

Brussels, 23 June 2017

COST 036/17

DECISION

Subject: **Memorandum of Understanding for the implementation of the COST Action “Realising the therapeutic potential of novel cardioprotective therapies” (EU-CARDIOPROTECTION) CA16225**

The COST Member Countries and/or the COST Cooperating State will find attached the Memorandum of Understanding for the COST Action Realising the therapeutic potential of novel cardioprotective therapies approved by the Committee of Senior Officials through written procedure on 23 June 2017.



MEMORANDUM OF UNDERSTANDING

For the implementation of a COST Action designated as

COST Action CA16225
REALISING THE THERAPEUTIC POTENTIAL OF NOVEL CARDIOPROTECTIVE THERAPIES (EU-CARDIOPROTECTION)

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

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

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

The main aim and objective of the Action is to discover new therapeutic targets and innovative treatment strategies for cardioprotection, and improve the pre-clinical and clinical evaluation of these new cardioprotective therapies, so as to improve their translation for patient benefit. This will be achieved through the specific objectives detailed in the Technical Annex.

The economic dimension of the activities carried out under the Action has been estimated, on the basis of information available during the planning of the Action, at EUR 92 million in 2016.

The MoU will enter into force once at least five (5) COST Member Countries and/or COST Cooperating State have accepted it, and the corresponding Management Committee Members have been appointed, as described in the CSO Decision COST 134/14.

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

OVERVIEW

Summary

Acute myocardial infarction (AMI) and the heart failure that often follows are the leading causes of death and disability in Europe. As such, new treatments are required to protect the heart against acute ischaemia/reperfusion injury (IRI) in order to preserve cardiac function and prevent heart failure – a strategy termed ‘Cardioprotection’. Despite intensive research, there are currently no effective cardioprotective therapies in clinical practice. The challenge has been to successfully translate novel cardioprotective therapies discovered in the laboratory setting into the clinical setting.

This EU-CARDIOPROTECTION COST ACTION will address this challenge by setting up a pan-European Research Network of leading experts in cardioprotection, to jointly develop innovative strategies for translating novel cardioprotective therapies into the clinical setting for patient benefit. This will be achieved through 4 main objectives each linked to a WORKING GROUP [WG]:

- (1) To use innovative strategies to discover novel targets for cardioprotection (WG1:NEW TARGETS).
- (2) To investigate the effects of combination therapy directed to multiple targets as an innovative cardioprotective strategy (WG2:COMBINATION THERAPY).
- (3) To use more clinically relevant animal models for testing novel cardioprotective therapies taking into account the confounding effects of co-morbidities and co-medication (WG3:CONFOUNDERS).
- (4) To set up a European network of research centers (European Cardioprotection Consortium, ECC) for:
 - (a) Multi-center preclinical testing of novel cardioprotective therapies using small/large animal models of acute myocardial IRI; and
 - (b) Proof-of-concept clinical testing of novel cardioprotective therapies in AMI patients (WG4:CONSORTIUM).

The EU-CARDIOPROTECTION COST ACTION aims to improve the translation of novel cardioprotective therapies for patient benefit.

<p>Areas of Expertise Relevant for the Action</p> <ul style="list-style-type: none"> ● Basic medicine: Pharmacology, pharmacogenomics, drug discovery and design, drug therapy ● Clinical medicine: Cardiovascular diseases 	<p>Keywords</p> <ul style="list-style-type: none"> ● Cardioprotection ● Myocardial Infarction ● Ischaemia Reperfusion Injury ● Animal models ● Ischaemic conditioning
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Specific Objectives

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

Research Coordination

- WORKING GROUP 1 - NEW TARGETS:
To use innovative strategies such as multi-omics (transcriptomics, epigenetics, proteomics and metabolomics) and innovative in silico network biology evaluation in the setting of ischemic conditioning to identify new therapeutic targets for cardioprotection.
- To discover novel therapeutic targets for cardioprotection directed to novel signaling pathways and

targets both within the cardiomyocyte and outside the cardiomyocyte (microvasculature, inflammatory cells, red blood cells, and platelets).

- **WORKING GROUP 2 - COMBINATION THERAPY:**

To test the effects of combination therapy to target multiple signaling pathways within and outside the cardiomyocyte (microvasculature, inflammatory cells, red blood cells, and platelets).

- **WORKING GROUP 3 - CONFOUNDERS:**

To investigate the efficacy of novel cardioprotective therapies in the presence of co-morbidities using diabetic, aged, hypertensive and hypercholesterolemia animal MI models, and in the presence of co-medications such as anti-platelet agents, statins, anaesthetics.

- To investigate the mechanisms through which these confounders impact on the efficacy of these novel cardioprotective therapies.

- **WORKING GROUP 4 – CONSORTIUM:** To improve the pre-clinical evaluation of novel cardioprotective therapies by setting up a multicenter network of research centers for multi-site testing of novel cardioprotective therapies in clinically relevant experimental small and large animal models.

- To improve the clinical evaluation of novel cardioprotective therapies by setting up a multicenter network of research centers for multi-site proof-of-concept testing of novel cardioprotective therapies in clinical studies of acute myocardial infarction and cardiac surgery patients.

Capacity Building

- Build capacity by connecting high-quality scientific communities related to cardioprotection throughout Europe and worldwide.

- Provide networking opportunities for Early Career Investigators (ECI) and facilitate their training to be the next research leaders in Europe in cardioprotection with an emphasis on competencies relevant to work in the academic, clinical, and industrial sectors. It will take into account both gender balance and geographical distribution.

- Coordinate the dissemination of the project's outputs to the scientific community and target the right audience to facilitate and ensure translation of research findings into commercial applications.

- Create a unique network of highly interdisciplinary researchers who have all made substantial contributions to the field of cardioprotection, but have not yet interacted in a consortium of this kind. This network will be amenable to all COST and non-COST researchers

- To create a multi-disciplinary and trans-disciplinary network of researchers including groups from academia and industry with broad knowledge in computational/wet chemistry, biochemistry, mitochondrial physiology, cell biology, genetic models, drug and diagnostics development, imaging and in vitro/in vivo pharmacology/physiology, -omics and bioinformatics.

1) S&T EXCELLENCE

A) CHALLENGE

I) DESCRIPTION OF THE CHALLENGE (MAIN AIM)

Acute myocardial infarction (AMI) and the heart failure that complicates it, are the leading causes of death and disability in Europe and worldwide. The most effective treatment for limiting myocardial infarct (MI) size and preventing heart failure following AMI, is timely myocardial reperfusion using primary percutaneous coronary intervention (PPCI). However, despite timely treatment, mortality and morbidity following AMI remain significant, with 7% death and 22% hospitalisation for heart failure at one year¹. Accordingly, new treatments are required to reduce MI size, in order to preserve left ventricular (LV) systolic function and prevent the development of post-MI heart failure – a treatment strategy termed ‘cardioprotection’. After myocardial reperfusion the most powerful intervention for reducing MI size in the experimental setting is by ‘ischaemic conditioning’, an endogenous cardioprotective phenomenon in which brief episodes of ischaemia and reperfusion applied to the heart or a remote organ/tissue can limit MI size². Intensive investigation of ischaemic conditioning over the last 30 years, has identified a large number of signalling pathways and therapeutic targets for cardioprotection. However, despite this, there are currently no effective therapies for protecting the heart against acute ischaemia/reperfusion injury (IRI) in clinical practice. A large number of cardioprotective therapies have been investigated in AMI patients treated with PPCI including a growing number of high profile clinical studies, but the vast majority of these have failed to show benefit in terms of reducing MI size and improving clinical outcomes^{1,3-7}. The **main challenge**, therefore is to improve the translation of novel cardioprotective therapies shown to be effective in the pre-clinical setting into the clinical arena for patient benefit. This COST Action (termed EU-CARDIOPROTECTION) aims to address this challenge by setting up a Europe-wide network of research centres tasked with: (1) the discovery of new therapeutic targets and innovative strategies for cardioprotection; (2) testing the effects of combination therapy to target multiple signalling pathways both within and outside the cardiomyocyte; (3) investigating the effects of confounders (co-morbidities and co-medications) on cardioprotection; (4) multi-center pre-clinical and clinical testing of novel cardioprotective therapies.

II) RELEVANCE AND TIMELINESS

The reasons for the failure to translate novel cardioprotective therapies into the clinical setting are multiple and complex and have been reviewed in a number of recent papers⁸⁻¹¹. Here the Action will focus on several of the most important factors and outline how this COST Action will address these issues.

Therapeutic targets for cardioprotection: The majority of experimental studies have focused on targeting well-established signalling pathways/targets many of which have not proven to be beneficial in the clinical setting. As such, novel therapeutic targets and strategies need to be discovered in order to improve the translation of cardioprotection into the clinical setting. This COST Action will utilise the joint knowledge and expertise of the European

network members to discover novel signalling pathways and therapeutic targets within and outside the cardiomyocyte, and identify innovative strategies for cardioprotection Objective 1 NEW TARGETS).

Single targeted cardioprotective therapies: The majority of experimental studies have used a single-targeted approach, directed to a single signalling pathway/target restricted to the cardiomyocyte. However, there exist a number of different cardioprotective pathways underlying ischaemic conditioning. Furthermore, the detrimental effects of acute IRI on the heart are complex, and involve a number of players outside of the cardiomyocyte such as the microvasculature, inflammatory cells, red blood cells and platelets. As such, in Objective 2 COMBINATION THERAPY, the COST Action will utilise the joint expertise of different European network members to investigate combination therapy directed to multiple cardioprotective pathways and targets both within and outside the cardiomyocyte as an innovative treatment strategy for cardioprotection.

Experimental models with low translational value: The majority of experimental studies have used healthy juvenile animal MI models, which do not adequately reflect the clinical setting given that most IHD patients are middle-aged, have co-morbidities (such as diabetes, hyperlipidemia, hypertension), and are on co-medications (such as anti-platelet therapies, statins and beta-blockers, ACE inhibitors, anaesthetics). There are also obvious species differences in cardioprotective signalling between rodents, larger mammals and humans. These factors have been shown to confound the efficacy of cardioprotective therapies and need to be taken into consideration when evaluating novel cardioprotective therapies in the experimental and clinical setting¹². As such, in Objective 3 CONFOUNDERS, the COST Action will utilise the joint expertise of the European network members to investigate factors which confound cardioprotection in order to improve the translational value of the animal MI models.

Therapies with inconsistent cardioprotective efficacy: Many of the cardioprotective therapies which have failed in the clinical setting, did not show consistent and robust cardioprotection in the experimental setting. This can be attributed to methodological limitations of the pre-clinical studies including lack of randomisation, non-blinded treatment allocation, non-blinded data analysis, lack of standardised animal models and IRI protocols, and the lack of rigor in statistical methods. Therefore, more rigorous testing of novel cardioprotective therapies in the experimental setting are required to ensure that only the most promising therapies are investigated in the clinical arena. As such, in Objective 4 CONSORTIUM, the COST Action will put in place a European Cardioprotection Consortium (ECC) for: (a) multi-center experimental testing of new cardioprotective therapies in clinically relevant small/large animal and human models of acute IRI; and (b) testing new cardioprotective therapies in proof-of-concept clinical studies in patients subjected to acute IRI including ST-segment elevation myocardial infarction (STEMI) and coronary artery bypass graft (CABG) patients.

B) SPECIFIC OBJECTIVES

I) RESEARCH COORDINATION OBJECTIVES

The main objective of this COST Action will be to discover new therapeutic targets and innovative treatment strategies for cardioprotection, and improve the pre-clinical and clinical evaluation of these new cardioprotective therapies, so as to improve their translation for patient benefit. These aims will be divided into 4 inter-related objectives each linked to a specific WG and led by experienced partners, who will take responsibility for ensuring progress according to the overall schedule.

OBJECTIVE 1 NEW TARGETS: To discover and disseminate new therapeutic targets and innovative strategies for cardioprotection. The European network members will jointly investigate novel signalling pathways underlying ischaemic conditioning in order to discover novel therapeutic targets and strategies for cardioprotection which can then be shared amongst research network members and industrial partners. The specific research objectives will be:

- To use innovative strategies such as multi-omics (transcriptomics, epigenetics, proteomics and metabolomics) and innovative *in silico* network biology evaluation in the setting of ischaemic conditioning to identify new therapeutic targets for cardioprotection.
- To optimise cardioprotective interventions directed to established therapeutic targets in order to improve their translation into the clinical setting.
- To discover and disseminate novel therapeutic targets for cardioprotection directed to novel signalling pathways and targets both within the cardiomyocyte and outside the cardiomyocyte (microvasculature, inflammatory cells, red blood cells, and platelets).

OBJECTIVE 2 COMBINATION THERAPY: To test the effects of combination therapy to target multiple signalling pathways within and outside the cardiomyocyte (microvasculature, inflammatory cells, red blood cells, and platelets), identified in Objective 1 NEW TARGETS, as being more effective to a single-target strategy.

OBJECTIVE 3 CONFOUNDERS: To improve the pre-clinical evaluation of novel cardioprotective therapies identified in the experimental setting by investigating the effect of confounding factors such as co-morbidities (age, diabetes, hypertension, hyperlipidemia) and co-medications (anti-platelet agents, statins, beta-blockers, anaesthetics) on their cardioprotective efficacy. Importantly, the mechanisms through which these confounding factors interfere with cardioprotection elicited by ischaemic conditioning are not clear and will also be investigated in this objective, as this will provide mechanistic insights into cardioprotection. The specific research objectives will be:

To investigate the efficacy of novel cardioprotective therapies, directed to new therapeutic targets identified in Objective 1 (NEW TARGETS) in the presence of co-morbidities using diabetic, aged, hypertensive and hypercholesterolemia animal MI models, and in the presence of co-medications such as anti-platelet agents, statins, anaesthetics.

To investigate the mechanisms through which these confounders impact on the efficacy of these novel cardioprotective therapies, directed to new therapeutic targets identified in Objective 1 (NEW TARGETS)

OBJECTIVE 4 CONSORTIUM: To improve the pre-clinical and clinical evaluation of novel cardioprotective therapies by setting up a multicentre network of research centres capable of undertaking pre-clinical and clinical cardioprotection studies (termed the European Cardioprotection Consortium or ECC). The ECC will allow multi-site testing of novel cardioprotective therapies in clinically relevant experimental small and large animal models and is, in part, modelled on the National Institute of Health-sponsored CAESAR collaborative network (Consortium for Preclinical Assessment of Cardioprotective Therapies) in the United States¹³. The ECC will improve upon the NIH CAESAR collaborative network by: (a) building on the infrastructure and knowledge obtained from the other 3 objectives, in identifying novel cardioprotective targets and innovative strategies; (b) using human research models such as human iPSCs and human volunteers studies (eg. forearm unilateral ischaemic exercise models); and (c) undertaking proof-of-concept clinical studies in STEMI and CABG patients.

II) CAPACITY-BUILDING OBJECTIVES

C) PROGRESS BEYOND THE STATE-OF-THE-ART AND INNOVATION POTENTIAL

I) DESCRIPTION OF THE STATE-OF-THE-ART

- Build capacity by connecting high-quality scientific communities related to cardioprotection throughout Europe and worldwide.
- Provide networking opportunities for Early Career Investigators (ECI) and facilitate their training of to be the next research leaders in Europe in cardioprotection with an emphasis

on competencies relevant to work in the academic, clinical, and industrial sectors. It will take into account both gender balance and geographical distribution,

- Coordinate the dissemination of the project's outputs to the scientific community and will target the right audiences; to facilitate and ensure translation of research findings into commercial applications. Tasks in this work package will aim to provide a general framework for engagement with the public and translation of results yielded by this COST Action for patient benefit.
- Create a unique network of highly interdisciplinary researchers who have all made substantial contributions to the understanding of acute myocardial IRI and cardioprotection, but have not yet interacted in a consortium of this kind. Although, many of the partners may have interacted with each other, they have not jointly worked as a Europe-wide collaborative effort previously. The consortium will allow the future participation of further (non-) member countries.
- The network is multi-disciplinary and trans-disciplinary and includes groups from academia and industry with broad knowledge in computational/wet chemistry, biochemistry, mitochondrial physiology, cell biology, genetic models, drug and diagnostics development, imaging and in vitro/in vivo pharmacology/physiology, -omics and bioinformatics. All participants are leaders in their fields, and many have a track record of successful translation and application of cardioprotection. The participating groups are currently funded by national or international funding bodies for their own research.

Given its flexible structure, this COST Action represents the most appropriate means for establishing a dynamic research network, and will allow additional groups from and beyond the EU to join even after its launch date. Many of the current COST participants have active collaborations with other leading researchers in North America and elsewhere, both in Academia and/or Industry and these relationships will enrich the COST Action.

II) PROGRESS BEYOND THE STATE-OF-THE-ART

Objective 1 NEW TARGETS: To identify new therapeutic targets by investigating new signalling pathways and targets both within the cardiomyocyte (intracellular) and outside the cardiomyocyte (microvasculature, inflammatory cells, red blood cells, and platelets).

To optimise cardioprotective therapies which are directed to established therapeutic targets in order to facilitate their translation into the clinical setting.

Objective 2 COMBINATION THERAPY: The Action will investigate combination therapy directed to signalling pathways/targets both within and outside the cardiomyocyte (microvasculature, inflammatory cells, red blood cells, and platelets), as this therapeutic approach is likely to be more effective than a single therapy approach.

Objective 3 CONFOUNDERS: The Action will use more clinically relevant animal models which take into account co-morbidities and co-medications relevant to MI patients. Although studies have reported co-morbidities such as age, diabetes and left ventricular hypertrophy to attenuate the efficacy of cardioprotective therapies, the mechanisms underlying this effect are unknown and will be investigated in this objective. In addition, further studies are required to investigate the effect of co-medication such as anti-platelet agents, statins, anaesthetics and their impact on the efficacy of new cardioprotective therapies.

Objective 4 CONSORTIUM: The Action will set-up a ECC of Research Centres: (a) to allow multi-center testing of new cardioprotective therapies using standardised IRI protocols in small and large animal MI models; (b) human research models such as human iPSCs and human volunteers studies (eg. forearm unilateral ischaemic exercise models); and (c) to allow testing of new cardioprotective therapies in proof-of-concept clinical studies and discuss the design and execution of future multi-center randomized clinical outcome studies. This innovative strategy will be able to rigorously test the cardioprotective efficacy of new therapies using a multi-center randomised placebo-controlled double-blinded approach. This strategy has been implemented in the United States with the establishment of the National Institute of Health-sponsored CAESAR collaborative network¹³. This network has found that nitrites and hydrogen sulphide which have been shown to be cardioprotective in individual studies, failed to

cardioprotect when tested in the CAESAR network. The findings from Objectives 1, 2 and 3 of this COST Action will enable the investigation of novel therapeutic targets, innovative treatment strategies (combination therapy) using more clinically relevant animal MI models (taking confounders into account). The findings from the pre-clinical study will ensure that only novel cardioprotective therapies showing consistent and robust protective effects are tested in the clinical setting for patient benefit.

III) INNOVATION IN TACKLING THE CHALLENGE

Objective 1 NEW TARGETS: To use innovative strategies such as multiomics (transcriptomics and epigenomics to metabolomics) and innovative bioinformatic approaches to target prediction by network analysis. The innovative multidisciplinary approach will identify novel therapeutic targets for cardioprotection on the mitochondrial, cellular and organ level.

Objective 2 COMBINATION THERAPY: Combination therapies to targeting different therapeutic targets both within and outside the cardiomyocyte is an innovative approach to cardioprotection.

Objective 3 CONFOUNDERS: The mechanisms through which co-morbidities and co-medications confound cardioprotection are not known and will be systematically investigate here for the first time. Understanding these mechanisms may provide new insights into the cardioprotective signalling pathway. The COST Action will identify the most important co-morbidities and co-medications to target in pre-clinical and clinical cardioprotection studies.

Objective 4 CONSORTIUM: There currently exists no European Network of Research Centres jointly investigating new cardioprotective therapies in the laboratory or clinical setting. The ECC will allow multi-centre testing of new cardioprotective therapies to screen promising therapies and identify those that are truly effective in relevant experimental models and, thus, most likely to be effective in patients.

D) ADDED VALUE OF NETWORKING

I) IN RELATION TO THE CHALLENGE

The European Research Network of partners set-up by this COST Action is essential as it will allow us to utilise the joint knowledge and expertise of different European network members to discover and share new therapeutic targets for cardioprotection and improve the pre-clinical animal and human MI models used to test the efficacy of novel cardioprotective therapies in the laboratory setting. Furthermore, the following added value will be created by the research network:

- Shared interdisciplinary and complimentary expertise among COST Action members in the fields of medicinal chemistry, physiology, pathophysiology, biochemistry, mitochondrial bioenergetics, epidemiology, molecular cardiology and clinical cardiology.
- Shared access to clinically relevant animal and human models of myocardial acute IRI; harmonization of acute IRI protocols, database and technology sharing.
- Generation of joint ESC position papers and research guidelines.
- Interdisciplinary training and mobility across the COST Action of ECIs allowing them to gain specialist knowledge and experience in cardioprotection in different disciplines and laboratories.
- Facilitated access to Biotech/Pharma small and medium enterprises (SMEs through industry members of the COST Action.
- Increased impact on policy and public awareness related to the need for cardioprotection.
- Facilitating gender and social equality in research by including countries with less resources for research capacity.

II) IN RELATION TO EXISTING EFFORTS AT EUROPEAN AND/OR INTERNATIONAL LEVEL

Current cardioprotection research in Europe is mostly confined to individual research laboratories, although there are limited collaborations between 2 or more research groups. The COST Action will create a collaborative research network across Europe and beyond. **This COST Action will establish the first European Network of Researchers focused on cardioprotection research.** The COST Action will allow to network with existing efforts at the European and International levels.

- This COST Action will encourage and enable cardioprotection researchers from less research-intensive countries across Europe to join the COST Action by including Inclusiveness Target Countries (ITC). The COST Action will counterbalance research communities' unequal access to knowledge, infrastructures, funding and resources. It will provide strong means to increase the visibility and integration of cardioprotection researchers to the leading knowledge hubs of Europe, as well as to acquire their necessary leadership skills, regardless of their location, age or gender. The COST Action will help to facilitate structural changes in the national research systems of COST Member Countries. By identifying excellence across Europe the COST Action will contribute to Horizon 2020 objectives.
- The Short-term Scientific Missions (STSMs) from ITCs will provide technological transfer. In the short term, the training of young researchers (PhD students and postdocs) in a highly-collaborative academic environment will allow them to acquire a relevant scientific background, the ability to conduct research independently, and generate high-quality data that will be jointly published, thus increasing the international scientific visibility of the network. In the long-term, offering better career perspectives is ultimately aimed at preventing emigration/brain-drain of scientists.
- Build on existing COST Actions already established which are closely related to the topic of cardioprotection. These include those investigating Personalized Nutrition in aging society: redox control of major age-related diseases, Mitochondrial Fitness Mapping (MITOEAGLE), PROTESTASIS, TRANSAUTOPHAGY and Biomaterials and advanced physical techniques for regenerative cardiology and neurology.
- The COST Action will involve the participants which are active committee members of the European Society of Cardiology (ESC) Working Groups, the ESC Program committee, and the ESC Heart Failure Association. This will help to generate potential research collaborations and networking opportunities in the field of cardioprotection and related topics with members of these societies and allow the discoveries made in this COST Action to be disseminated in Europe and beyond.
- The COST Action will be built on the experience of ESC Position Papers related to improving the pre-clinical and clinical assessment of novel cardioprotective strategies^{8,9,14}, and in the International Society of Heart Research, thereby helping to generate potential research collaborations and networking opportunities in the field of cardioprotection and related topics with members of these societies and allow the discoveries made in this COST Action to be disseminated internationally.
- The COST Action will have a close collaboration with the NIH CAESAR (Consortium for preclinical assessment of cARdioprotective therapies) in USA¹³.

2) IMPACT

A) EXPECTED IMPACT

I) SHORT-TERM AND LONG-TERM SCIENTIFIC, TECHNOLOGICAL, AND/OR SOCIOECONOMIC IMPACTS

The impact of this Action will be reached through creation of a European network of research centers and establishing relationships with research users in order to discover and disseminate novel therapeutic targets and to define strategies for cardioprotection, to treat patients with co-morbidities, and reveal possible variability due to gender differences regarding the efficacy and safety of these novel strategies. The Action will acknowledge the expertise and active roles played by research users in making impact happen and will involve users at all stages of the research, including working with user stakeholder and participatory groups. The short-term impact will be achieved by exchanging ideas, knowledge, tools and data of scientists working on different but related systems using various approaches.

Short term scientific, technological and socio-economic impact:

- To provide the knowledge basis for research scientists at all levels and industrial players to increase the number of successful innovative development projects aimed at discovering novel cardioprotective therapies. The COST Action will provide state-of-the-art, detailed protocols for measuring MI size in mice, rabbits, and pigs in a manner that is rigorous, accurate, and reproducible, thereby helping to inform which therapies are taken forward by industrial partners for further development and commercialization.
- COST Action members will jointly apply for a Horizon 2020 grant to set up the European Cardioprotection Collaboration network of research centres for the pre-clinical and clinical testing of novel cardioprotective therapies as outlined in WG 4.
- To validate the efficacy and safety of current cardioprotective strategies such as ischaemic postconditioning and remote ischaemic conditioning in the treatment of AMI in the real world, i.e. in patients with major co-morbidities and co-medications.
- Provide data for early exclusion of candidate strategies unlikely to succeed in AMI patients.

Long term scientific, technological and socio-economic impacts

As a long-term impact, this networking exercise will accumulate the critical mass to understand problems with high level of complexities such as cardioprotection that can only be solved by a concerted effort of multidisciplinary teams. It will enable researchers from less research intensive countries to interact and share ideas, resources and personnel with scientists from countries where research enjoys a high priority. Our endeavours to promote gender and age balance will benefit women and ESR scientists immediately as well as in the long-term. In addition, our Action will create new, and strengthen existing interactions of European scientists with international experts via our external advisory board.

- To set up the European Cardioprotection Collaboration (ECC) network of research centres for the pre-clinical and clinical testing of novel cardioprotective therapies.
- This will lead to successful development of cardioprotective therapies thereby solving an unmet need in the treatment of ischaemic heart disease currently the leading cause of morbidity and mortality in the EU.
- By increasing the number and success rate of innovative development projects, creation of new jobs and increased competitiveness of innovative SMEs are expected.
- Increase the impact of cardioprotection research on policy makers, regulatory bodies and national decision makers as well as on the private sector.
- By the development of novel technologies and services within the scope of the project, the current project will impact on the growth of the knowledge-driven economy of the EU.
- The results of the project will contribute to healthy aging in the European population and will have a major impact on quality of life.

B) MEASURES TO MAXIMISE IMPACT

I) PLAN FOR INVOLVING THE MOST RELEVANT STAKEHOLDERS

The EU-CARDIOPROTECTION COST Action is aiming to create a European network of collaborating research institutions and enterprises to identify new targets and develop novel (possibly combination) therapies for cardioprotection. It will include relevant stakeholders as stated in the European Commission directive for Responsible Research and Innovation (RRI). The Action will use the RRI toolkit <http://www.rri-tools.eu/about-rri> to help achieve the aims of the RRI to foster the ethical acceptability, sustainability, and social desirability of research and innovation outcomes.

- **Researchers:** Basic scientists, clinician scientists and Bio-informatics experts will work as a collaborative network across the COST Action to provide synergy in terms of translating cardioprotection into the clinical setting.
- **Policy makers:** The COST Action will interact with and inform the major grant funding bodies at the European level (European funding agencies and HORIZON 2020) and national levels (eg British Heart Foundation in UK) to ensure that cardioprotection remains a relevant and important area of research which should be funded. Drug/medical device regulatory authorities - novel devices and pharmacological agents identified in WGs 1 and 2 and tested in the ECC in WG4 will need to discuss with relevant drug/medical device regulatory authorities at the national level (eg MHRA in UK) and Europe (European Medicines Agency) before testing in Phase 1 and 2 clinical studies. The Action will involve regulatory authorities who will be interested in assessing the data exchange procedures, research protocols and then devising guidelines for similar activities.
- **Educators:** Major European and International cardiovascular societies such as the European Society of Cardiology (ESC), International Society of Heart Research (ISHR), and local national cardiovascular research societies. The interaction with the ESC and ISHR is crucial in order to disseminate the findings of the COST Action and influence guidelines and recommendations through Position Papers.
- **Business and industry innovators:** The COST Action will involve Biotech/Pharma companies and SMEs involved in development of new cardioprotective technology and therapies (drugs, advanced therapy medicinal products, medical devices, as well as their combinations) and repurposing drugs for cardioprotection. This is in line with EU initiative to promote drug repurposing that comprises "drug repositioning, reformulation and combination" as recently addressed by European Commission, a concept highly supported by the pharmaceutical industry. The COST Action will also involve SMEs (including Biotech and Medical Device companies) who are interested in or developing solutions focused on improving clinical outcomes in patients with IHD. Our COST Action will enable fruitful collaborations between cardioprotection researchers and industry by providing a natural platform for them to meet and build mutual trust. It will also help increase the impact of cardioprotection research in the industrial sector, by promoting the use and development of technologies and knowledge of new targets, as well as the exploitation of our COST Action results and outcomes through dedicated dissemination and exploitation activities targeting SMEs and large companies in Europe involved in cardioprotection drug discovery and development. Promising novel cardioprotective therapies and targets identified by WG1 and 2 and further developed by the SMEs may be taken forward by partnering with large pharma/biotechnology companies interested in cardioprotection.
- **Civil society organisations:** The COST Action will interact with and inform the major grant funding bodies at the European level (HORIZON 2020) and national levels to ensure public engagement with our COST Action.

II) DISSEMINATION AND/OR EXPLOITATION PLAN

Involvement of representatives of stakeholders, including multidisciplinary technology specialists (e.g. bioinformatics), large pharma/biotech companies, as well as drug/medical device regulatory authorities will be ensured by a robust dissemination plan. The target membership of the cost Action at the end of the first year is 50, based on careful selection. The EU-CARDIOPROTECTION consortium is eager to show their research efforts and expertise to the scientific community, industry, and regulatory authorities (EMA). The consortium is going to disseminate the project progress and outcome in the following ways:

Progress report symposia: These will be organized separately as well as in collaboration with appropriate scientific and/or industrial conferences, e.g. FCVB, ISHR, ESC, and Bio Europe. Partners will also seek to afford visibility and discussion of work at national and international events organized by relevant professional societies.

Early Career Investigators (ECIs): The Action members will aim to showcase the network in lectures and seminars where appropriate to inform young researchers about the possibilities and benefits of international collaborative research and highlight European cutting edge science. The mobility programs and STSMs will help young investigators and early stage researchers to join networks of excellence and gain experience in collaboration with high level research teams.

Scientific publications: The results of the research in this Action will be made available to the larger scientific community via “position papers” as well as reviews on top of individual papers on original results of the members of the consortium. To reach the widest scientific and non-scientific readership, the current network will participate in “Open Access” pilot of the Horizon 2020 programme for its publications, choosing the “gold model”. The consortium members will send publications about their research results to the following “Open Access” European journals or in journals that provide an “Open Access” possibility by author’s request, including European Heart Journal, Cardiovascular Research, Basic Research in Cardiology, Journal of American College of Cardiology and Circulation amongst others.

Dissemination to the general public and other stakeholders:

It is very important to communicate the advances of the field to the public, who are the final targeted beneficiaries of our endeavours. Therefore, the Action will increase the media coverage on EU-CARDIOPROTECTION in TV, radio and non-scientific newspapers. The Action will also dedicate a section of our website to create a channel between non-scientific and our scientific community and social media (tweets etc, facebook). The Action will publish newsletters annually that will introduce our experts and feature major COST related news, publications and events. The Action will disseminate findings to other stakeholders such as the British Heart Foundation and patient groups.

The major aims of the dissemination strategy are to:

- Raise awareness about the COST Action
- Provide access to latest scientific information to the scientific and non-scientific community
- Increase learning from experience
- Maximize the impact by informing scientists (through publications and attending on scientific conferences) and physicians about EU-CARDIOPROTECTION research results at an early stage to take benefit of the new knowledge and to reduce redundant research
- Place the EU-CARDIOPROTECTION project in the scientific landscape as a major interest especially in terms of future European funding support.
- Enable junior and senior researchers outside the project to ponder collaborations or understanding processes and scientific networking
- Increasing the international visibility of the participating institutions, research groups and novel direction of EU-CARDIOPROTECTION research itself

C) POTENTIAL FOR INNOVATION VERSUS RISK LEVEL

I) POTENTIAL FOR SCIENTIFIC, TECHNOLOGICAL AND/OR SOCIOECONOMIC INNOVATION BREAKTHROUGHS

The innovation/risk profile of this COST Action is optimal.

The Action consider high potential for innovation due to the following reasons:

- Cardioprotection is an important area of unmet medical need and high cost to the multiple national health systems and therefore positive results at the therapeutic level will be received favourably by the community.
- To date there is still no successful model of open collaboration that works in practice due to some important challenges pertaining to the exchange of valuable information between interested stakeholders. Because the project will work not only on the scientific aspects but also on some of the relevant business challenges, the Action expect the lessons learned to be useful to the wider community that will wish to set up similar collaborative frameworks.
- Combination therapies are increasingly being recognized as a way to develop novel therapies that promise to improve clinical outcomes. However as this is still early days, the community needs successful case studies that can inform future efforts. The Action believes that our project will produce outcomes that can be used for this purpose.
- While the Action will research novel therapies and possibly novel drugs, the drug repositioning element of the approach provides reasonable reassurances that the Action will develop novel therapies that meet a basic level of safety and can at the same time address the challenges of comorbidities and negative drug-drug interactions.
- Failure at the clinical trial stage is often due to poorly designed trials (end points, patient selection etc). Identifying sub-populations at risk and therefore sub-populations with a higher probability for positive response is an important element of successful translational research. Through the use of Adverse Drug Reaction (ADR) predictive technologies, the Action expect to be able to identify possible sub-populations at risk and thereby optimise trial design. To date, such capability has not been widely used and the Action expects success in this respect to contribute to its uptake by the community.
- Unravelling important cardioprotective effects of currently used clinical therapies (such as anticoagulants, statins, empagliflozin, ACE inhibitors) and co-morbidities, e.g. the dissection of the cardioprotective and off-target mechanisms could then lead to the discovery of drugs that only target the cardioprotective mechanism in conditions where the on-target goal is not present anymore. It will also demonstrate that the cardioprotective therapy does work in the clinical setting. Therefore, this approach offers potential gain with little to no risk
- As with any drug development program, translation of basic research into therapies has a high reward/high risk profile. In order to be successful in our drug development program, the Action should be able to unravel the toxicology of the drug so that specific therapeutic interventions could be tested, without undesired side effects. Multi-center testing of new cardioprotective therapies using small/large animal MI models and standardised IRI will be encouraged.
- Our strategy, is designed to deal with these risks and to prioritize potential disease targets, mediators, drug delivery systems, and drugs in an effort to reduce the high rate of attrition in drug development.
- On the risk side the Action see the factors below and present briefly our mitigation plan for each.
- *Failure to streamline data exchange and use between collaborating organizations:* while an objective of the project and the network is to demonstrate how collaborating organizations can set-up and exploit common data pools, this is still a challenge. Work on the data exchange and use front will be “backed-up” by the direct exchange of the necessary data between partners requesting and supplying the relevant data. In this way the “medical” outcomes of the project will be isolated from this risk.

- While the Action may identify promising novel targets, these may turn out not to be so. Our intention to develop combination therapies that work through known targets offsets the risk of not developing viable treatments.
- The lack of standard animal models for cardioprotection that are sufficiently predictive has frustrated past efforts in improving the outcomes of translational research. In the project the Action will be using in-silico predictive tools that will provide additional insights into expected efficacy. Furthermore, work on repositioned drug candidates with alternative mechanisms of action will suggest additional animal models that are more descriptive and more predictive, thereby mitigate this risk.

3) IMPLEMENTATION

A) DESCRIPTION OF THE WORK PLAN

I) DESCRIPTION OF WORKING GROUPS

The network will consist of top European institutions and highly specialized biotechnology companies with the complementary competences needed to produce both outstanding research results and an excellent training environment for ECIs, ensuring a high standard of scientific research. The scientific programme will span all the way from idea to pre-clinical target validation by utilising a number of different research models and pharmacological tools and by combining actors from different sectors and disciplines. The WGs will ensure freely moving and extensive exchange of ideas and knowledge, promoting a high credibility of the COST Action. Furthermore, the Action will create an innovative environment through multidisciplinary research and targeted training, resulting in important new discoveries in cardioprotection research.

WG1 NEW TARGETS

Different signalling molecules and mechanisms of ischaemic conditioning have been identified. The COST Action will include world leading experts in cardioprotective signalling and mitochondria, the researchers with expertise in cardioprotection using experimental models of acute IRI in isolated subcellular structures (e.g. mitochondria), isolated cardiomyocytes, global or regional myocardial IRI ischaemia *ex and in vivo*. The proteins which consider as the end-effector of cardioprotection such as the mitochondrial permeability transition pore have been identified, also the RISK and SAFE pathways have been discovered as mediators of reperfusion cardioprotection. The WG will build on these strong expertises. This research will benefit from the complementary expertise within the COST Action.

Milestones

To identify novel therapeutic targets by investigating new and previously undescribed cardioprotective signalling pathways and targets within the cardiomyocyte and outside the cardiomyocyte (microvasculature, inflammatory cells, red blood cells, and platelets).

To use innovative strategies such multiomics approaches (transcriptomics, epigenetics, proteomics and metabolomics) and *in silico* network biology evaluation to identify new therapeutic targets for cardioprotection.

Research Deliverables

To identify 5 to 6 novel targets for cardioprotection either within the cardiomyocyte (newly discovered signalling pathway) or outside the cardiomyocyte (involving inflammatory cells, the microvasculature, red blood cells, or platelets).

To identify 2 to 3 innovative strategies for cardioprotection such as epigenetics or multi-omics strategies (genomics, transcriptomics, metabolomics or proteomics) to identify novel cardioprotective targets.

WG2 COMBINATION THERAPY

Based on expertise in computer modelling and drug docking simulations, the medicinal chemists associated with COST Action will synthesize an array of new molecules and the

pharmacologists will subsequently evaluate their pharmacologic properties in isolated enzyme preparations or in vitro cell-based systems. The potency, efficacy and selectivity of these compounds will be determined. Those compounds found to be of interest will be used in preliminary cell-based or *ex vivo* experiments (isolated organ preparations). Lead compound structures will be used as a mould to derive improved molecules. Additionally, the members of the COST Action use different methodologies from biochemical to immunoblotting techniques, from pharmacological agonist to antagonist approaches to transgenes and transfections. However, the ultimate end point of protection is reduction of MI size or its surrogate in more reductionist models.

Milestones

In this research objective the Action will investigate combination therapy directed to different cardioprotective signalling pathways/targets and other components of acute IRI such as the microvasculature, inflammatory cells, red blood cells, and platelets, as this therapeutic approach is likely to be more effective than a single therapy approach.

Research Deliverables

To identify 5 to 6 promising treatment strategies which are likely to have synergistic effects when administered in combination and which are directed to within the cardiomyocyte (newly discovered signalling pathway) or outside the cardiomyocyte (involving inflammatory cells, the microvasculature, red blood cells, or platelets) for testing in pre-clinical acute IRI models.

WG3 CONFOUNDERS

The COST Action will be based on expertises in different animal models and comorbidities and in all major cardiometabolic co-morbidities as well as in common factors such as mitochondrial dysfunction and oxidative stress, thereby providing a unique opportunity to achieve the objectives of the WG. For example AMI and heart failure models as well cardioprotection models of ischaemic conditioning will be used to assess the role of mitochondrial dysfunction and ROS formation together with the utilization of cutting edge technologies such as next generation sequencing and proteomics to highlight new mitochondrial signalling routes involved in metabolic pathologies. These techniques will allow us to build databases for network analysis where the Action aim to develop an integrative model in order to pinpoint key players in the regulation of mitochondrial oxidative metabolism. This database can be interfaced with that created by a member of this COST Action for the MITOEGLE COST Action. Results of this WG will serve as basis for comparison of mitochondrial mechanisms in different co-morbidity models of IHD.

Milestones

To improve the pre-clinical evaluation of new cardioprotective strategies in the laboratory setting by investigating the effect of confounding factors (co-morbidities such as age, diabetes, hypertension, and hyperlipidemia) on their cardioprotective efficacy.

To improve the pre-clinical evaluation of new cardioprotective strategies in the laboratory setting by investigating the effect of co-medications such as anti-platelet agents, statins, anaesthetics, beta-blockers etc.

Research Deliverables

To identify the 1 to 2 most important co-morbidities to take into account when designing pre-clinical and clinical cardioprotection studies out of age, male gender, diabetes, hypertension, hypercholesterolemia.

To identify the 1 to 2 most important co-medications to take into account when designing pre-clinical and clinical cardioprotection studies out of anti-platelet agents, statins, anaesthetics, nitrates).

To investigate the mechanisms through which the selected comorbidities and co-medications identified above interfere with cardioprotection.

WG4 CONSORTIUM

The main objectives of this WG are to set up a European Cardioprotection Consortium (ECC) of research centres for pre-clinical and clinical testing of novel cardioprotective therapies.

Milestones

Establish multi-center experimental testing of novel cardioprotective therapies using standardised acute IRI protocols in small and large animal MI models.

Establish human research models such as human iPSCs and human volunteers studies (eg. forearm unilateral ischaemic exercise models);

Establish proof-of-concept clinical testing of novel cardioprotective therapies and discuss the design and execution of multi-center randomized clinical outcome studies.

Research Deliverables

To decide which European research centres (COST and non-COST) should be selected to participate in the ECC.

To standardize the acute IRI protocols and choose which small animal (mouse, rat, rabbit) and large animal (pig, dog) MI models, and human research models to include in the ECC.

To identify 3 to 4 novel cardioprotective therapies from WG 1, 2, 3 and confounders highlighted in WG3 and results from the combination therapy studies in WG 2 when designing the multicentre animal MI studies for this WG.

To identify 3 to 4 novel cardioprotective therapies from WG 1, 2, 3 for testing in proof-of-concept clinical studies in STEMI and CABG patients.

To apply for EU grant funding to sustain the running of the ECC and to undertake multicentre testing of novel cardioprotective therapies.

To discuss and propose guidelines for optimizing study trial design for clinical cardioprotection studies using major clinical outcomes as a primary endpoint.

General Deliverables for all 4 WGs

For each of the 4 WGS, the Action will organize 1 WORKING GROUP meeting per year; Presentations at international conferences; Support of early stage researchers and a Training School; STSMs; Attract international top scientists (min. 15, incl. EU and Non-EU); A website (WS) providing access to the generated knowledge and annual e-newsletters; Scientific publications disseminating knowledge and raising awareness of this research field (e.g. high impact, key publications of the field, including at least 3 joint scientific papers and reviews) (SP); Gender balance (female support; encourage females to present at meetings, inclusion of more women in network); Industry interest and professional translation, economic and patient impact (filed patents, 2 drugs/diagnostics entering clinical development) (Patent); Establishing a European research area by implementing an EU Framework work program followed by an application (1 successful FP Program application).

Research Network Activities for the 4 WGs

The following **instruments** will be used within COST Action: WG meetings (years 1-4), Training Schools (in total 4, years 2 and 4), Workshops (years 1 and 3), website (year 1-4), International Closing Conference (year 4)

WG Meetings: The WG meeting will allow the COST partners to disseminate and share knowledge relevant to the WG. Each WG will organize a WG meeting once every two years, and this may take place in conjunction with another WG. Invited speakers and chairs will be considered in respect to gender balance and geographical distribution. ECIs will be encouraged to chair sessions and present at the WG Meeting. The Action will invite leading international leading cardioprotection basic science and clinical researchers in both EU and non-EU scientists to attend the meeting. The Action will also invite international researchers who have expertise in setting up a similar research consortium in the US – the NIH CAESAR Network (for example Dr David Lefer).

Training schools: In order to support the training and development of ECIs, a training school will be organized by each WG once every 2 years to highlight: (1) novel methods for discovering novel targets for cardioprotection and innovative cardioprotective strategies such as multiomics approaches; (2) the use of combination therapies; (3) highlight the animal models based on comorbidities and take into consideration co-medications; and (4) multicentre experimental studies and proof-of-concept clinical studies.

Short-term Scientific Missions (open all year): In order to achieve long-lasting effects of this COST Action, ECIs will be supported in their networking activities by STSMs (duration of one week to 3 months and supported by a fixed grant of EUR 2500) organized by each of the 4 WGs (8 STSMs in total every year). These will allow ECIs to learn from an institution or laboratory in another COST country. Increasing collaboration is important to make Europe more competitive. Exchanging ideas and knowledge across borders and will lead to more successful projects.

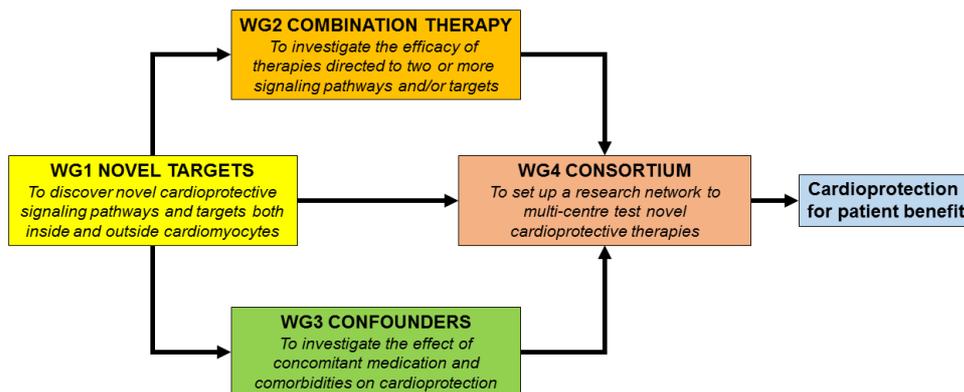
Other activities Industry interest and professional translation, economic and patient impact (filed patents, 2 drugs/diagnostics entering clinical development). Establishing a European research area by implementing an EU Framework work program followed by an application (1 successful FP Program application)

Dissemination activities: A website providing access to the generated knowledge and annual e-newsletters, with mutual links to websites relevant for this COST Action. Scientific publications disseminating knowledge of the WG will be published as original articles, reviews and Position Papers in conjunction with the ESC.

II) GANTT DIAGRAM

Activity	Year 1	Year 2	Year 3	Year 4
Kick off meeting: Appointment of Chair, Vice-Chair, WG coordinators, web manager	+			
Web site establishment (update: continuously)	+			
WG meetings	1 or 2	1 or 2	1 or 2	1 or 2
Training schools	1	1	1	1
STSMs	8	8	8	8
MC meetings	2	2	2	2
Newsletter	1	1	1	1
Scientific Publications	At least 2	At least 4	At least 4	At least 4
Presentations in International Conferences	At least 2	At least 4	At least 4	At least 4
Patent				1
Progress reports	1	1	1	1
Final conference				1
Implementation of an EU framework program				Horizons 2020 application

III) PERT CHART (OPTIONAL)



IV) RISK AND CONTINGENCY PLANS

The network brings together most established European researchers working in the field of cardioprotection, therefore, the project presents minor risks to its implementation, since it was scheduled to permit flexibility and superposition of working packages.

	Risk description	Risk level	Contingency Plan
WG 1-4	Delays in reaching milestones	Low	WG review communication (skype, email, etc), and regular work follow-up allowing adjustment of effort to ensure milestones are reached in a timely fashion.
WG 1-4	Delays in reaching deliverables	Low	MC meetings and/or communication and intensive work follow-up allowing adjustment of effort to ensure deliverables are reached in a timely fashion.
WG1-4	Delays due to disagreement between partners	Medium	Open discussions, close communication and referring to the agreed work plan and deliverables.
WG1-4	Partners leaving the network	Low	Scheduled MC meetings to recruit new MC members
WG1-4	Coordinator, or WG leader, leaving the network	Low	Scheduled MC meeting to vote new coordinator or WG leader

The potential risk of isolating different disciplines in separate WG's will be overcome by organising joint WG meetings and by inviting international experts who conduct interdisciplinary research.

B) MANAGEMENT STRUCTURES AND PROCEDURES

Network organisation and management structure

The network organisation and management structure of COST Action has been designed to be efficient and transparent, with a highly integrated structure to ensure that all of the scientific and training objectives are of high quality, and delivered in a time- and cost-efficient manner.

Management Committee (MC): The MC will coordinate the scientific and administrative actions of COST Action and its membership will take into account gender balance and geographical distribution. At its first (kick-off) meeting, the Chair, Vice-Chair and WG leaders as well as website coordinator will be elected. The WG structure can be modified if required. The WGs will organize WG Meetings (WGM) at least once every 2 years to introduce the advancement in knowledge and know-how by lectures, discussions and also by invitation of other experts not involved in this Action coming either from Europe or other parts of the World. The WGM will be held towards the end of each year. In parallel with the yearly meetings, talks to members in the pharmaceutical industry will be organized in order to secure greater industry involvement. Furthermore MC meetings will be held annually and will be linked to WGM thus reducing travel costs and improve interaction.

Steering committee (SC): The COST Action will establish a SC composed of the Chair and Vice Chair of the MC, the WG coordinators, the Website coordinator and the STSM Chair. The SC will meet every month through web-meetings.

Website: This will be an important communication tool within the Action and beyond. The website coordinator will be responsible for establishment and maintenance (monthly update) of the website.

Monitoring and evaluation: The COST Action will closely monitor its progress and activities by evaluation forms handed out after each MC and WG meeting. The outcomes of this internal evaluation will be available on the website and an agenda item at the next respective meeting. Further, each STSM will conclude with a report generated by the guest and the host for the MC and WG. These reports will allow improving the outcomes of STSM.

Network body	Responsibilities
Management Committee(MC)	<ul style="list-style-type: none"> ■ Coordination of the scientific and administrative actions of COST Action ■ <i>Promotion of gender balance and ECI involvement</i> ■ <i>Distribution of funds within the Action</i> ■ <i>Increase of visibility by publication of COST Action activities</i> ■ <i>Draft scientific and financial reports to COST</i>

	<ul style="list-style-type: none"> ■ <i>Recruitment of new members</i> ■ <i>Organization, planning and coordination of meetings, conferences, workshops and training schools</i> ■ <i>Establishment of a panel that reviews STSM applications</i> ■ <i>Promotion and establishment of collaborations between COST Action members with other COST ActionS, EU- and internationally programmes</i> ■ <i>Communication with societies</i> ■ <i>Support of interactions with industrial partners, commercial exploitation and translation of research results.</i>
Steering committee (SC)	<ul style="list-style-type: none"> ■ <i>Facilitation of efficient communication and decision-making by preparing MC meetings</i> ■ <i>Coordination of COST activities.</i>
Website coordinator	<ul style="list-style-type: none"> ■ <i>Disseminating progress of COST Action towards reaching its aims</i> ■ <i>Share of progress between COST members</i> ■ <i>Seek for tools/technology support</i> ■ <i>Communication of the new scientific insights to the broader scientific community</i> ■ <i>Online education tools for ECIs.</i>

C) NETWORK AS A WHOLE

The COST Action will set up a pan-European Research Network of leading experts in cardioprotection, to jointly develop new initiatives and new strategies for finding innovative and more effective approaches to cardioprotection and for optimizing the pre-clinical and clinical evaluation of new cardioprotective therapies, so as to improve their translation into the clinical setting for patient benefit. The COST Action will co-ordinate and strengthen European research in the field of cardioprotection and accelerate scientific progress through the dissemination and sharing of new therapeutic targets, among network members and industrial partners, thereby facilitating the discovery of new cardioprotective therapies. By utilising the joint expertise of different European network members the Action will investigate factors which confound the efficacy of new cardioprotection therapies including comorbidities (such as age, diabetes, and hypertension) and co-medications (such as anti-platelet therapies, statins and beta-blockers). Finally, the Action will set up a European network of research centres for multi-center laboratory testing of new cardioprotective therapies using small and large animal models of acute IRI in order to select those therapies most likely to succeed in the clinical setting. All aspects of this COST Action require a critical mass of partners across a wide geographic distribution across Europe in order to deliver the objectives outlined in the MoU. The discovery of novel signalling pathways and targets underlying cardioprotection both within and outside the cardiomyocyte (WG1 NEW TARGETS), and the testing of different combinations of cardioprotective therapy (WG2 COMBINATION THERAPY) requires investigators with different experience and expertise across Europe. The ability to test the effect of confounders of cardioprotection (WG3 CONFOUNDERS) requires the expertise of different partners in the different co-morbidities and testing of co-medications. Finally, the most important objective of this COST Action requires the setting up of a Europe-wide research network for (a) multicentre testing of novel cardioprotective therapies using small and large animal models (WG4 CONSORTIUM) and (b) testing of novel cardioprotective therapies in proof-of-concept clinical studies and optimization of multi-center clinical outcome cardioprotection studies. By definition this requires a critical mass of research partners distributed across Europe.

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