European Cooperation in the field of Scientific and Technical Research
- COST -

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COST 023/14

MEMORANDUM OF UNDERSTANDING

Subject :	Memorandum of Understanding for the implementation of a European Concerted Research Action designated as COST Action BM1402: Development of a European network for preclinical testing of interventions in mouse models of age and age-related diseases (MouseAGE)

Delegations will find attached the Memorandum of Understanding for COST Action BM1402 as approved by the COST Committee of Senior Officials (CSO) at its 190th meeting on 14 May 2014.

MEMORANDUM OF UNDERSTANDING
For the implementation of a European Concerted Research Action designated as

COST Action BM1402
DEVELOPMENT OF A EUROPEAN NETWORK FOR PRECLINICAL TESTING OF INTERVENTIONS IN MOUSE MODELS OF AGE AND AGE-RELATED DISEASES (MouseAGE)

The Parties to this Memorandum of Understanding, declaring their common intention to participate in the concerted Action referred to above and described in the technical Annex to the Memorandum, have reached the following understanding:

1. The Action will be carried out in accordance with the provisions of document COST 4114/13 "COST Action Management" and document COST 4112/13 "Rules for Participation in and Implementation of COST Activities" , or in any new document amending or replacing them, the contents of which the Parties are fully aware of.

2. The main objective of the Action is to form a network of scientists, clinicians, industrial partners and regulatory affairs experts from European countries with multidisciplinary expertise to define best practice on how preclinical interventions in mouse models of age and age-related disorders should be tested so to accelerate the translation to the clinic.

3. 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 60 million in 2014 prices.

4. The Memorandum of Understanding will take effect on being accepted by at least five Parties.

5. The Memorandum of Understanding will remain in force for a period of 4 years, calculated from the date of the first meeting of the Management Committee, unless the duration of the Action is modified according to the provisions of section *2. Changes to a COST Action* in the document COST 4114/13.

A. ABSTRACT AND KEYWORDS

The number of people over 65 is predicted to double in the next 50 years. Age is the most important risk factor for stroke, heart attacks, cancers, diabetes, and many other chronic diseases. Tackling the effects of the ageing population in Europe has stimulated funding of research initiatives at both national and European levels. A key requisite to develop new interventions for age-related conditions and promote healthier ageing is the availability and use of preclinical murine models. There is currently a clear lack of such models and appropriate standardised methodologies to test interventions. Therefore, to improve the quality of European ageing research a coordinated interdisciplinary action is needed to standardise methodologies and animal welfare, and to define endpoints, as well as centralising information, models and technologies for the assessment of interventions. This COST Action proposes the formation of a highly interactive and flexible European network, which will create a critical mass of cross-disciplinary scientists, clinicians and industrial partners to reach consensus on ways to test preclinical interventions in ageing mice. It will consolidate current best practice across leading European institutions and researchers, maximise resource efficiency, and provide a platform to help train the next generation of scientists.
Keywords: Ageing, mouse models, interventions, imaging, computational models

B. BACKGROUND

B.1 General background

The burden of age-related diseases continues to be a major European challenge and several initiatives are underway across the European Union to address the many different aspects of healthy ageing. These range from the strategic agenda of the European Innovation Partnership in Active and Healthy Ageing, through multiple Framework funded collaborative research projects such as EURHEALTHAGEING to many national or locally funded initiatives tackling specific aspects of age-related diseases. Many of these initiatives involve interventions to delay adverse age-dependent changes in multiple cells and tissues. Successful development and pre-clinical testing of such approaches depend heavily on animal models that are relevant for human ageing.

Testing in mouse models is a critical step in the development of interventions for the prevention and treatment of ageing associated diseases. However, there is a real need for a Europe-wide consensus on the scientific approach. At present, there is a lack of meaningful, standardised testing conditions and agreed endpoints that facilitate the transition to clinical testing across European centres, as well

as a lack of tools that allow an integrated and multi system assessment of the effects of interventions. Moreover, to conduct scientifically robust preclinical intervention studies, expensive resources and interdisciplinary expertise are required. For these reasons it is necessary that the research community on ageing comes together to share resources and know-how, avoid duplications, maximise outputs and be more competitive worldwide.
In the USA the National Institute of Health (NIH) has recognised the importance of reaching consensus and sharing resources in preclinical interventions and so has established a centralised intervention testing programme (NIA ITP) at the NationaI Institute of Ageing (NIA). This COST Action will allow scientists in Europe to come together to communicate effectively, share expertise and collaborate more effectively, so providing an integrated network that will make European scientists and industry more competitive in ageing research worldwide and, by doing so, benefitting clinicians, their patients and ultimately society as a whole. Moreover, this COST Action will build an innovative and forward looking programme that will enhance the visibility of this area of research and ensure capacity building of a new generation of scientists with interdisciplinary and cutting edge expertise. COST is the only mechanism that funds networking, exchange and training programmes in the biological sciences area at the European level, so this Action will ensure European consensus on key research issues and provide a clear road-map to help target future research funding programmes.

B.2 Current state of knowledge

The over 65s are the fastest growing segment of the population. With advancing age, chronic diseases become increasingly prevalent and age is the single largest risk factor for stroke, heart attacks, cancers, diabetes, and most other chronic diseases (http://www.silverbook.org/Chronic Disease and Medical Innovation in an Aging Nation). About 80% of adults over 65 years of age have at least one chronic disease, and 50% have two or more (http://www.cdc.gov/nchs/data/nvsr/nvsr56/nvsr56_10.pdf). Studies in animal models have shown that mutations (e.g. telomerase overexpression) or interventions (e.g. dietary restriction) that cause extension of lifespan result in the delay of onset of multiple chronic diseases [1, 2]. These data suggest that by targeting the fundamental mechanisms of ageing, it may be possible to delay or prevent age-related diseases and disabilities as a group, rather than one at a time. In addition, models of ageing are required to develop new therapies and prevention strategies against specific major disease that occur during ageing, e.g. Alzheimer's Disease, regenerative dysfunction or cancer. Both approaches (targeting of specific ageing associated diseases and targeting of basic

mechanisms of ageing) will have significant impact on improving health span and lowering health costs in the older population.

Testing interventions in mice is an important step in the drug development process for age-related diseases. Regulatory requirements almost always call for definitive studies in at least two laboratory animal species, one of which is rodent. Despite differences between humans and mice in metabolism, lifespan and susceptibility to diseases, mice are considered the species of choice and have proven to be a valuable model to understand the biology of ageing and to determine the capacity of interventions to impact lifespan, healthspan and frailty. This is because they are relatively economical, require lower amounts of drugs and there is a huge volume of literature on their genetics and genomics, physiology, behaviour and biochemistry.

However in Europe, intervention studies in ageing cohorts of mice are limited by resources and are mostly performed by individual centres, in one mouse strain, with very limited endpoints. They are often underpowered, leading to poor and inconclusive results. There is a real need for a Europe-wide consensus on the scientific approach because of the following common problems:

1. *Variability in outcomes due to lack of standardised testing methodologies across laboratories*

Reports from different laboratories in Europe and elsewhere, analysing the same interventions, often report inconsistent results. Variables such as strain of mice, sex, diet, housing environment and husbandry conditions are the main contributing factors. For example, the introduction of 40% dietary restriction (DR) to 41 different inbred strains of mice resulted in the predicted extension of lifespan in only 5% of the strains in male and 21% in female. Dietary restriction either had no effect or shortened lifespan in the other strains when compared to their respective ad libitum-fed littermates [3]. At the NIA ITP, despite standardisation of some of these variables, testing of aspirin, nitroflurbiprofen (NFP), 4-OH-alpha-phenyl-N-tert-butyl nitrone (4-OH-PBN), or nordihydroguiaretic acid (NDGA) resulted in large variability in survival [4]. Among the possible causes was the type of food used for the breeding stock or for weaning the mice prior to the start of the intervention. Another source of variability is the environment, which is known to impose a chronic stress state, affecting health and lifespan. Factors such as housing males separately from females, fighting between males, physical handling and exposure to different people, sounds and ultrasounds, odors and temperature are known to change the physiological and behavioural responses. However, their subsequent impact on lifespan, healthspan (defined as the period that is relatively free from the burden of age-related disease and disability before death) and frailty (defined as the incapacity to respond to stress and return to homeostasis) are poorly understood. This COST Action will agree on new standard operating procedures and will create consensus among the major research centres and industries in Europe (many of which are already part of this

Action) to ensure they will be adopted at the European level.

2. Lack of appropriate endpoints and models which facilitate transition into clinical applications

Translating intervention is a long term process (average 17 years). To speed it up, it is important that objective, robust and consistent outcomes, obtained in mice, reflect clinically relevant measures applicable to human trials. However, at present, gaps in knowledge and communication between scientists in preclinical phase, geriatricians, industrial partners and regulatory bodies, are a barrier to the identification of relevant validated measures. For example, endpoints such as healthspan and frailty are used in clinical research to monitor interventions. In contrast, most studies in mice focus on lifespan [5]. Ways to assess healthspan and frailty in mice have not yet been agreed. While measuring lifespan may be important, it is not the measurement of effectiveness which is useful for clinical translation. Clinicians and regulatory bodies find it unrealistic to expect to intervene in all younger, asymptomatic individuals based upon the expectation of a much later impact. Also, the likelihood of side effects can be high. For example, whilst Rapamycin increased median survival in both male and female mice, those mice had also more severe cataracts and greater testicular damage than the control mice [6].

The choice of animal models in which to accurately assess healthspan and frailty also requires careful consideration. At present the common practice is either to extrapolate data obtained from interventions in genetically homogeneous animal models or in disease models that develop the condition early in life. There are several European programmes such as EUMORPHIA, EUMODIC, European Mouse Mutant Archive (EMMA) and Infrafrontier, all targetting the generation and phenotypic analysis of knock out mouse mutants as models of disease but there has been little or no work to test the effect of age on disease development (see Section B4 for details).

Human populations are genetically heterogenous and nearly all chronic diseases develop in humans over time and manifest later in life. Although no single cause is responsible for more than 25-30% of human mortality, in C57BL/6, the most common strain of mouse used for preclinical testing at present, 86-89% die of cancer [1]. For comparison, cancer accounts for 23% of the deaths in many developed countries (http://www.cdc.gov/nchs/data/nvsr/nvsr56/nvsr56_10.pdf). However, it is not clear that any other inbred strain or the 4-way cross used by the NIA ITP to increase genetic diversity is better, or whether genetically-modified animal models developing chronic diseases similar to humans in later life need to be developed. Moreover, animals are bred in environments that do not take in consideration behavioral and environmental factors such as nutrient excess, physical inactivity, tobacco use, and excess alcohol consumption, all of which are prevalent mediators of chronic disease in humans, and presumably accelerate biological ageing. Whilst these differences between human disease and animal models may not be a barrier to translation of results,

this COST Action will bring together clinicians, research scientists and industrial partners to create a common innovative framework for identifying endpoints and comparing mouse data to find out whether different mouse models/strains or environmental conditions would improve the relevance of research data.

3. Resource-intense and multidisciplinary requirements for testing interventions in ageing mice

The cost of long-term intervention studies using statistically significant number of animals followed for long periods of time (24-30 months) is high. According to power calculations executed by the NIA ITP, each intervention should be tested in 44 male and 36 female mice, and this should be repeated in at least 3 independent sites [7]. This type of approach focuses only on lifespan as endpoint. If healthspan and frailty need to be used, this will require monitoring of the responses to challenges under multiple conditions (e.g. chemotherapy, wound healing, surgery, sepsis, cold exposure, pneumonia, metabolic challenges), possibly in more than one strain or disease model or in modified conditions to mimic exposure to tobacco or alcohol, excess nutrients etc. This will increase the number of animals, technology and infrastructure required. Many research laboratories do not have the resources, equipment or the expertise to conduct scientifically robust intervention studies of such a kind on their own. Moreover, scientists tend to have a single discipline approach whereas ageing affects multiple organ systems, requiring multidisciplinary expertise. A way to centralise expertise and plan allocation of resources at the European level is required and this COST action would provide that.

The advancing of imaging technologies and mathematical modelling offers opportunities for the development of faster and more cost-effective methods of assessment. For example, the three-dimensional trabecular microstructure of intact bones analysed by micro computed tomography in vivo [8] gives information on bone formation rates previously only assessed by histology. Similarly, comparing imaging of cerebral glucose metabolism with 18F-fluorodeoxyglucose (18F-FDG) using Positron Emission Tomography (PET) has allowed monitoring of age-related cognitive decline [9]. Optimization of new minimally invasive imaging methods that can be used in other tissues has the potential to detect age-related morphological and functional changes in mice, reducing the need of more invasive and post-mortem analysis. The continuous development of computational methods for biomedicine makes it now possible to generate highly individualised mechano-biological multiscale models of the human musculoskeletal, cardiovascular and neural systems, such as those developed within the FP7 European programme of the *Virtual Physiological Human* (VPH) [10]. A similar framework is available in rats but very little is available in mice. The FP7 programme RESOLVE aims at building computational models to study Metabolic Syndromes and comorbidities in patients and mouse models and identify drug targets. The multi-scale

computational approach ADAPT aims at modelling long-term, progressive changes in metabolism related to disease development (Metabolic Syndrome, dyslipidemia, hepatic steatosis) and the effect of therapeutic interventions in mice [11]. These prove that such approaches are viable in mice. However a wider technological and methodological research program beyond the monitoring of metabolic syndromes is required. This would create the ability to characterise the murine phenotype with much greater accuracy and sensitivity, and establish predictive models to directly test interventions, thus reducing substantially the number of animal experiments to be conducted and increasing the speed of testing. More importantly it would allow the simulation of parameters which change between mouse and humans, potentially giving more accurate prediction when translating from the preclinical model to the human cohort.

This COST Action will provide the opportunity for the European research community in this area to identify and agree innovative ways to build on its most advanced existing infrastructure and optimize resource development to accelerate progress and avoid duplication.

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B.3 Reasons for the Action

To achieve consensus on the issues described in Section B2 and ensure the outcomes are adopted by researchers across Europe it is imperative the major European stakeholders are actively participating. This Action will establish a multi-disciplinary network comprising the major groups of European researchers into ageing, including participants from clinical and non-clinical disciplines, academic and industrial institutions, as well as experts in regulatory affairs. Several of these groups have already enthusiastically joined in the preparation of this proposal. The clear mission is to address the major limitations to the testing of preclinical interventions of ageing using mouse models by:

- developing a consensus between all stakeholders;
- producing clear guidelines on issues such as endpoints, methodology and types of measurements as well as models
- creating a roadmap for the development of future technologies to speed up testing of interventions;
- establish a common European platform for the selection and testing of interventions performed cooperatively according to agreed SOPs;
- boosting training capacity in Europe in the areas of preclinical intervention and attract the best talent;

This will avoid duplications, allow direct comparison of interventions, maximise the use of resources and speed up the transition from preclinical to clinical applications. This will put network's participants in a position to improve the quality of research outputs and their competitiveness. It will respond to an unmet need to train junior researchers and clinical fellows with interdisciplinary knowledge, in ageing basic biology, imaging and mathematical tools, models of age related diseases and geriatric clinical endpoints, how to design and conduct pre-clinical and clinical studies and to navigate the regulatory framework necessary to translate recent advances into successful outcomes.

All of this will ultimately allow potential interventions against the effects of ageing progress faster to the clinic and so bring enhanced scientific, economic and health value to the EU.

B.4 Complementarity with other research programmes

The core of this Action is novel and not covered by any other programme in Europe or outside. However, there are a number of complementary programmes that will feed into this COST Action. For example SWITCHBOX, focuses on the role of the hypothalamus to regulate whole body homeostasis during the lifecourse. Part of this programme concerns standardization of methodology for endocrine and behavioural assessments and the study of the influence of stress (e.g. nutritional, psychological) on brain activity with age. This programme may provide useful information to this Action on how to standardise protocols and on the effect of stress. Modelling disease and biological processes has been a priority of many successful EU programmes. These include; EUMORPHIA, a programme to develop standardised SOPs for the phenotyping of disease models, EUMODIC, the generation and phenotypic analysis of knock out mouse mutants, and the European Mouse Mutant Archive (EMMA), an infrastructure for the archiving and distribution of mouse mutants. The generation of mouse mutants continues with the International Mouse Phenotyping Consortium. Underpinning this effort is Infrafrontier, providing a Europe-wide infrastructure network for the generation, distribution, and analysis of mouse models. In addition to these programmes there are disease specific programmes, in which potential members of the COST action are already leading figures such as MARK-AGE and RESOLVE. Some of the technologies used for the phenotypic characterization of mutant mice can be used to assess health status in older mice. Moreover, some of the mutants could be used as a starting point to generate conditional animals able to develop diseases later in life. This Action will ensure that it capitalises on the knowledge and resources developed by these programmes, that the ageing agenda is included in the existing programmes and a that coordinated effort is presented to European research community through existing portals in a standardised manner.

C. OBJECTIVES AND BENEFITS

C.1 Aim

The aim of this Action is to form a unique well-coordinated network of scientists, clinicians, industrial partners and regulatory affairs experts from different European countries currently working on different aspects of preclinical intervention in ageing mice models and with

complementary expertise in imaging, mathematical modelling, pathology, metabolic, endocrine, musculoskeletal, immunity, cognitive function and mouse welfare. This network will ultimately define best practice on how preclinical interventions in mouse models should be tested in Europe, with a view to accelerate the translation of any intervention to the clinic for patient benefit.

C.2 Objectives

Specific objectives and deliverables are to:

1. Establish and publish guidelines on standardisation of administration protocols, methods of assessment and measures of outcomes for intervention in preclinical studies (Task 1-5).
2. Create a publicly available web-based database which centralises all existing resources (including existing models), reports on the developments of the MouseAGE task-forces and acts as reference point for all researchers of ageing undertaking preclinical work (All Tasks).
3. Liaise with existing European programmes for the generation of models which develop chronic diseases late in life, review existing models of age-related diseases, identify new ones and coordinate efforts to generate the required models by submitting at least one funding application (Task 4).
4. Identify and agree among researchers in the biology of ageing, geriatricians, industrial partners and regulatory affairs experts on criteria to select intervention for preclinical testing and identify at least two interventions suitable for testing (Task 5).
5. Select and coordinate existing European infrastructures for preclinical testing so that testing is performed in an integrated way. Identify partners, a pipeline and funding to progress the testing of at least two new interventions (Task 6).
6. Constitute a collaborative group with expertise in imaging and sensing; review the existing imaging technologies available for the monitoring of intervention in ageing cohorts of mice and identify new required developments (Task 7).
7. Constitute a collaborative group on mathematical modelling, which can interact with imaging experts to publish a roadmap document towards the development of predictive digital models in ageing mice (Task 8).
8. Train early career researchers, particularly clinician scientists, with the appropriate interdisciplinary skill set to be better prepared to conduct preclinical intervention and to translate into clinical practice or reverse translate in an iterative process (All Tasks).

C.3 How networking within the Action will yield the objectives?

Networking within the Action will yield the objectives by:

1. Establishing a highly interactive network of experts with an interest in intervention on ageing and age-related diseases that will enable a full and accurate exchange of information (All Tasks).

2. Creating a network platform to allow the transfer of knowledge among the members of the Action and enhancing communication through a web-based resource, annual meetings, workshops and the organization of mobility programmes, all of which will enable researchers and students from the different groups of the Action to undertake short term exchanges for work and/or studies. The network will remain open to additional groups throughout the duration of the Action (All tasks).

3. Defining consensus criteria on healthspan and frailty; standardising the type techniques to assess healthspan and frailty and measures of outcomes; developing, validating and publishing Standard Operating Procedures (SOPs) to perform preclinical interventions; agreeing on variables including husbandary conditions, strains, diet, housing environment and appropriate models to use for the testing of intervention in line with a speedy clinical translation. This will also generate joint publications and delivery of workshops (Tasks 1 and 2).

4. Organising training schools (once a year) on specialised topics in a) models of age related diseases, b) endpoints and technologies to assess preclinical interventions, c) regulatory processes to approve new interventions, d) the role of imaging and computational models to monitor preclinical interventions in ageing mice. This will train early career researchers, both basic scientists and clinician scientists, in the range of multidisciplinary skills required for effective testing of preclinical intervention with clinical relevance (Tasks 1, 3, 4, 5, 7 and 8).

5. Improving European/international visibility of the network by establishment of a dedicated website and organisation of meetings and workshops to attract researchers, investors and industry (All Tasks).

6. Disseminating results and informing the scientific community, regulatory authorities, pharmaceutical industry and general public on the current status of important topics in the field of healthy ageing through publications, workshops and outreach events (all Tasks).

7. Increasing the interaction with the local regulatory boards and European Medicines Agency (EMA) in order to streamline the regulatory process. This will speed up the early clinical development and enable reciprocal education and mutual understanding of the specific expertise needed to develop safe interventions towards the goal of healthier ageing (Task 5).

8. Enable the acquisition of joint funding to create shared infrastructures for the preclinical testing of interventions at the European level (Tasks 6, 7 and 8).

C.4 Potential impact of the Action

The immediate benefits will be:

1. Increased visibility of the European research in the field of ageing.
2. The creation of a network for preclinical intervention in ageing and age related diseases will facilitate the collaboration of European researchers and increase scientific outputs.
3. Provision of a better framework for the design of preclinical intervention studies and better infrastructure around the latest technologies for assessment, which lead to a more rapid clinical translation.
4. Avoid duplication for testing of interventions and maximize the use of resources (all tissues analysed), so better adhering to the principle of the 3Rs by reducing of the number of animals used and ensuring all assessment protocols used cause the least discomfort to the animals.
5. Improved dissemination to the pharmaceutical industry of knowledge developed in preclinical interventions for healthier ageing, leading to faster development of potential solutions.
6. Better education, training and mobility of ESRs, which will guarantee the establishment of a new generation of research leaders in healthy ageing and preclinical intervention.
7. Provision of a networking platform that will form the basis for future major effective European grant funding applications.

Long term aims:

1. Uphold and accelerate the principles of reduce, refine, replace in animal experiments.
2. Create a positive personal and social impact for patients, their families and overall society by improving the management of older patients with multiple chronic diseases.
3. Reduce the economic burden of these chronic and debilitating diseases in Europe by less frequent hospitalization through the increased health of patients.

C.5 Target groups/end users

The end users of this Action are:

1. Academic researchers and clinicians interested and/or involved in development of interventions in healthy ageing and age-related chronic diseases.
2. Pharmaceutical industry and biotech companies involved in development of interventions to improve age-related chronic diseases and promote healthier ageing (e.g. micronutrients, pharmaceuticals).

3. Older patients suffering from multiple chronic diseases, their families and patient organizations.
4. Society at large, particularly through economic savings and diversion of funds into other areas of need.
Academic researchers, clinicians and members of the pharmaceutical industry were all involved in the development of this proposal.

D. SCIENTIFIC PROGRAMME

D.1 Scientific focus

The key scientific Tasks required to achieve the aims of this Action are listed below:
1. Define, review and produce standard operating procedures (SOPs) for the key variables affecting the outcome of preclinical intervention studies towards healthy ageing.
2. Define and establish guidelines of endpoints with SOPs of correspondent assays to use to monitor preclinical intervention studies.
3. Review the literature and cooperate with existing European programmes to determine which existing murine models are suitable for intervention studies in ageing and age-related diseases. Publish the outcome of the review and issue guidelines.
4. Determine which models need to be generated, liaise with existing European programmes to submit applications for funding to generate the missing models.
5. Review the literature and discuss with industrial partners, clinicians and regulatory bodies, which criteria should be used for the selection of interventions to test at the preclinical stage. Publish the review for wide dissemination.
6. Identify a strategy to ensure all countries in the European Union have access to facilities to test interventions in the ageing field, building on the best existing infrastructure and wide-ranging expertise and according to the agreed guidelines and SOPs. Facilitate exchange of early stage researchers to standardise techniques for the assessment of endpoints according to the agreed SOPs.
7. Review the existing imaging and sensing technologies in the light of the agreed endpoints and define which technologies could be used as non-invasive methods, making them more effective in time and costs. Identify methods for new developments. This will focus mainly but not exclusively on imaging to substitute for histological analysis.
8. Establish a roadmap towards the establishment of predictive computational murine models to test interventions in ageing mice.
9. Define ways to centralise data collection and sharing and establish a web-based resource.
10. Define a roadmap to acquire funding for the new developments.

The scientific research Tasks will be implemented by 4 Working Groups (WGs) consisting of participants already leading funded research in their own countries. Researchers involved in this Action have the scientific expertise to perform the research, as well as the technical means to do that locally. Furthermore, Short Term Scientific Missions (STSM) will be arranged to allow participants the opportunity to learn new methods in different laboratories and implement them in their own institutions or in specifically designated institutions where interventions may be performed on behalf of European investigators according to agreed SOPs. This will depend on the outcome of discussions in Tasks 1-6. Participation of Early Stage Researchers (ESRs) will be encouraged. ESRs will also take part in yearly training schools where the latest developments of the working groups in specialised and focused areas will be presented.

The WGs will carry out their scientific objectives organised in 8 Work-Packages or Tasks. Although these Tasks will have independent goals and deliverables, there will be a continuous feedback and scientific interaction between them. WGs will meet on a six-monthly basis to evaluate targets set at the previous meeting, draw conclusions, determine modes and timings for data dissemination (guidelines, protocols, website update and specific meetings, workshops) and set new targets for the next meeting. Given that research in the field is in constant progress, the Action will be structured to allow close communication with other research programmes and deliverables will be continuously monitored and updated. This framework will allow new groups (academic, clinical, industry or regulatory) interested in participating in the Action to be incorporated during the implementation period. Well-coordinated efforts will aim to limit overlap and render the field of preclinical intervention in ageing mice more efficient and cost-effective.

D.2 Scientific work plan methods and means

Working Group 1 (WG1) and Working Group 2 (WG2): Definition of Variables, Endpoints, Methods of Assessments (WG1) and Models (WG2):

These WGs will bring together scientists with expertise in pathology, veterinary science, intervention in ageing cohorts of mice, methods of assessment in different organ systems, as well as clinicians, industrial partners, and regulatory bodies, to review the literature, discuss knowledge developed in their own laboratories in testing intervention in preclinical models. They will aim to reach consensus on endpoint measurements, standardized methodologies which reflect the clinical endpoints, as well as examining the effects of variables such as environment, diet and mouse strain on the endpoints. In collaboration with members of existing programmes such as EUMORPHIA, IMPC, EUMODIC, WG2 will review which models suitable for testing preclinical interventions in

ageing cohorts are available. It will establish a wish list of models required, a roadmap to generate them and how resources can be centralized and shared.

Task 1: Endpoints, Lifespan, Healthspan, Frailty.

Although lifespan is a more commonly used endpoint, healthspan and frailty are much more desirable from a clinical perspective. However, they are both more difficult to assess and require the assessment of multiple parameters which have not yet been agreed. A number of healthspan measures have emerged to assess the state of multiple organs, physiological systems and behaviours in mice. Measures of physical performance, cognitive function, body composition, immune function, sensory acuity, and metabolic state have been proposed as they are clinically relevant and capture important aspects of ageing. However, there remains a critical need for refinement, optimization and standardisation of these measures. Similarly there is an unmet need to develop methods to determine how they may affect the resilience of mice to common late-life stressors. A number of clinically relevant perturbations and insults have been proposed (i.e., chemotherapy, anesthesia, pneumonia, hip fracture, surgery, sepsis, hypovolemia, cold exposure, and wound healing), but these remain largely untested, particularly in older mice. Similarly, so is the rate of recovery and tolerance for another perturbation and the way this may be assessed by measures such as food intake, body weight, grooming, habitual physical activity or other physiological variables. Finally, similarly to humans in the Baltimore Longitudinal Study of Aging there is a need to agree whether longitudinal study of laboratory mice are required to comprehensively assess the natural history of changes in measures of healthspan. Understanding the onset, order, rate and magnitude of changes in parameters of healthspan may foster better design, execution and interpretation of studies of anti-ageing interventions.

This Task Force will conduct a thorough analysis of literature. Based on shared experiences and in consultations with geriatricians and experts in regulatory approval processes it will identify the best parameters to define healthspan, frailty and methods of assessments, which will be used to draw up SOPs that can be used to inform further work across Europe. This Task is open to extend its scope to other important parameters of assessment.

Task 2: Variables – Focus on Diet and Husbandry Conditions.

Diet regime has been shown to be one of the major confounding factors in anti-ageing preclinical intervention studies, not only during the time of administration but also during breeding and weaning before the start of testing. Environmental variables, including time of day and light conditions, temperature, housing in individual cages or in group and protocol variables, including the method of acclimation and details of protocol administration, have neither been standardised nor consistently reported and yet they are important stressors, which can influence lifespan and

potentially healthspan and frailty. It is critical for these protocols and outcomes to be validated in older mice. Moreover, whether it is important to introduce stressors such as excess nutrients or alcohol or exposure to environmental hazards such as tobaccos as part of the assessment of the effects of interventions to healthspan and frailty requires discussion.

This Task Force will identify the important sources of variability in diets and husbandry conditions, and examine their effects on lifespan, healthspan and frailty through thorough examination of the literature and discussion of shared experiences, to produce SOPs that will be published and presented at conferences.

Task 3: Variables - Effect of Strains on Endpoints.

It is clear that different mouse strains have different lifespans. However their effects on healthspan and frailty have never been reported. This Task Force will review the evidence of the effects of mouse strains on these endpoints from the literature and from personal experiences. The Task aims to propose guidelines on the best strains to use in preclinical intervention studies and publish the outcomes. This Task will be aligned closely with Task Forces 1, 2 and 4.

Task 4: Models of Age-Related Chronic Diseases.

Another key measure of healthspan is the susceptibility to tolerance of a mouse for disease. Determining whether an intervention alters the onset of a disease in older mice is a complex Task. This may require the introduction of a mutation which makes it susceptible to a disease. This is usually best achieved by generating conditional knock outs, which allow the manipulation of the onset of disease later in life. However, there are a limited number of such transgenic lines. Disease models often develop the condition early in life and spontaneously, in contrast to humans in whom nearly all chronic diseases develop over time and manifest in later life.

Task Force 4 will liaise with members of existing European programmes and members of Task Force 1 and 5 to review what suitable models are already available and what need to be generated. It will ensure that information on suitable existing models are available on the COST Action website. Through review of the literature and discussion it will formulate indications for the use of each model and publish guidelines. It will apply for funding to generate the new models required.

Specific outputs over 4 years for WG1 and WG2:

- At least six peer-reviewed papers, including review papers.
- Specific SOPs on endpoints, assessment techniques and rearing of animals published on the MouseAGE Website.
- Two Training Schools aimed at education of ESR.

- At least four Workshops aimed at dissemination of results of the Action, education of ESR and interactions with industry and regulatory authorities.
- Submitting at least one funding application.

Working Group 3 (WG3): Testing Novel Interventions.

Despite the great potential of interventions (both lifestyle interventions or pharmaceuticals) to promote healthy ageing, progress is limited by the financial, organizational resources, infrastructure and specialised personnel required to conduct robust studies. Moreover, there are no accepted criteria which reflect clinical and regulatory demands by which interventions are selected for testing. In Europe there is excellent expertise and resources to address this problem but they are fragmented. WG3 will address how these expertise can come and work together to streamline the interventions to test, apply standardised methods of testing, maximise resources and avoid duplication in the delivery of preclinical interventions.

Task 5 – Selection of Interventions for Future Testing (set criteria, review the existing novel interventions available).

There are several important issues to consider when choosing which long-term interventions to test. First is the evaluation of the preliminary data supporting the interventions. Preliminary data often comes from studies in a variety of model systems ranging from invertebrates to humans. For pharmaceutical agents one may need to consider issues such as the ease of administration; the stability of the compound; the rate at which the agent is eliminated or metabolised in mice; and the cost of administration.

This Task Force will review criteria for the prioritization of intervention to test, review existing data on a variety of novel interventions (e.g. type of diet, micronutrients, pharmaceuticals) available in the literature and from data produced by members of the group. The involvement of clinicians, industrial partners, and members of regulatory bodies will help to reach consensus on two interventions to prioritise for testing during the duration of the COST Action. Funding will be sought for performing the testing.

Task 6: Strategy for Establishing European Infrastructures Equipped to Test Intervention.

Considering the costs for the necessary instrumentation to perform many of the measures required, the personnel and organisational infrastructure and wide-ranging expertise required, the possibility of creating centres to underpin testing for all EU researchers would make economical sense, avoid duplication and ensure testing is rigorous and comparable. At present most centres are excellent in one or two areas, (e.g. bone analysis, cognitive analysis, or metabolism) but effective assessment of interventions require multisystem approaches. A centralised testing intervention programme, where

the mice cohorts are housed in agreed centres and expertise from EU research members are gathered so that a higher number of measurements can be performed, according to a well-established pipeline as informed by Task Force 1-5, is appealing. It would maximise resources and collect a larger amount of data from the same animal in a standardised fashion. STSM can be used for the transfer of technologies where required. However, this is an ambitious goal. To succeed it requires consensus on the way it may be achieved among the major stakeholders in Europe. This COST Action aims to achieve this.

This Task Force will review and discuss the options to ensure all countries in the EU have access to facilities able to run preclinical interventions according to the agreed SOPs and guidelines as determined by Tasks 1-5. It will establish whether the existing mouse infrastructure in Europe could be used as starting point and produce a position paper with timetables and milestones for the realization of the proposal. They will identify the appropriate expertise required and apply for funding. They will benefit from STSM to establish common technologies in key centres.

Specific outputs for WG3:

- At least two peer-reviewed papers, including review papers.
- One Training School aimed at education of ESR.
- One position paper on generating suitable European facilities for testing.
- Twelve STSM, not exclusively ESR.
- Reports from STSM.
- One Workshop aimed at dissemination of results of the Action, education of ESR and interactions with industry and regulatory authorities.
- At least two joint funding applications.

Working Group 4 (WG4): Novel Technologies and Future Developments.

For the EU to be world leading in this field it is necessary to ensure continuous development of technologies which accelerate testing, reduce costs and improve quality of data and animal welfare. Imaging technologies and multiscale predictive models of organisms are emerging as areas of strength in Europe, which can fulfil these needs. Task 7 (Imaging Technologies) and Task 8 (Towards the Digital Mouse) will work closely together.

Task 7: Imaging Technologies.

Task 7 will review the existing imaging and sensing methods in relation to the requirements identified in Task 1 and Task 8 to optimise and standardise the methodologies to fulfil their needs.

It will also identify new developments, which could improve the existing testing and apply for funding for their development.

Task 8: Towards the Digital Mouse.

Task 8, in collaboration with Task 7, will draw a roadmap for the development of imaging and sensing and predictive modelling to refine, reduce and replace animal experimentation, speed up the examination of the effects of intervention, and explore better ways to translate observations on mice to humans. The roadmap will also explore the possibility of developing shared European infrastructures and e-infrastructures, for example a digital repository of mouse imaging, sensing, and modelling, along the lines of the VPH initiative. This will be done in close collaboration with industrial partners, who can develop the use in industry of in- *silico* methods for the pre-clinical and clinical assessment of new biomedical products. It will also coordinate the application for funding to realise some of these collaborative initiatives, and publish its main conclusions as a position paper. Both Task Forces will benefit from STSM of ESRs to exchange technologies.

Specific outputs for WG4:

- At least one peer-reviewed paper.
- One Training School aimed at education of ESR.
- One position paper on the roadmap toward the development of the digital mouse.
- Six STSM, not exclusively ESR.
- Reports from STSM.
- At least two workshops.

E. ORGANISATION

E.1 Coordination and organisation

The main goal of this COST Action is to establish a network of researchers with complementary and interdisciplinary expertise in testing preclinical interventions against ageing in mouse models in a coordinated and robust way, according to standardised SOPs and supported by a critical mass of experts. Their core funding is assured by different national and international programs and one of the objectives from this Action will be to secure further funding. COST is the ideal framework for the establishment of the network required to generate such cooperation and coordination.

To achieve this, MouseAGE will deliver its Action through four Working Groups (WG) and will

implement the following organisational structures:

Management committee (MC):

As outlined in "Rules and Procedures for Implementing COST Actions" (doc. COST 4154/11) the MC will be composed of up to two representatives from each Party, and one representative of the non-COST institution. Wherever feasible, the proxy shall be an ESR who is expected to work closely and support the representative member to deliver the aims of the MC. The Chair, Vice-Chair and grant holder will be elected at the first meeting of the Action with a balance of gender on all levels. In the MC each Party will have one vote.

The MC will be responsible for the overall strategy of the Action and delivery of milestones as well as the allocation of funds. The MC will appoint the WG Leaders (WGLs), who will implement the Action. The MC will solicit and approve a Work Plan for each WG, review and approve the reports of the WGs and coordinate their interaction. The MC will monitor the progress of the Action, in accordance to the timetable specified in Section F. In order to avoid delayed progress of the Action, WGs will send a short report every 6 months to the MC. The MC will also be responsible for the establishment of contacts with other European and international programmes and associations, as well as governmental bodies and for the dissemination of results throughout the whole community. The MC will be in charge of boosting visibility of the research on ageing in preclinical models in Europe. The MC will approve the admission of new partners. Future partners will be welcome and integrated in the existing structure. The MC will meet twice a year for the duration of the Action and will remain in close contact at other times.

Steering Committee (SC):

The Chair, Vice-Chair and the WG leaders will constitute the Steering Committee. The SC will be responsible for the daily management and general organisation of the Action. The SC will meet at least twice per year and will have meetings through internet/teleconferences when necessary. It will report to the MC. An animal welfare coordinator (AWC), an ESR coordinator (ESRC), an equality and diversity coordinator (EDC) and a website and dissemination coordinator (WebDC) will also be elected by the MC and will be part of the SC. Wherever possible these will be ESRs and will be responsible for the appropriate implementation of these particular aspects across the working groups. In all its activities and committees, the Action will respect an appropriate gender balance and enforce ESR involvement. The SC and Coordinators will have executive powers; they will plan the work implementing the decisions of the MC and reporting to the MC. They will organize regular meetings with the MC, WGs and conferences. A public and private website will be established and kept current.

E.2 Working Groups

This Action will have four WGs as detailed in Section D. All participants of the Action will be invited to join one or more of the WGs, according to their expertise and scientific interests. Additional WGs or modification of any WG may take place during the Action. This flexible framework facilitates the integration of new parties, favoring the integration of data and incorporation of emerging issues. Each WG will have a WG leader and a deputy-WG leader (the latter, wherever feasible, being an ESR) elected by the MC. WG leaders will organise the schedule of the WG meetings in coordination with the MC, and lead the scientific discussions and report to the MC on progress every 6 months.

E.3 Liaison and interaction with other research programmes

Liaison with other programmes will be overseen by the MC. Representatives from complementary programmes such as EUMORPHIA, EUMODIC, SWITCHBOX and RESOLVE are already part of this network and will be tasked to ensure appropriate coordination between these programmes and the relevant WGs. The organisations that are not already part of the COST action will be invited to take part in or contribute to relevant work packages. Members of the COST action will attend relevant EU programme meetings to highlight and disseminate developments and findings. Web portals will be coordinated and links to and from other programmes established. This will allow the Action to integrate with existing infrastructures and to build on the current efforts, and to feed current data back from cutting edge research efforts in areas such as mutant generation and in disease-specific areas and the virtual physiological organisms. If possible the utility of embedding some COST meetings within or in parallel with existing programme meetings will be instigated. Paramount to the success of this COST action is the interactions with disease specific programmes, clinical studies and the soon to be established Horizon 2020 programmes where ageing is a priority. As these programmes begin the Action will establish relevant links and portals for communication. An important interaction will also be initiated with members of the US based National Institute for Ageing Intervention Testing Programme (NIA ITP). This Action will actively involve NIA ITP leaders to participate as external experts in the scientific workshops and educational activities. It will also try to establish synergies with groups of the NIA ITP for applying for joint research funding. Regulatory authorities such as EMA will be invited for specific meetings to discuss consensus statements and guidelines defined in this Action.

E.4 Gender balance and involvement of early-stage researchers

This COST Action will respect an appropriate gender balance in all its activities and the Management Committee will place this as a standard item on all its MC agendas. The Action will also be committed to considerably involve early-stage researchers. This item will also be placed as a standard item on all MC agendas.

An Equality and Diversity Coordinator will be nominated to ensure an appropriate gender balance is kept in the distribution of responsibilities of the Action. Special attention will be paid to gender balance among invited speakers at the educational events and Workshops organised by the Action. MouseAGE will also encourage ESR female scientists to participate in the management roles offered to ESRs part of the Action and in the scientific activities such as STSM and Scientific Workshops.

This Action will promote the training of a new generation of researchers that will become leaders in interventions to promote healthy ageing and translation into clinical applications. This aspect is considered of high priority for the Action, as reflected the nomination of an Early-Stage Researcher Coordinator (ESRC) that will be responsible for ensuring maximum engagement of ESRs in the Action at all levels.

F. TIMETABLE

The Action is scheduled over a period of four years. The setup of the web-based platform will be completed by Year 1 and then continuously updated. The MC, SC and WG meetings will be organised on the same dates, during 1-2 days, wherever possible with non-overlapping schedule, favouring the participation of the members of the Action. Groups will meet twice a year, approximately every 6 months. Wherever possible these meetings will be 1-2 days before the yearly training school or the workshops, improving interactions and reducing travel costs. Alternatively scientific workshops may be timed just before or after major international conferences for maximum dissemination. Scientific workshops will be delivered at different times across the four WGs so that every member of the Action can take part. STSM will start as soon as the review of the data/information in the WGs has occurred for maximum transfer of technologies and knowledge in line with the SOPs and guidelines produced by each WG. Below is an abbreviated Timetable showing the main activities for each WG and Task.

	Months							
	0-6	7-12	13-18	19-24	25-30	31-36	37-42	42-48
Kick off meeting	X							
Website and dissemination	X	X	X	X	X	X	X	X
Systematic review, collection of info	X	X	X	X				
Publish guidelines, SOP, roadmaps				X	X	X	X	X
STSM and reports			X	X	X	X	X	X
Scientific workshops			X	X	X	X	X	X
Training/summar schools		X		X		X		X
Funding applications				X	X	X	X	X

G. ECONOMIC DIMENSION

The following COST countries have actively participated in the preparation of the Action or otherwise indicated their interest: AT, BE, CH, DE, DK, EL, ES, FR, HU, IL, IT, NL, NO, PT, UK. On the basis of national estimates, the economic dimension of the activities to be carried out under the Action has been estimated at 60 Million € for the total duration of the Action. This estimate is valid under the assumption that all the countries mentioned above but no other countries will participate in the Action. Any departure from this will change the total cost accordingly.

H. DISSEMINATION PLAN

H.1 Who?

This Action will target the following groups (TG):

TG1 - The partners in this COST Action; i.e. present researchers, who will be able to produce better scientific outputs, and ESRs, who will be trained in an area where establishing a critical mass of young researchers with the appropriate interdisciplinary knowledge is very important. In this way future testing of preclinical intervention will become more effective.

TG2 - Other Research Institutes/University researchers involved in the testing of preclinical interventions. This target audience will be very relevant for recruitment of new partners to the Action and to establish links and synergies with related networks. Also other research entities outside the EU such as the NIA ITP will benefit.

TG3 - Pharmaceutical and biotechnology companies interested in the development of specific diets and micronutrients or pharmacological agents, imaging and software tools. There are already three industrial participants proposed as active members of this Action. More industrial partners will be

actively contacted in order to attract interest in the exploitation of results. Companies in the European biotechnology/bioengineering industry will take advantage of progress made by the Action and thus gain a competitive edge.
TG4 - Regulatory Agencies (National and European level policy makers), in particular EMA: the Action aims to set-up guidelines and consensus statements for the standardisation of preclinical intervention to promote healthy ageing. The Action is expected to work with regulatory bodies to facilitate the subsequent design and approval of clinical trials.
TG5 - National and European government policy makers will be informed on these novel therapeutic approaches for common pathological conditions with a high socio-economic impact in Europe. Moreover, they will also be informed of the important requirements in terms of infrastructure and research funding which would make the MouseAGE research community more competitive worldwide in this area of research.
TG6 - Patients (individuals and associations) and their families: these are the target audience of this Action, as it aims to accelerate the translation of therapies to promote healthy ageing, so improving quality of life of senior citizens with age-related chronic diseases.
TG7 - Society at large, for the direct impact of these therapies on patients and general public and on the health and social care system, with significant impact on costs.

H.2 What?

Several dissemination methods will be applied. They will be adjusted and targeted to the specific audiences that the Action intends to address.
1. Electronic Methods.
Action website, with different access levels:
• Researchers involved with MouseAGE (password protected), posting working documents and other relevant information and documents related to the execution of the Action (TG 1).
• Public website of the Action with different sections (announcement of events of the Action, scientific publications, participation of the Action in international conferences, educational forum etc.) open to scientists and companies, and a section aimed at patients, policy makers and the general public (TG 1-6). The Website will also offer information for new parties interested in joining the Action.
• Email network among the members of the Action for internal communication.
• Use of videoconferences/Skype for specific issues and WGs of the Action when necessary.
2. Organisation/Participation in Scientific Events:

• *Action meetings:* MC, SC, and WGs meetings (twice a year). In addition to researchers already involved in the Action, researchers from the pharmaceutical and biotechnology industry as well as clinicians (TG 2, 3) or members of regulatory agencies (TG 4) will be invited to participate in meetings in order to exchange experiences and interests, to start collaborations, and/or partner in applications for joint funding proposals.

• *Scientific Workshops* of MouseAge (see Section F for frequency and timing) for reporting the scientific progress of the concerted Action as well as individual research related to the Action. These will be organised as a forum for informal but intensive interaction and networking between scientists. These Workshops will be also open to other researchers interested in preclinical interventions for ageing and chronic diseases, clinicians (TG2) and pharmaceutical companies and regulatory agencies for active participation as presenters and discussion partners (TG 3, 4). Participation of ESR (gender balanced) will be encouraged.

• Participation at national/international *Congresses, Conferences and Symposia*, presenting data resulting from the Action. Participation of ESR (gender balanced) will be encouraged (TG 2, 5).

• Participation in scientific *divulgation events* (local institutions, local scientific organisations, local press and radio), presenting the aims of the Action and the relevance of preclinical testing to develop advanced therapies for age-related chronic diseases.

3. Training activities:

• *Training/Summer Schools,*(one/year) addressed to ESR participants of the Action, but also open to other scientists interested (TG 1, 2). Invitation to partners of the industry or regulatory agencies (TG 3, 4).

• *STSM*, to exchange scientific data and technical knowledge among parties of the Action to favour joint research and scientific collaboration (TG1). The participation of ESR will be encouraged.

4. Networking. Meetings with:

• Regulatory agencies (TG4).

• Other research programs and EU consortia (TG1, 2).

• International networks, i.e. NIA ITP (TG2).

5. Publications:

• Guidelines and recommendations for regulatory agencies and policy makers (TG1, 3, 4).

• Standard Operating Procedures (SOPs) (TG1, 2, 3, 4).

• Reports of the progress of the Action (all TGs).

• Scientific articles in peer-reviewed journals (TG1, 2, 3, 4).

H.3 How?

A central task of MouseAGE will be the dissemination of its activities and results. At the MC meetings, dissemination will be placed as a standard item in the Agenda. To ensure the development and updating of the dissemination plan a Website and Dissemination Coordinator (WebDC) will be nominated by the MC. The WebDC, (preferably an ESR) will be responsible for the continuous update of the Website. They will obtain the pertinent information from the MC, SC and WGs leaders and any other participant in the Action. The Website will be organised taking into account both the needs of the participants (with details of the different participant groups, links of interest, funding opportunities, etc.) and the dissemination or exploitation of the results of the Action (publications, networking, training activities and scientific events). It will be an important tool to increase the visibility of MouseAGE. The Website will also offer information for further groups to participate in the Action. The Website will provide flexibility to acquire additional contents that may become necessary along the progress of the Action. The WebDC will work closely with WGLs to coordinate all scientific dissemination activities (workshops, conference, publications, etc) and will be supported by WG members designated by the WGL for each dissemination activity. The WebDC will also be supported by the ESRC for the coordination of training events, i.e. STSMs and the Training Schools. These interactions will stimulate this Action to coordinate research and future grant applications and liaise with invited speakers and experts from other parties (e.g. Innovative Training Network (ITN), companies, European Agencies) not involved in the Action. Every effort will be made to organise some of the workshops as satellites to other international conference in the field to increase the dissemination aspect.
The MC, (particularly the Chair) will coordinate communication with external parties to the Action, facilitating interactions and synergies with other European initiatives (e.g. EUMORPHIA, EUMODIC, RESOLVE, VPH), international networks (such as the ITN) and coordinating common position of the Action in the form of regulatory agencies such as EMA or pharmaceutical/biotech companies. The MC will also coordinate the incorporation of new parties.