore, the annual conference will be an inspiring event for these young researchers to present their work, be stimulated to continue their career in this exciting field and get embedded in the network. Finally, the network already has 10 open PhD positions for young researchers and is strongly committed to multiply this amount in future years.

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

The network aims to translate research results into know-how, products, therapies, diagnostics, and business activities, but also to make scientific knowledge accessible to a broader audience. The Action will draw up a general dissemination and exploitation plan that will be updated regularly during the lifetime of the Action, in collaboration with the marketing and communication offices of the partners.

Table 2 *Outline of the general dissemination and exploitation plan*

Target groups	Addressed through (how)	Objective & impact	Indicator (targeted value)
OA health care providers	• Participation in OARSI, EULAR, ICRS, EORS, ISEAT conferences, newsletters, social media • Position papers	• Connect and inform health professionals, caregivers, patient organisation of research results, preventive policies	Health care professional survey participants feedback (50% response rate, approx. 3K participants)
OA patients and patient organisations	• Action workshops • Online video (YouTube) & social media (LinkedIn, Instagram, Facebook, and Twitter) & website • Patient participation groups	• Enhance knowledge of OA and its prevention and treatment	# of participants of workshops (3-6K)
Industry	• Trade fairs (Medtechlive) • Social media & Online video • Website	• Connect and inform industries of research results	# visits by companies (100)
Basic, translational, implementation, and clinical researchers	• Scientific articles • Participation in OARSI, EULAR, ICRS, EORS, ISEAT conferences	• Awareness of and participation in ESOA • More collaboration throughout Europe	# articles (40) # conference presence (20)
Policy makers	• Lobbying as a network and through academic	• Evidence based policies for reimbursement	Two specific regulatory updates generated

	institutions, NGOs, patient organisation	• Regulatory framework for pan EU exchange of bio samples & data	
Schools/universities	• Visits to schools and other types of professional training centres • Visits by students to clinics research laboratories and companies • Online video & social media	• Career opportunities in academic and industrial research related to OA • PhD positions • Awareness of OA and how to prevent it?	# participation in workshops and conferences (16) # of hits video, website, and views on social media (40-50K) # PhD's recruited (>30)
General public	• Articles in/press releases to interviews in general newspapers in Europe • Presence at fairs, events and Science Festivals • Website • Social media, webinars, podcasts	• Enhance knowledge of OA and its prevention and treatment • Mobilisation of research funds • Setting scope of funding schemes	# articles (120) # press releases (8) # interviews, webinars & podcasts (150) # unique website visitors (10K)

A Dissemination Coordinator will be in charge and will supervise all dissemination activities.

- Themed **Action Workshops** will be organised by working groups and open to all participants.
- There will also be three themed **Training Schools** (years 2, 3, and 4 of the Action), targeting PhD students and ECIs/ESRs. The Schools will have keynote lectures by patients, renowned academics, and clinical experts from Europe or IPCs, participant poster or oral presentations, panel discussions, academic debates, and mini-training sessions aiming at skills development.

Indicatively 40 **Short Term Scientific Missions** (STSM) will be carried out during the Action's lifetime.

4. IMPLEMENTATION

4.1. COHERENCE AND EFFECTIVENESS OF THE WORKPLAN

4.1.1. DESCRIPTION OF WORKING GROUPS, TASKS AND ACTIVITIES

Figure 1 Schematic overview of Working Groups

The Action will be structured in four Working Groups (WG). Because the network puts the interest of the patient first, WG1 will organise the interaction with patients and patient organisations. This interaction goes beyond the dissemination of research results to these target groups. The patients and patient organisations will also provide input for setting the research agenda and prioritising topics for research identified by patients. A second important theme is the translation of exciting (fundamental) scientific results to the clinic, with the key objective to contribute to reduce the increasing burden of OA in society. This can be achieved by both primary prevention as well as new means to reduce the impact and progression of established OA. WG2 will focus on this theme. WG3 will focus on the main scientific challenges as identified in Chapter 1. There will be close interaction between the themes since they are closely related and have many interdependencies. Part of the work will be analysis of existing research, road mapping of these initiatives and creating a general overview of the state-of-the-art in Europe. The Action will deliver a new and commonly shared view on OA stratification, sub-type-based treatments, and roadmaps for future therapies and drug discoveries. Finally, WG4 will develop an organisation model, including a plan to finance the continuation of the coordination activities, for the period after this COST Action.

WG1: Patient engagement & information programme on AO

Objective: To engage with patients, and to identify novel and effective approaches to engage with patients and patient representation groups.

Task 1.1: Give patients a voice in research planning, including all activities of EU-netwOArk.

Task 1.2: Experiment with social media “influencers” / patient experts, alongside more traditional patient organisations, to improve the communication between patients, clinicians, and researchers.

Task 1.3: Give patients a prominent place in the conferences, workshops and training schools of EU-netwOArk, both in dedicated patient workshops as well as contributing to clinical and scientific sessions.

Task 1.4: Survey OA patients across Europe to assess their level of understanding of their condition and determine what they know about treatment guidelines.

WG2: Speed up translation from bench to bedside

Objective: Improve the translational approach in research to increase the number of new treatments and prevention strategies that will become available in health care for OA patients

Task 2.1: Technical and economic hurdles associated with establishment and implementation of translational research models (crossing the Valley of Death).

Task 2.2: Guidelines for data collection, sampling, phenotyping, endotyping and clinical trial designs for companies bringing products targeting OA to the market, to avoid common repeated failures in phase 2 and 3 clinical trials.
Task 2.3: Identification of the major challenges associated with translation from preclinical models to humans without intermediate translational models
Task 2.4: European consensus on Chronic Disease Self-Management Program CDSMP program for OA prevention

WG3: OA Phenotypes, patient stratification and comorbidities
Objective: To develop consensus on OA phenotyping, how these can be exploited to learn more about OA subtypes and understand the comorbidities associated with OA. Draft roadmap on existing research and defining the major gaps in basic, translational, and clinical research.
Task 3.1: Understanding OA Phenotypes and provided patient stratification guidelines
Task 3.2: Development of (sub) type-based OA therapies
Task 3.3: Understanding comorbidities associated with OA sub-types

WG4: Building the European Society for Osteoarthritis (ESOA)
Objective: To develop the foundations in terms of strategic objectives, partners, governance, and finance for ESOA and to start its implementation
Task 4.1: Expanding the network with partners throughout the value chain, from care, health insurance, public bodies, and policy makers to include all relevant stakeholders
Task 4.2: Organise an annual conference, bringing together European stakeholders in OA
Task 4.3: Set up and run training schools every year
Task 4.4: Organise a call for proposals for STSM and conference grants for ITCs every 6 months
Task 4.5: Develop a sustainable model for the OA research platform after ending the COST action in terms of activities, governance, and finance

4.1.2. DESCRIPTION OF DELIVERABLES AND TIMEFRAME

The timeframe of WGs and individual WG-tasks is shown in the GANTT diagram in section 4.1.4 below.

Working Group	Deliverables	Timeframe
WG1	D1.1 Report on results of the European survey D1.2 Report on patient research priorities D1.3 Report on novel, social media-based interaction with patients	M12 M24, 36, 48 M24, 48
WG2	D2.1 Guidelines for clinical trial set-up for companies D2.2 Report on challenges translation preclinical models to humans D2.3 European CDSMP for OA prevention	M24 M36 M24, 48
WG3	D3.1 Consensus report on stratification of patients in OA phenotypes D3.2 Consensus report on (sub) type-based therapies D3.3 Consensus position paper on OA co-morbidities	M24 M36 M48
WG4	D4.1 Project Action website life D4.2 Training material for training schools D4.3 Report on results of calls for proposals for STSM and conference grants D4.4 Foundation plan for a sustainable European OA research society	M3 M18, 30, 42 M12, 24, 36, 48 M48

4.1.3. RISK ANALYSIS AND CONTINGENCY PLANS

Risk 1: Insufficient scientific consensus. This could potentially lead to reduced interest of partners and hence slower than expected progress of the objectives of the Action. Mitigation: the risk will be mitigated to assure that sufficient broad participation in the respective working groups is available, ranging from scientists, clinicians to patient representatives.

Risk 2: Clear stratification and hence identification of population-based medicine to engage these sub-types might conflict with the interests of the pharmaceutical industry to service large populations. Interest from pharmaceutical industry for this more targeted approach might be low. This risk may be mitigated through innovative start-up companies. The network will actively scout these companies and generate interest that attracts them to join the Action.

Risk 3: Is related to the interaction with and acceptance by clinicians. The traditional views of OA as a "wear and tear" disease caused by excessive load of joints must be replaced by more updated and mechanistic insights onto subtypes and related comorbidities of a more complex and heterogeneous disease.

Risk 4: Insufficient participants per WG or in Action events. Mitigation: In the development of this COST action many meetings and online sessions have already been organised with the founding members. The engagement of the founding members was remarkably high, and the topics addressed in this Action address an unmet need in the founding network, and with the foreseen expansion of the network, even greater participation is expected. In the unlikely event of insufficient participation, a pro-active requirement of participants will be implemented.

Risk 5: Since this Action also involves industrial Biotech participants, the stratification of OA for example, could lead to a conflict of interest between participants. Mitigation: From the early start of this Action the communication and meetings have been open to all stakeholders, leading to open and transparent discussions. Also, during implementation, the meetings and workshops and their respective agendas will be established in a highly transparent way. Instalment of a neutral government body of this action will mitigate any potential conflicts of interest between participants.

Risk 6: Insufficient knowledge exchange in and between WG's. Mitigation: Since this Action addresses a clear and unmet need in OA research and overcomes the current insufficient international knowledge exchange, we believe this risk is limited. The researcher will be motivated by nature to collaborate, since the scientific challenges are too ambitious to resolve from a single perspective. By facilitating international cooperation, and the regular workshop meetings, knowledge exchange will be greatly enhanced.

4.1.4. GANTT DIAGRAM

		Year 1				Year 2				Year 3				Year 4			
WG1	Task 1.1																
	Task 1.2																
	Task 1.3																
	Task 1.4																
	Deliverable 1.1																
	Deliverable 1.2																
	Deliverable 1.3																
WG2	Task 2.1																
	Task 2.2																
	Task 2.3																
	Task 2.4																
	Deliverable 2.1																
	Deliverable 2.2																
	Deliverable 2.3																
WG3	Task 3.1																
	Task 3.2																
	Task 3.3																
	Deliverable 3.1																
	Deliverable 3.2																
	Deliverable 3.3																
WG4	Task 4.1																
	Task 4.2																
	Task 4.3																
	Task 4.4		call 1		call 2		call 3		call 4		call 5		call 6		call 7		
	Task 4.5																
	Deliverable 4.1																
	Deliverable 4.2																
	Deliverable 4.3																
	Deliverable 4.4																
General	**MC Meeting**	1				2				3				4			5
	Training schools							1				2				3	
	Scientific Missions & Conference Grants																
	Conferences				1				2				3				4

5. REFERENCES

[1] M. Hiligsmann and J. Reginster, “The economic weight of osteoarthritis in Europe,” *Medicographia,* pp. 197-202, 2013.

[2] D. Huner and S. Bierma-Zeinstra, “Osteoarthritis,” *Lancet,* vol. 393, pp. 1745-59, 2019.

[3] W. Kaplan, V. Wirtz, A. Mantel, P. Stolk, B. Duthey and R. Laing, “Priority Medicines for Europe and the World - Update 2013 report,” WHO, Geneva, 2013.

[4] D. Hunter, L. March and M. Chew, “Osteoarthritis in 2020 and beyond: a Lancet Commission,” *The Lancet,* no. online 4 november 2020, 2020.

[5] E. Nüesch, P. Dieppe, S. Reichenbach, S. Williams, S. Iff and P. Jüni, “All cause and disease specific mortality in patients with knee or hip osteoarthritis: population based cohort study,” *BMJ,* no. 342, 2011.

[6] Osteoarthritis Research Society International, “Osteoarthritis: A Serious Disease,” 2016.

[7] E. Losina, G. Silva, K. Smith, J. Collins, D. Hunter, S. Shrestha, S. Messier, E. Yelin, L. Suter, A. Paltiel and J. Katz, “Quality-Adjusted Life-Years Lost Due to Physical Inactivity in a US Population With Osteoarthritis,” *Arthritis Care & Research,* vol. 72, no. 10, pp. 1349-1357, 2019.

[8] I. Ackerman, J. Kemp, K. Crossley, A. Culvenor and R. Hinman, “Hip and Knee Osteoarthritis Affects Younger People, Too,” *The Journal of Orthopaedic and Sports Physical Therapy,* vol. 47, no. 2, pp. 67-79, 2017.

[9] K. Allen, P. Choong, A. Davis, M. Dowsey, K. Dziedzic, C. Emery, D. Hunter, E. Losina, A. Page, E. Roos, S. Skou, C. Thorstensson, M. v. d. Esch and J. Whittaker, “Osteoarthritis: Models for appropriate care across the disease continuum,” *Best Pract Res Clin Rheumatol,* vol. 30, no. 3, pp. 503-535, 2016.

[10] V. Wylde, A. Beswick, J. Bruce, N. Howelis and R. Gooberman-Hill, “Chronic pain after total knee arthroplasty,” *Effort Open Reveiws,* vol. 3, no. 8, pp. 461-470, 2018.

[11] T. Vincent, “Of mice and men: converging on a common molecular understanding of osteoarthritis,” *The Lancet Rheumatology,* vol. 2, no. 10, 2020.

[12] D. Hunter, “Osteoarthritis Management: Time to Change the Deck,” *Journal of Orthopaedic & Sports Physical Therapy,* vol. 47, no. 6, pp. 370-372, 2017.

[13] S. Ahn, R. Bsu, M. Lee Smith, L. Jiang, K. Lorig, N. Whitelaw and M. Ory, “The impact of chronic disease self-management programs: healthcare savings through a community-based intervention,” *BMC Public Health,* 2013.

[14] T. McAlindon, R. Bannuru, S. M. N. Arden, F. Berenbaum, S. Bierma-Zeinstra, G. Hawker, T. Henrotin, D. Hunter, H. Kawaguchi, K. Kwoh, S. Lohmander, F. Rannou, E. Roos and M. Underwood, “OARSI guidelines for the non-surgical management of knee osteoarthritis,” *Osteoarthritis and Cartilage,* vol. 22, no. 3, pp. 363-388, 2014.

[15] W. Damon, “Peer education: The untapped potential,” *Journal of Applied Developmental Psychology,* vol. 5, no. 4, pp. 331-343, 1984.

[16] M. Ory, S. Ahn, L. Jiang, M. Lee Smith, F. Ritter, N. Whitelaw and L. K, “Successes of a National Study of the Chronic Disease Self-Management Program: Meeting the Triple Aim of Health Care Reform,” *JSTOR,* vol. 51, no. 11, pp. 992-998, 2013.

[17] Vianney Delplace, Marie-Astrid Bouteta, Catherine Le Visagea, Yves Maugarsa, Jérôme Guicheuxa,Claire Vinatier, “ Osteoarthritis: From upcoming treatments to treatments yet to come” Société française de rhumatologie 2021.