EUROPEAN COOPERATION IN SCIENCE & TECHNOLOGY

Brussels, 25 May 2021

COST 061/21

DECISION

Subject: Memorandum of Understanding for the implementation of the COST Action “Bench to bedside transition for pharmacological regulation of NRF2 in noncommunicable diseases” (BenBedPhar) CA20121

The COST Member Countries will find attached the Memorandum of Understanding for the COST Action Bench to bedside transition for pharmacological regulation of NRF2 in noncommunicable diseases approved by the Committee of Senior Officials through written procedure on 25 May 2021.

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MEMORANDUM OF UNDERSTANDING

For the implementation of a COST Action designated as

COST Action CA20121
BENCH TO BEDSIDE TRANSITION FOR PHARMACOLOGICAL REGULATION OF NRF2 IN NONCOMMUNICABLE DISEASES (BenBedPhar)

The COST Members through the present Memorandum of Understanding (MoU) wish to undertake joint activities of mutual interest and declare their common intention to participate in the COST Action, referred to above and described in the Technical Annex of this MoU.

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

The main aim and objective of the Action is to share basic, pharmacological, and clinical knowledge about transcription factor NRF2, master regulator of multiple cytoprotective functions, and to integrate it into the stream of EU social, clinical and economic sectors with capacity to translate this knowledge into innovative therapeutics for several non-communicable diseases. This will be achieved through the specific objectives detailed in the Technical Annex.

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

OVERVIEW

Summary
Non-communicable diseases (NCDs) such as cancer, diabetes, cardiovascular, neurodegenerative, respiratory or immune diseases, account for 77% of all deaths in Europe and remain the most prevalent and without effective therapy. Networking among multidisciplinary teams that explore disease from a perspective of causative pathomechanisms rather than clinical symptoms is the most appropriate approach to overcome this problem. Such pathomechanisms imply the loss of homeostatic functions leading to the pathologic formation of reactive oxygen species, chronic inflammation, metabolic unbalance and proteinopathy. The transcription factor NRF2 is a master regulator of multiple cytoprotective responses and a key molecular link among many NCDs. It provides a unique strategy for drug development and repurposing that is now starting to be translated to the pharmacological and clinical arena. This Action will build a network of excellence for integrating and spreading the existing knowledge and providing innovative services, drugs and tools related to NRF2-pharmacology, with the final goal of boosting the translation to the European industry sector. To achieve this, the Action has already gathered a wide set of professionals from different disciplines (medical chemistry, pharmacology, clinical research, molecular biology, bioinformatics, etc.) and sectors (universities, research centres, hospitals, biobanks, biotech SMEs and pharma companies, etc.). The Action will expand among COST countries IPCs and NNCs, will actively involve SMEs and ECIs, and will respect gender balance.Thanks to COST tools the Action will boost the career of young researchers, wide participation (especially from ITC countries), and spread excellence.

Areas of Expertise Relevant for the Action	**Keywords**
● Basic medicine: Pharmacology, pharmacogenomics, drug discovery and design, drug therapy	● Nrf2 ● Homeostasis ● Noncommunicable diseases ● Pharmacology ● Chronic Diseases

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

Research Coordination
● Building a cohesive multidisciplinary and highly interactive pan-European network of stakeholders in the NRF2 field and synergistically bundle their individual expertise towards the integrative understanding of NRF2 pathomechanisms, their relation to NCDs and their future implementation in new pharmacologic and therapeutic approaches.
● Coordination of research-generated knowledge in the field of NRF2 to provide research tools, guidelines and harmonized procedures, aiming at increasing research efficiency.
● Channelling of knowledge towards the European Biopharmaceutical and clinical sectors by providing NRF2-related inventories of clinically relevant drugs, preclinical models and documentation for design of clinical trials.
● Dissemination of knowledge towards general public and policy makers regarding the potential of NRF2-based new therapeutics from a very realistic and scientifically validated view.

Capacity Building

● Establishment of technology transfer and collaboration agreements between scientists and SMEs to help in the economical exploitation of the network outcomes towards improved NRF2-targeted therapeutics
● Creation of technological platforms for NRF2 research: 1) database of small molecule modulator 2) systems-based database on genetic and biochemical biomarkers, 3) registry of animal models 4) toolbox with relevant reagents for NRF2 research, 5) repositories of clinical samples.
● Promotion of the interdisciplinary training of a new generation of young scientist with interdisciplinary skills in the field of NRF2-related pathology.
● Facilitation to access state-of-the-art biomedical technologies (i.e. genomics, transcriptomics, proteomics and metabolomics profiling) as well as bioinformatics tools for translational research on NRF2

TECHNICAL ANNEX

1. S&T EXCELLENCE

1.1 Soundness of the Challenge

1.1.1 DESCRIPTION OF THE STATE-OF-THE-ART

The burden of Non-Communicable diseases (NCDs) and their relationship with NRF2.

According to the World Health Organization, chronic Non-Communicable Diseases (NCDs) account for an estimated 86% of the deaths and 77% of the disease burden in Europe. The treatment of NCDs is a completely unresolved problem. It is now evident that traditional approaches based on handling specific clinical symptoms provide insufficient input to finding a cure. However, the fact that many NCDs share common pathomechanisms and exhibit a high degree of molecular connectivity is supporting a new concept of disease where a common molecular target may provide, **at least partially**, therapeutic benefit for several dysregulated cellular responses. One such molecular link is the **transcription factor NRF2** (nuclear factor (erythroid-derived 2)-like 2). Evidence gathered for the past 10 years strongly points towards a NRF2-related strategy for drug development and repurposing in these NCDs. This statement has been widely supported for the past years with the *Nrf2*-knock-out mouse, the "systems medicine" analysis of the role of NRF2 in the connectivity networks among NCDs (**Fig. 1 A**), and the genetic association between several NCDs and functional polymorphisms in the NRF2 coding gene. Extensive knowledge in the field is now at a mature stage to transform this basic knowledge into **social, scientific and clinical awareness** and to implement new strategies for drug development and repurposing in those NCDs underlined by low-grade chronic inflammation, oxidative stress, metabolic impairment and proteinopathy, which are the main targers of NRF2 (**Fig. 1B**).

¿What is NRF2?. Function and opportunity for pharmacological and clinical development

NRF2 regulates the expression of ~250 genes encoding a network of enzymes involved in NADPH-, glutathione- and thioredoxin-mediated reactions, inhibition of inflammation, induction of autophagy genes, etc. (**Fig. 1B**). Through this transcriptional network, **NRF2 coordinates multifaceted responses to diverse forms of stress for maintaining a stable internal environment.** The main mechanism of NRF2 regulation is the control of protein stability by **KEAP1** (Kelch-like ECH-associated protein 1). Under homeostatic conditions, KEAP1 targets NRF2 for ubiquitin/proteasome degradation. However, electrophiles inhibit KEAP1 and lead to increased NRF2 activity and induction of its target genes. These electrophiles reinforce homeostatic and protective responses through NRF2 activation and provide the basis for drug development. Pharmacological research on NRF2, targeting KEAP1, is very advanced in preclinical models of several NCDs, and is now **starting to evolve to the level of clinical practice** (see below and Table 1).

NRF2 activators are being used in preclinical and clinical trials of many NCDs where its activity is abnormally low. Two strategies are being used to activate NRF2 in NCDs: **a)** Electrophile drugs alter the structure of KEAP1 through the interaction with several cysteine sensors. **At least 30 patents** are indexed in the World Intellectual Property Organization protecting a variety of molecularly unrelated

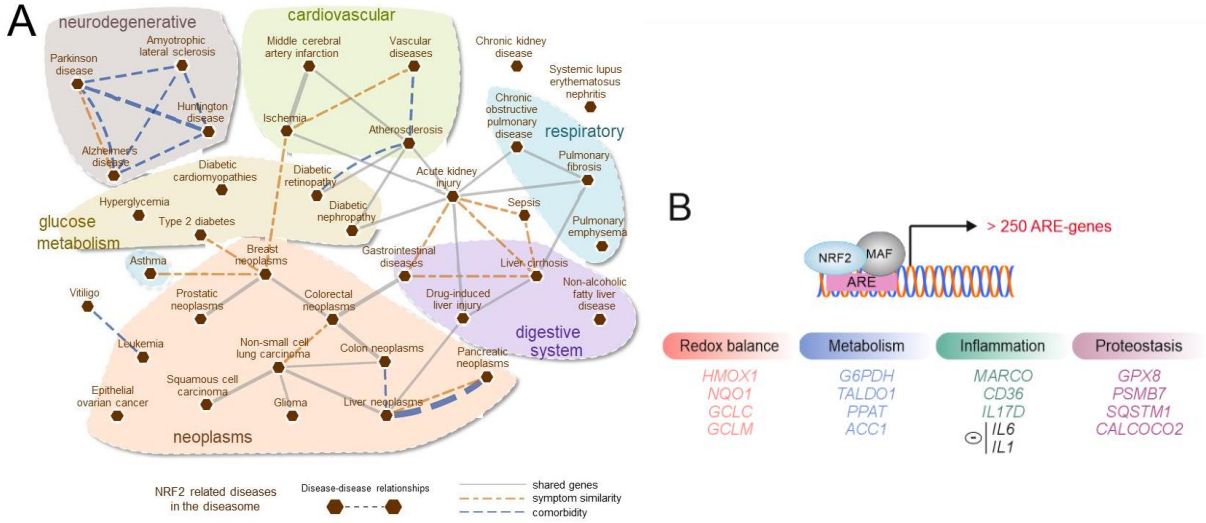

Figure 1. A, systems medicine perspective on the alterations of NRF2 activity as a common pathomechanism of NCDs. **B**, NRF2 regulates the expression of ~250 homeostatic genes with multiple cytoprotective functions. The figure illustrates just some very well established target genes.

Company/ Molecule	Disease	Stage and trial code
BIOEN: Dimethyl fumarate (DMF)	Multiple Sclerosis	Marketed
	Psoriasis	Marketed
BIOGEN: ALK8700/BII089	Multiple Sclerosis	Phase 3: NCT03093324
REATA PHARMACEUTICALS: Bardoxolone methyl (BARD, RTA402)	CTD-PAH	Phase 3: NCT02657356
	Pulmonary hypertension-ILD	Phase 3: NCT03068130
	Alport síndrome	Phase 3: NCT03749447
	Autosomal dominant polycystic kidney disease	Phase 3: NCT03918447
	IgA Nephropathy, Type 1 Diabetes, Focal Segmental Glomerulosclerosis	Phase 2: NCT03366337
REATA PHARMACEUTICALS: Omaveloxolone (RTA408)	Friedreich's ataxia	Phase 2: NCT02255435
KYOWA HAKKO KIRIN: Bardoxolone methyl (BARD, RTA402)	Type 2 diabetes mellitus Chronic kidney disease	Phase 2 (completed): NCT02316821
		Phase 3: NCT03550443
EVGEN PHARMA: SFX01	Subarachnoid Hemorrhage	Phase 2: NCT02614742
	ER+ Metastatic Breast Cancer	Phase 2: NCT02970682
ARBOR PHARMACEUTICALS: XP23829	Psoriasis	Phase 2 (completed): NCT02173301

Company/ Molecule	Disease	Stage and trial code
COMPLEXA: CXA10	Primary Focal Segmental Glomerulosclerosis	Phase 2: NCT03422510
	Pulmonary Arterial Hypertension	Phase 2: NCT03449524
COLBY PHARMACEUTICALS: OT-551	Dry Eye Macular Degeneration	Phase 2 (completed): NCT00485394
VTV THERAPEUTICS: HPP971	Immunological Disorders, Bone, Eye, Lung, Blood diseases	Preclinical
V CLINBIO: VCB-101	Multiple Sclerosis	Preclinical
V CLINBIO: VCB-102	Psoriasis	
GlaxoSmithKline: Compound A	COPD	Preclinical
MOCHIDA: TFM-735	Multiple Sclerosis	Preclinical
CATABASIS: CAT4001	FRDA, ALS	Preclinical
C4X DISCOVERY: ML334 and derivatives	ND, T2DM, COPD	Preclinical
KEAPSTONE THERAPEUTICS: KEAP1 inhibitors	Parkinson's disease Amyotrophic lateral sclerosis	Preclinical
DAIICHI SANKYO CO: RS9	Retinovascular disease	Preclinical
ACLIPSE HERAPEUTICS:M102	ALS and other ND	Preclinical

Table 1. Pharmaceutical and clinical development of NRF2-targeting drugs.

electrophiles. These and many other compounds have proved to be active in preclinical studies and a few are now in phase 2/3 clinical trials (**Table 1**). The case of maximal success is dimethyl fumarate, which is **approved for clinical use by the US Food and Drug Administration (FDA) and the European Medicines Agency (EMA)**. It is currently used for the treatment of relapsing-remitting multiple sclerosis and psoriasis, and is in phase 2 for rheumatoid arthritis, cutaneous T cell lymphoma and obstructive sleep apnea. However, this success also evidences the **weakness of EU** in NRF2-related pharmacology considering that this compound was initially discovered in Germany but it is now economically exploited in the USA. **b)** Protein-protein interaction (PPI) inhibitors are designed to interfere with the docking of NRF2 onto KEAP1, hence preventing proteasomal NRF2 degradation.

Several NRF2/KEAP1 PPI inhibitors are under patent protection. These compounds remain to be validated in clinical trials, thus providing a **unique opportunity for European pharmaceutical industry**.

NRF2 inhibitors hold a great promise in cancer therapy, as its inhibition will result in a significant loss of the capacity of tumor cells to maintain growth and adapt to the hostile tumor microenvironment. Several biopharmaceutical companies have active pipelines for discovery of selective NRF2 inhibitors. **Again, this field offers a unique pharmacologically and clinically relevant window of opportunity for timely development of such compounds within Europe**.

1.1.2. DESCRIPTION OF THE CHALLENGE (MAIN AIM)

Most NCDs do not have a cure. Networking among multidisciplinary teams that could have the training and capacity to face disease from a perspective of causative pathomechanisms, such as NRF2 related dysfunction, rather than "only" the specific clinical symptoms, is the most appropriate approach to overcome this drawback. Therefore, the challenge of BenBedPhar is to share NRF2-related knowledge generated by evidence-based pharmacological and clinical research, and to integrate it into the stream of European social, clinical and economic sectors with capacity to translate this knowledge into innovative therapeutics for a set of NCDs. Obviously, not all NCDs will benefit equally from NRF2-related therapy and the Action will define the most suitable ones. However, overwhelming evidence supports a focus on: metabolic [diabetes, nonalcoholic steatohepatitis (NASH)], cardiovascular, neurodegenerative disease, and at least two types of cancer (lung cancer where over 30% have KEAP1/NRF2 mutations, and glioblastoma where NRF2 is activated by signaling mechanisms.

The timeliness of this Action relies on the current situation of the traditional and alternative medicine landscape. Pharmaceutical companies are slowly but steadily developing NRF2 activators (Table 1) and inhibitors. However, the pharmaceutical industry in Europe is lagging behind Japan and the USA. More concerning, Europe is losing leadership in this field as demonstrated by the fact that the only compound marketed presently as a NRF2 activator (dimethyl fumarate; Tecfidera) was initially investigated by a German company but it has been exploited by an US company.
On the other hand, several **parapharmaceutical companies** have jumped into this field and are marketing natural NRF2 modulators, often originating from herbal traditional medicine. Not at all questioning the important value of natural products for drug discovery, these compounds are propagated as alternatives to school medicine and magic bullets against various diseases without evidence for bioavailability, efficacy, quality control or risk assessment. While this fact demonstrates the increasing public interest in NRF2-therapy, **BenBedPhar** will raise awareness about the current limitations of NRF2-related compounds and their use without clinical proof of efficacy or safety.

1.2 Progress beyond the state-of-the-art

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

COST is instrumental in approaching this challenge by supporting the organisation of a pan-European and multidisciplinary network with an innovative **social, technological and economic** view of NRF2-related therapies and their application to NCDs. For the first time, this Action brings together leading experts in the NRF2 field to progress beyond the state of the art along following aspects:

1) Standardization and harmonization of existing concepts and tools (methods, reagents drugs, etc.) for the study of NRF2 biology, pharmacology and medical use. Just as an example of the critical need to standardize research protocols, many commercial antibodies recognize a 60 kDa protein that is not NRF2, contaminating the literature with false results and flawed conclusions.

2) Confirmation of the set of NCDs where NRF2-based therapy will be most significant either as **monotherapy or as add-on therapy** in combination with other medicines. Extensive evidence from the

Nrf2-knockout mouse model and data mining in human NCDs strongly suggest that at least the NCDs depicted in section 1.1.2. will benefit from NRF2-targeted therapy.

3) Creation of a database of relevant patient metadata (under ethical regulation), which will address **NRF2-related genetic and biochemical biomarkers** for disease monitoring and drug-target engagement in NRF2-related NCDs. BenBedPhar already has access to large databases with thousands of highly standardized patients suffering NCDs. NRF2-relevant blood biomarkers to be identified in the Action are intended to be translated to clinical practice by providing the ground for a later development of a user-friendly biochip with clinical value. Action participants with expertise in transcriptomics, hematology and from the SMEs, that will be further enriched with additional recruitments, will have a central role in designing the clinically-relevant biochip.

4) Somatic mutations in the KEAP1/NRF2 system in non-small lung cancer can be detected by sequencing of tumour-derived cell free DNA (cfDNA). A **targeted sequencing panel** containing these genes will be designed and documented by the geneticians recruited to the Action, to be exploited clinicaly for personalized NRF2-targeted treatments.

5) Development of a calatogue of optimized animal models of NCDs, that combine NRF2 alterations with other disease-specific pathophenotypes such as hyperglycemia, insulin resistance, hypertension, hypercholesterolemia, cardiomyopathy, fibrosis, amyloidopathy, etc. Many promising compounds tested in preclinical studies of NCDs are ineffective in patients. In many cases, this is due to the poor reproducibility of NCD pathomechanisms in laboratory animals. Animal models will be analyzed from a "reverse translational" perspective (from patient to animal models), using metadata from clinical databases. The most relevant animal models identified in this Action will support and reciprocally benefit from the EU initiative on preclinical animal models (www.preclinicaltrials.eu) for increasing the relevance of pre-clinical studies in the pipeline of drug development

6) Development of a **virtual technology platform** through specific free software tool *openBIS* that will comprise research infrastructures and advanced technologies existing in the network, as well as a meta-archive of biologic samples highly relevant for NRF2 research, available in several EU biobanks. This platform will facilitate the acces of participants, especially ITC members, to art technologies and to relevant biologic samples for fostering coordinated research across the Action.

7) Documentation of new compounds regulating NRF2/KEAP1, with higher specificity and superior ADMET (absorption, distribution, metabolism, excretion and toxicity) profile, to be achieved by integrating results from "machine learning" in network pharmacology, structural biology and systems medicine, together with the preclinical data obtained in improved animal models for facilitating the selection of promising drug candidates. Additionally, a strategy of **repurposing existing drugs** that have proven clinical benefits in particular diseases underlined by NRF2-related pathomechanisms will be considered in close collaboration with pharmaceutical companies engaged in this Action.

8) Documentation for future clinical trials with lead NRF2-targeting compounds. The Action will provide new directions from a systems medicine and pharmacology perspective for fostering clinical research in the field of NRF2-related therapeutics. The knowledge shared within the network will be used by several participants from the clinical sector to elaborate the strategy for organizing a clinical trial in NASH and liver cirrhosis. Other innovative clinical trials will also be persued during the Action.

9) Economic exploitation of outcomes in the form of provision of knowledge and innovative services according to a strategy developed in the Action in collaboration with participating SMEs. Always bound to confidenciality agreements, the SME members of the Action will have access to expert advice on their drug depelopment pipelines in NRF2.

10) All these approaches will be transversally addressed in the **training of young researchers.** The Action will create a critical mass of highly trained young researchers, able to continue and foster research in the field of NRF2-related therapeutics.

1.2.2 OBJECTIVES

1.2.2.1 Research Coordination Objectives

(1) Building a **cohesive multidisciplinary and highly interactive pan-European network** of stakeholders in the NRF2 field and synergistically bundle their individual expertise towards the integrative understanding of NRF2 pathomechanisms, their relation to NCDs and their future implementation in new pharmacologic and therapeutic approaches. The expected outcome will be a strong consortium in Europe with capacity to translate to the society an innovative strategy for the clinical treatment of several currently incurable NCDs.

(2) Coordination and integration of existing and ongoing research-generated knowledge in the field of NRF2 and its relation to NCDs. The number of basic and translational studies on NRF2 physiopathology has been growing exponentially for the past 15 years, as can be seen by the number of NRF2 publications in Pubmed. However, many research teams and even SMEs have jumped into this field without the necessary background. Due to misleading information and poor quality of many published studies, this objective is very timely and will provide a set of research tools, guidelines and harmonized procedures, aiming at increasing research efficiency.

(3) Channelling of knowledge towards the European Biopharmaceutical and clinical sectors by providing inventories of new or repurposed NRF2-targeting drugs with clinical potential, the most valuable animal models of NCDs for analysis of NRF2-pathomecanisms, genetic and biochemical biomarkers and support documentation for design of preclinical and clinical trials. These measures will positively impact on the technological development of European countries and will be coordinated through MC/WG meetings, and scientific conferences.

(4) Dissemination of knowledge towards general public and policy makers. It is the moment to communicate to the general public the potential of NRF2-based new therapeutics for NCDs from a very realistic and scientifically validated view as well as to advice against the magic bullets sold by parapharmaceutical companies without clear evidence of safety and efficacy. By the same token, the EU policy makers must be aware of the impact that this field will have in NCDs therapy and provide a lead in Europe. This objective will be achieved through press articles, opinion papers, JRC technical reports, the Action webpage, participation in communication activities (i.e. Researcher's Night), and presence in social networks, among others.

1.2.2.2 Capacity-building Objectives

(1) Establishment of **technology transfer and collaboration agreements** between scientists and SMEs to help in the economical exploitation of the network outcomes towards improved NRF2-targeted therapeutics in various NCDs. This objective will narrow the gap between Academy and Industry by facilitating consulting with experts and Biopharma-funded collaborative projects.

(2) Creation of several technological platforms by making use of publicly available informatics software: 1) **database of small molecule modulators** of the NRF2 pathway with available information about their pharmacological profile and preclinical and clinical development, 2) a systems-based database on quantitative NRF2-related **genetic and biochemical biomarkers** related to NRF2 pathophysiology and on the effects of NRF2 in NCDs; 3) a **registry of animal models**, already existing or developed during the Action, that best recapitulate particular human NCDs regarding NRF2-related pathomechanisms; 4) coordination of an **open-source toolbox** with relevant commercial or customized reagents for NRF2 research, such as antibodies, expression and silencing vectors, reporters of NRF2 activity, etc.; 5) information about **repositories of biological samples** from well-characterized NCDs patients and controls. Together, these platforms will be instrumental to build and substantially increase the EU

capacity in NRF2 research and therapeutics. Their coordination will be achieved through MC/WG meetings, and scientific conferences, among others.

(3) Promotion of the **interdisciplinary training of a new generation of young scientist** with interdisciplinary skills in the field of NRF2–NCDs. The end goal is to promote a timely scientific community of NRF2 basic, pharmacological and clinical researchers and entrepreneurs and to develop a "sense of belonging" to the EU scientific community. The networking tools will include 2 calls/year for STSMs; 3 TSs, as well as 3 MOOCs and a mentoring programme.

(4) Facilitation to **access state-of-the-art biomedical technologies** existent in the Action (i.e. genomics, transcriptomics, proteomics and metabolomics profiling) and bioinformatics tools, which represents an additional benefit particularly for ITCs that may have a limited access to some advanced technologies. The Action participants from ITCs will benefit from collaborative activities through STSM, among other activities.

2. NETWORKING EXCELLENCE

2.1. Added value of networking in S&T Excellence

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

NRF2 is now envisioned as a new strategy to reinforce overall homeostatic responses. This is best exemplified by two conferences held in the EU: a) "Colloquium on NRF2 and Cancer" (UK ***Feb 27th to March 2nd, 2018***) and b) "Transcription factor NRF2: New opportunities for pharmaceutical innovations in chronic diseases" (Spain, ***April, 11th to 13th, 2018***). These two meetings attracted many of the leading basic and clinical experts as well as 9 biopharmaceutical companies from USA, Japan and the EU in an unprecedented discussion about NRF2-targeting for the therapy of NCDs. Additionally, there have been five top NRF2 conferences hold in Japan, termed Environmental Response conference. The latest appointment was in 2019 (***Sep 12th to 14th, 2019***).**Currently there are no European networks focusing on NRF2-based pharmacology and medicine**. There are some scattered bilateral collaborations in EU-funded small-scale projects addressing particular NCDs. While important as preliminary exploration, such projects cannot accomplish the ambitious objectives of BenBedPhar relying on the efficient use of COST tools.

Synergy with other COST Actions. The current Action will add value and will be built on the achievements of previous or ongoing COST Actions: a) **BM1203** (EU-ROS: The European Network on Oxidative Stress and Redox Biology Research) which has some connection with NRF2-related pathophenotypes at the level of redox-related diseases. b) **CA15120** (OpenMultiMed: Open Multiscale Systems Medicine) will provide some bioinformatics support for the systems medicine and network pharmacology approach to NRF2-related pathologies. c) **BM1307** (Proteostasis) will strengthen the connections between NRF2 and regulation of protein synthesis and degradation under normal and pathological conditions. This Action will also synergize with the **European Chronic Disease Alliance (ECDA),** which gathers several EU associations on NCDs, and provides expert communications with policy makers and general public. The exchange of knowledge with this Pan-European alliance will result in moving forward towards a new strategy to control NCDs. The Action will also synergize with **EIT Health,** one of the largest public funded initiatives for healthy living and active aging worldwide.

Considering that this Action will use biological databases and repositories based in COST countries, supported with public or private resources, the added value of networking is highly relevant not only for the COST Action but also for these platforms by increasing their sustainability, developing a specific sub-dataset related to the NRF2-interactome and its role in NCDs, along with a selected repository of NRF2-related biosamples located in EU biobanks. Several proponents of this Action are either members of these platforms or contribute to the Action with new sample collections. Other members of the

mentioned EU platforms will be recruited later in the course of the Action.

2.2. ADDED VALUE OF NETWORKING IN IMPACT

2.2.1. SECURING THE CRITICAL MASS AND EXPERTISE

BenBedPhar provides a strong interdisciplinary network capable of designing new therapeutic approaches for those NCDs where altered NRF2 activity is at least one dysregulated pathomechanism. The Action includes and will further recruit: **a)** European research teams with specific expertise in NRF2 regulation and its role in NCDs; **b)** a set of clinical researchers from highly reputed hospitals and biobanks and others with interest in developing a pioneer clinical trial in Europe for NRF2-related therapeutics in NASH and liver cirrhosis; **c)** experts in medicinal chemistry and drug development that belong or interact with several SMEs; **d)** bioinformaticians with excellence in data mining, systems medicine, network pharmacology, machine learning and biostatistics.

Additionally, the affiliation of several participants to **Centres of Excellence** will enable the access to cutting-edge technologies and forefront knowledge on NRF2 research at three levels: basic mechanisms, pharmacological R&D and outstanding clinical experience in NRF2-related pathophenotypes. Beyond the academic and clinical sectors, **BenBedPhar** counts for the active participation of **biotech/pharma companies** with NRF2-related developments in their pipelines, or interested in exploring this emerging field. Their involvement will be crucial to accelerating the knowledge transfer objectives, and will channel part of the economic exploitation of the Action's outcomes. Active envolvement **of Cost countries, particularly ITCs, is expected** (**73 proposers from 24 COST members out of which 14 are ITCs countries).** In addition, the Action involves leading experts from **International Partner Countries** (**USA and Japan),** which are now leaders the field of NRF2 research, and will provide key expertise in basic and clinical translation. The inclusion of **NNCs (Russia and Egypt)** brings into the Action unique chemo-physical expertise. The Action will further increase the geographical diversity needed to address the challenge efficiently. The Action will strive for high involvement of ECIs and having a balanced gender distribution during its lifetime. BenBedPhar **will further increase** the critical mass of experts with complementary expertise, as well as research resources such as databases, virtual platforms and research tools (reagents, methods, animal models, technologies, etc.). Emphasis will be given to attract stakeholders with expertise in areas that may reinforce the network with more SMEs and participants from the clinical sector,and active search for more biobanks and repositories in COST countries.

2.2.2. INVOLVEMENT OF STAKEHOLDERS

Involvement of the Research Community

Benefits: Access to databases, repositories and "state of the art" technologies. Research harmonization in NRF2 medicine through guidelines and standard procedures. Large-scale and multidisciplinary collaborative research. Participation in consortia for grant applications. Economic valorisation of research by collaborating with participating SMEs. **Role:** Exchange of knowledge and research tools. Set up and feeding of databases and repositories. Training of young researchers through STSMs and Training Schools (TS). Promotion and dissemination of results. **Engagement actions:** Interaction through COST tools (bi-annualmeetings, STSMs exchanges, etc.) with researchers with relevant complementary expertise. Participation in national and international congresses. Invitation to scientific meetings of the Action.

Involvement of Clinicians

Benefits: Access to up-dated information on hot research topics in NRF2-related therapeutics. Access to new biomarkers for patients stratification and disease/therapy monitoring in NCDs. Creation of the evidence and momentum to obtain funding for clinical trials. **Role:** Feed the Action's databases with data of patient cohorts. Provide biological samples of patients and controls for repositories. Elaborate the documentation for future clinical trials on new/repurposed compounds identified by the Action. Strive in the development of new clinical trials with funding from other sources, but with the input of the Action. Participate in TSs and STSMs. **Engagement actions:** Seminars in clinical centres related to the topic of the Action. Direct contacting of clinicians with relevant expertise in NCDs. Networking at medical congresses. Invitation to scientific meetings of the Action. Publications in specialized media.

Involvement of the pharmaceutical industry (including SMEs) and economic sectors

Benefits: Access to new concepts and mechanistic insights for designing innovative NRF2-targeted drugs. Access to specialized groups for collaborative research. **Role:** Accelerate the translation of NRF2 related therapies. Impulse the intrepreneur culture within the Action in the field of drug development. Strategy for economic exploitation of NRF2-therapeutics. **Engagement actions:** participation in STSMs and TSs. Networking at EU strategic events (infodays, brokerage events, newsletters, etc.). Dissemination of the Action biotechnological activities in digital media such as https://labiotech.eu/ and partnership offers through the European Enterprise Network (EEN). Invitation to scientific meetings of the Action. Mentorship.

Involvement of Young Scientists and early Career Investigators (ECIs)

Benefits: Interdisciplinary training in the TSs and several STSMs, and participation in the Action's scientific meetings. Participation in high-level international research. Career development opportunities. Sustain research excellence. **Role:** Participation in STSMs, TSs and WGs. Communication and publication of results. Exchange of knowledge between research teams through the COST tools. **Engagement actions:** Networking in national and international scientific meetings. Website dissemination. Recruitment of other ECI participants among their contacts (ECI managed Twitter account of BenBedPhar).

Involvement of Patient Associations

Benefits: Increased awareness of research efforts made by EU in their benefit. Participation in the process of developing new therapeutic strategies. **Role**: Participation in the Action's scientific meetings. Improve dissemination of the Action's outcomes to patients and policy makers. **Engagement actions:** Public Action promotion through the website. Invitation to scientific meetings. Networking on specialized forums (health infodays, brokerage events). Participation in clinical trials.

Involvement of Policy Makers

Benefits: Receive advice of the EU healthcare funding programmes for R&D&I in NRF2-related medicine and therapeutics. **Role:** Joint press sessions for providing information on NRF2 involvement in several major diseases, and the promise of the newly identified therapies. **Engagement actions:** Provide feedback to the Action. Publication of Joint Research Centre (JRC) Technical Reports and opinion papers.

Involvement of Society as a whole

Benefits: Awareness of new achievements on the NRF2-related pharmacology and medicine. Increased consciousness of the research efforts made in the benefit of the European citizens. Awareness of the irresponsible use of NRF2 modulators without appropriate medical control. **Role:** Feedback to the Action regarding their needs and expectations from medical research in Europe. **Engagement actions:** Participation in informative events (European research night and similar national events). Open Doors Days (1 event per year) to research infrastructures and laboratories. Two open blogs and 2 forums organized by the Action and publicized through the EU-Citizen Science initiative.

The structure and timeline of these activities will be defined at the beginning of the Action. It is expected that the engagement of researchers, clinicians, SMEs and ECIs will be more intense at the onset of the Action, and engagement of the rest of stakeholders will be carried at middle-last phases.

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

In Europe there is a relevant critical mass of expertise in NRF2-related biology in health and disease, but it must be pointed out that the leading groups in the field are from Japan and USA. The involvement of these **IPCs** will provide: **a)** productive exchange of knowledge among researchers with complementary expertise, **b)** technology transfer between European and IPC teams, **c)** top level training provided in TSs and STSMs, **d)** input and access to databases, registries, repositories and technology platforms created in the Action. Regarding **NNCs**, Russia and Egypt, the Action plans to organize some of the TSs and one Annual meeting in NNCs with the purpose of increasing the visibility of European research. **In return, IPCs and NNCs will participate in and benefit from their inclusion in the Action's activities such as training, access to state-of-the-art technologies, the toolbox of reagents, animal models, methods, etc.**

3. IMPACT

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

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

	Short Term	Long Term
Scientific Impact	• Better understanding of the mechanistic regulation and function of NRF2 and its role in metabolism, inflammation, proteostasis etc. in NCDs. • Increased research efficiency and avoidance of overlaps due to harmonized procedures, protocols, shared databases, and fluent communication through networking events. • Adoption of a Systems Medicine approach that will break down former communication and knowledge barriers among different disciplines through active collaboration with specialists in the field and sharing of specific concepts and tools.	• Provision of the basis for implementation of NRF2-targeted monotherapy or add-on therapy complementing current treatments, starting with the selection of the most promising new or repurposed NRF2 modulators. • Establishment of reliable genetic polymorphisms and blood-based biochemical biomarkers related to the role of NRF2 in redox metabolism, inflammation and proteostasis in various NCDs, • Maximize the chance of success in transnational project calls. • Boost a generation of young scientists with expertise in NRF2-related medicine as well as entrepreneurship culture.

<table>
<tr><td></td><td colspan="2">Measurable outcomes (estimated): ~40 joint scientific/review publications; ≥5 methodological procedures and guidelines on preclinical approaches; ≥5 joint proposals submitted to international calls and >2 colaborative research projects granted; ~5 new born research groups led by ECIs (with a responsibility role in the 5 WGs); over 200 researchers participating over the Action course, out of which ~50 from ITCs and ~100 ECIs; ~20 researchers changing their focus to NRF2-related fields (see section 4 Implementation and 4.1.3. Risk).</td></tr>
<tr><td rowspan="2">Technological Impact</td><td>• Increased access to state-of-the-art research facilities, NRF2-related tools in preclinical settings: datasets, biobanks, animal models, methods, tools and drugs shared within the Action, especially through STSMs. Action members located in ITCs with limited resources will most benefit.
• Consulting and collaborative projects with biopharmaceutical companies.</td><td>• Increased armamentarium in clinical settings for NCDs (panel of NRF2/KEAP1 somatic mutations, panel of biochemical biomarkers, new or repurposed drugs, etc.).
• Progression of drug development pipelines towards clinical trials, based on the integrated preclinical data and the documentation for clinical trials ensuing from the Action.</td></tr>
<tr><td colspan="2">Measurable outcomes (estimated): ~10 animal models of NCDs and ~20 biomarkers validated; over 300 researchers worldwide using the generated datasets; ~10 new or repurposed drugs identified; 3 industry showcases; 10 technology transfer agreements; ~10 collaborative contracts with Biopharmaceutical companies (not financed by COST but by SMEs due to COST networking); ~10 preclinical studies initiated and ~4 clinical trials designed (at the time of this application two of the clinical proponents have already expressed this interest); customized array for analysis of somatic mutations, that will be exploited clinicaly for personalized diadnostics and treatment; design of a clinically-relevant biochip with the ~20 identified biomarkers (see section 4 Implementation and 4.1.3. Risk).</td></tr>
<tr><td rowspan="2">Socioeconomic Impact</td><td>• Increased presence of women researchers in international and high quality research environments for their career development.
• Increased social awareness about the efforts made by the scientific community for increasing health and well-being in Europe, through the dissemination/communication tools and events organized by the Action.
• Increased capacity to attract funds through successful submission of large-scale transdisciplinary project proposals in collaboration with industrial partners.
• Increased participation of young scientists to be achieved through STSMs, TSs, and other COST tools.</td><td>• Improved early diagnosis, more accurate monitoring, and personalized therapeutic approaches having NRF2 in central position.
• Increased competitiveness of the European pharma industry led by SMEs provided by reinforced networking between academia and industry.
• Improved strategy for new and repurposed drug discovery in NRF2 pharmacology by “SMART” use of NRF2 information.
• The identification of blood-based biomarkers will be used by participating SMEs to commercialize a biochip for disease monitoring.</td></tr>
<tr><td colspan="2">Measurable outcomes (estimated): ~40 women leading research on NRF2; ~500 citizens from professional and patient foundations attending the Action’s activities; Public section of the website including quarterly “news and views” section (measurable by number of accessions); presence of the Action in digital media and strategic events (yearly infodays, researchers’ night, etc); ~3 online open courses (MOOC) with over 100 expected participants per MOOC. Patenting and economic exploitation of the biochip of NRF2 biomarkers by participating SME (see section 4 Implementation and 4.1.3. Risk).</td></tr>
</table>

3.2. MEASURES TO MAXIMISE IMPACT

3.2.1. KNOWLEDGE CREATION, TRANSFER OF KNOWLEDGE AND CAREER DEVELOPMENT

Knowledge creation will arise through an integrative analysis of the publicly avalilable information related to NRF2, retrieved from bibliometric analysis, data mining or communication by the Action participants, by making use of the COST tools (see **section 4. Implementation).** This information will be used to create knowledge around the following themes: **a)** The molecular basis of NRF2 activity and regulation and its subversion in an array of selected NCDs that will be defined at the beginning of the Action but will surely include metabolic [diabetes, nonalcoholic steatohepatitis (NASH)], cardiovascular and neurodegenerative disease as well as at least two types of cancer (lung cancer where over 30% have KEAP1/NRF2 mutations, and glioblastoma where NRF2 is activated by signaling mechanisms). **b)** Tools and preclinical models, such as high quality antibodies, reporter cell lines, expression vectors, selected animal models, etc. **c)** A repository of biological samples and clinical data from disease-relevant cohorts. **d)** Existing, repurposed and newly identified NRF2 modulators with detailed information about their mode of action on NRF2 activity and impact on pathophysiology. **e)** Genetic variants of the *NFE2L2* and *KEAP1* genes and the transcriptional fingerprint of NRF2 in patients with the selected NCDs. All these points, together with the experience and complementary backgrounds of the Action participants, will increase the research efficiency and provide: **1)** increased understanding of NRF2 regulation; **2)** new NRF2-dependent pathophenotypes in NCDs; **3)** new biomarkers for disease prevention/monitoring; **4)** a toolbox for NRF2 research **5)** new or repurposed drug candidates with high therapeutic potential; **6)** optimized guidelines and procedures, both in clinical and preclinical settings.

The transfer of knowledge framework created during the Action will be achieved through the use of COST tools. Specific activities include: **a)** Scientific conferences. **b)** Guidelines and tutorials related to the information retrieved from the databases. **c)** Joint publications and communications. **d)** Knowledge transfer to the general public through the webpage, interviews and articles on social media. **e)** Consulting and Biopharmaceutics funded collaborative projects. In this context, the biopharmaceutical companies participating in the Action (7 proponents plus others recruited during te course of the Action) will receive strong support in key activities such as medicinal chemistry for designing new compounds, systems biology approaches applied to drug discovery, pre-clinical testing of new or repurposed drugs, and identification of biomarkers for monitoring NRF2-targeted therapies.

BenBedPhar will provide **Career development** opportunities, especially oriented to ECIs, PhD students, and researchers from ITC countries. The Action will invest strong efforts in attracting more ECIs (18 secondary proponents are ECIs) during the course of the Action. They will benefit from: **1)** participation in large interdisciplinary consortia, joint publications and project proposals in collaboration with internationally renowned scientists. **2)** Interdisciplinary training at the interface of medicine, biology, medicinal chemistry, pharmacy, clinical research, leadership and entrepreneurship. **3)** Access to relevant management positions in the Action. **4)** Grants to attend international science and technology related conferences. **5)** Access to a mentoring program, where the most experienced participants in the Action will offer advice and guiding to the youngest ones through science, technology and entrepreneurship. They will establish a close scientific relation through regular tele-calls, and have the chance to know each other during the events organized by the Action for further sustaining the Action sustainability. As a result, the Action will increase the capabilities of future researchers and enterpreneurs in Europe regarding to NRF2-related medicine.

Sustainability beyond the Action

This Action will assure the sustainability of the network through the following measures: **1)** Participants will continue to have access to the databases and repositories created in the Action, that will be maintained and updated in collaboration with the platforms available from the Action participants. **2)** The Action will be also kept active through future joint activities sustained by the functional consortium built

in the Action, such as grant applications, publications and collaboration with SMEs. **3)** The interdisciplinary training programs developed in the Action for students and ECIs will be sustained after the Action's completion by organizing satellite meetings at national and international conferences. **4)** Collaborations between players in the Action and the documentation for clinical trials are expected to sustain the initiation of clinical trials on potential drugs (including but not limited to the already planned trials on NASH and liver cirrhosis) and for implementing the identified biomarker and genetic panels into clinics (including the bio-chip designed in the Action).

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

The Action will follow the **"**Guidelines for the Communication, Dissemination and Exploitation of COST Action Results and Outcomes". BenBedPhar will use the **OpenAIRE's** guidelines, closely linked to the EU mission, to provide open access to research outputs. Because some information may need to be patent protected, the Action will follow the principle "as open as possible, as closed as necessary".

Plan for Dissemination.

1) The Action will strive to implement the capacities on NRF2-research in Biopharma and clinics through knowledge exchange, collaborative scientific publications complemented by communications at scientific meetings and at industry showcase events, as well as by position papers. The Action will give financial support to those publications and communications that represent collaborative work of the Action participants on the role of NRF2 in NCDs. **Outcomes**: **1)** ~40 joint scientific and review publications; ~5 methodological procedures and guidelines on preclinical approaches **2)** Three industry showcases; bi-annual scientific meetings.

2) BenBedPhar website containing both an intranet for participants and a public section. The intranet is aimed at disseminating knowledge and tools among the Action members and will include the multi-partner databases on biomarkers, the toolbox of reagents, methods and drugs, the registries of biological samples and animal models, guidelines and standard procedures, etc. The public section is aimed at promoting the Action towards the scientific community, pharmaceutical industry, healthcare systems and general public. It will contain on-line lectures, forum for discussions with stakeholders, quarterly newsletters and a "news and events" section. The public section will **increase awareness** about pharmacological targeting of NRF2 as well as about the need for controlling the NRF2 modulators, and will provide to the general public the message of EU integrated research for Health.

Plan for exploitation.

The Action will generate the following main outcomes to be further exploited:

1) Drug candidates or repurposed drugs will be evaluated in connection with Biopharmaceutical companies and with basic pharmacological inputs, with the purpose of accelerating and improving the development of NRF2-related drug development pipelines. IPR protection will be supported with customized confidentiality agreements. **Outcome:** database of NRF2 activators and inhibitors with a critical assessment of their clinical applications in the selected NCDs.

2) The identified **NRF2 transcriptional signature and associated biomarkers** for patient stratification, disease prognosis and monitoring as well as target engagement, having the potential for clinical validation and application, will be exploited as clinical predictors of disease onset and progression or response to NRF2-targeted therapies. **Outcomes**: **1)** Validation of ~20 blood biomarkers related to the role of NRF2 in redox metabolism, inflammation and proteostasis **2)** Transfer of this knowledge for development of a blood biochip for economical exploitation by one SME of the Action.

3) Given that somatic mutations in the KEAP1/NRF2 system in non small lung cancer can be detected by **sequencing of tumour-derived cell free DNA** (cfDNA), a targeted sequencing panel containing these genes along with other lung cancer relevant oncogenes will be developed for further clinical validation and economic exploitation. **Outcomes: 1)** dataset of mutations in *NFE2L2* and *KEAP1* genes in lung cancers (and possibly other cancers), **2)** development of a customized array for analysis of these

somatic mutations, that will be exploited clinicaly for personalized treatments.

Dialogue with the general public.
Project promotion to the general public will be done in social networks (e.g. Facebook and Twitter), the BenBedPhar webpage, and digital media such as https://labiotech.eu/. All Action members will try to reach a broad public audience/readership, announcing the Action's breakthroughs and highlighting the relevance of NRF2 as an innovative strategy to address therapeutics in NCDs but at the same time explaining the dangerous use of uncontrolled NRF2 modulators without evidence of safety and efficacy. **Outcomes**: **1)** Three Massive Open Online Courses (MOOCs) will be used for sharing seminars and lectures. **2)** The publications and the datasets created through the Action will be deposited in **Zenodo.** The Action will also use the **EU-Citizen-Science** platform (https://eu-citizen.science/) to promote the Action activities in two open 2 blogs and 2 discussion forums. **3)** Various dissemination events dedicated to the general public will include the European Researchers' Night, the annual Pint of Science festival, or dedicated Open Days in laboratories and research infrastructures. **4)** Online publications in social networks (Facebook, twitter) will show in a way understandable by non-specialized audiences the Action activities and explain key concepts of NRF2-related therapies in NCDs.

4. IMPLEMENTATION

4.1. COHERENCE AND EFFECTIVENESS OF THE WORK PLAN

4.1.1. DESCRIPTION OF WORKING GROUPS, TASKS AND ACTIVITIES

The structure of the Action will be established according to the well-established COST rules. In addition to the Chair, Vice-Chair, Management Committee (MC), and the leaders of 5 Working Groups (WPs), other management responsibilities will maximize the achievement of BenBedPhar objectives and the synergy with COST policies. The **STSM Coordinator** will coordinate the organization of TSs and STSMs and will manage the applications. The **ECI coach** will develop a subnetwork of ECIs by enrolling currently engaged ECIs and recruiting additional ones. S/he will identify specific needs on the skills and capabilities of ECIs that will be addressed in STSMs and TSs. In addition, s/he will coordinate with SMEs a mentorship programme for ECIs with entrepreneurship interest. The **Public Relations Coordinator** will establish and maintain the BenBedPhar webpage, will assist WG5 in collecting and disseminating materials in various communication channels, and will prepare a quarterly newsletter reporting the periodic achievements of the Action. The **Gender Equality Coordinator** will ensure gender balance with new recruitments and inform about special opportunities for women in science. The **Core Group** will support the MC by monitoring the Action progress. **For all management positions, candidates from ITCs, ECIs and females will be encouraged to apply.**

Common tasks to all WGs

1) Attraction of major players in the field of NRF2 including academia, research institutes, hospitals, SMEs, regulatory agencies and patient organizations. **2)** Organization of bi-annual WG sessions and scientific workshops at BenBedPhar meetings, including invitation of external experts. **3)** Contribute to the organization of TSs and STSMs. **4)** Assist WG1 in feeding databases, registries and repositories and the technological platform on NRF2. **5)** Assist WG4 in the organization of 3 industry showcase events (one per year **6)** Assist WG5 in promoting the Action and its results towards specialists, patients, other stakeholders and the general public. **7)** Assist WG5 in feeding the webpage **8)** Initiate joint

research proposals, patents, scientific publications and communications. **9)** Help to prepare reports for the MC and COST.

Specific tasks to the WGs

WG1: Tools for NRF2 research.

Activities: This WG will critically revise basic mechanisms of NRF2 regulation in health and disease from a systems biology perspective, and coordinate the access of the Action members to databases, standard procedures, state-of-the-art technologies and repositories containing high quality customized reagents, validated animal models and biological samples for NRF2 research.

Tasks: 1.1) Elaboration of guidelines with standardized procedures and protocols, and support for data processing and integration; **1.2)** Organize a toolbox with customized reagents (cells, antibodies, NRF2 modulators, etc.) for advanced studies on the physiopathological function of NRF2; **1.3)** Coordinate access to several biobanks which may provide biologic samples from patients with NRF2-related NCDs and matched controls, in compliance with local ethics regulations; **1.4)** Create a technologic platform based on the technologies and research tools available in the network, including advanced bioinformatics tools for data analysis from the perspective of systems medicine, machine learning and network pharmacology.

WG2: Pharmacological regulation and drugs.

Activities: This WG will coordinate all aspects along the pipeline of drug development, including preclinical studies. All the knowledge gathered and tools developed in WG1 will serve to guide the identification of existing and new compounds that target NRF2 and influence the course of selected NCDs in cellular and animal models. WG2 will strive for standardizing procedures and protocols to maximize the reproducibility of results, and for selecting accurate disease animal models.

Tasks: 2.1) Inventory of drugs suitable for repurposing in NRF2 therapeutics; **2.2)** inventory of new patented or patentable compounds that target NRF2 and influence the course of various NCDs in cellular and animal models of disease, including electrophiles, PPI inhibitors and NRF2 inhibitors developed by the Action participants; **2.3)** Coordinate a virtual repository of superior animal models for various NCDs with pathophysiological processes related to NRF2 deregulation, in reciprocal interaction with "**Preclinical Trials. EU**" organization; **2.4)** Critical analysis of preclinical results on the above mentioned NRF2-modulators in superior animal models.

WG3: Translational medicine.

Activities: This WG will pave the way towards a succesful transition from the preclinical to the clinical development of NRF2-targeted compounds. In this stage it is essential to identify reliable NRF2-related biomarkers to monitor disease progression and therapy outcome, equivalent both in patients and animal models. Thus, the main aim of WG3 will be to elaborate the template for future clinical trials on lead compounds identified in WG2 and to coordinate NRF2-related genetic and biochemical biomarker discovery in the selected NCDs.

Tasks: 3.1) Identification of NRF2-related genetic and biochemical biomarkers using available databases of NCD patients and, in collaboration with WG2, identification of animal models of NCDs that faithfully replicate these human biomarkers. **3.2)** Documentation of the panel of somatic mutations in the KEAP1/NRF2 system in non-small lung cancer that can be detected by cfDNA. **3.3)** Documentation of clinical *NFE2L2* genetic variants and endophenotypes, as well as drug response/resistance phenotypes of patients suffering from the subset of NCDs where NRF2 alterations have been identified; **3.4)** Documentation of NRF2-related blood biomarkers and the design of a clinically-relevant biochip; **3.5)** Elaboration of the preliminary documentation for future clinical trials with compounds identified in

WG2, that demonstrate efficacy in relevant animal models that replicate alterations in NRF2 pathophysiology.

WG4. Economic Exploitation.

Activities: As mentioned before, Europe is losing leadership and competitiveness in NRF2-related pharmacology since products initially developed in Europe are being exploited in third countries. In this context, this WG will design the strategy to retain innovation and facilitate the transfer of knowledge to European industry by building bridges between academia and industry, and provide training and advice in knowledge/technology transfer and entrepreneurship to the next-generation researchers.

Tasks: to coordinate the outputs of the Action with economic potential through various exploitation routes including recruitment of SMEs, consulting and proposals of projects funded by Biopharmaceutical companies. Specifically: **4.1)** Identification and active diffusion of BenBedPhar capabilities. **4.2)** Identification and attraction of additional SMEs to the Action. **4.3)** Elaboration of procedures, list of lead compounds, drug delivery systems, blood-based biomarkers for clinical implementation, or other technologic outcomes. **4.4)** reinforce the BenBedPhar-industry cooperation by organizing 3 industry showcase events.

WG5: Outreach and dissemination.

Activities: This WG will globally coordinate the exchange of knowledge, tools and results within the Action for maximizing the visibility of the Action to different stakeholders: general public, patient associations, researchers, pharmaceutical industry, clinicians, and policy makers. The content and format of the messages will be carefully adapted to the type of audience. This WG will be essential to reinforce and consolidate the collaborations of the major players in the NRF2 field and drug discovery with policy makers and other stakeholders, and to assure the sustainability of the network beyond the Action trough a functional network.

Tasks: 5.1) development of the BenBedPhar webpage; **5.2)** Identification of relevant social networks and events for promoting NRF2-related medicine and limitations in the lay public **5.3)** organization of a yearly "BenBedPhar Open Day". **5.4)** Coordination of joint publications/communications, newsletters, presence in social networks, etc.; **5.5)** Identification of funding opportunities for sustaining research and drug development (public and private funding calls).

Activities of BenBedPhar making use of the COST tools:

- **Biannual MC/WG meetings** will enable the coordination and monitoring of the different tasks.
- **Biannual scientific meetings** (coupled with MC/WG meetings) will provide to the Action members up-dated knowledge in the field of NRF2-related diseases and therapeutics, as well as the progress of the WGs (i.e. NRF2-targeted compounds, results from preclinical studies, new disease models, protocols, etc.). Moreover, the scientific meetings and the 3 industry showcases, given by members of the Action and invited experts will serve to: **a)** be informed about services offered by European institutions/infrastructures relevant to the Action (BBMRI-ERIC, EATRIS); **b)** share the latest advances in NRF2-related pathologies and therapeutics; **c)** be updated and receive counselling regarding regulation of clinical trials from representatives of regulatory bodies.
- **Training Schools** (TS) will be organized for the Action members (especially ECIs) as capacity-building activity in the following areas: **a)** Handling of tools and databases generated in WG1; **b)** IPR management, fundraising, technology transfer and entrepreneurship; **c)** Translational medicine for biomarkers and drug development.
- **STSMs** will enable knowledge and research tools exchange among the different laboratories within the Action for reinforcing collaboration. STSMs will address: **a)** experimental procedures in different cellular and animal models of disease; **b)** *in silico* screening techniques for compound identification (i.e. molecular dynamics, modelling, and docking); **c)** compounds optimization (medicinal chemistry

techniques); **d)** R&D on biomarkers. The Action will also pursue to reach agreements with pharma companies and SMEs for enabling "industrial STSMs" aimed at increasing the knowledge in drug development and entrepreneurship. ECIs from ITC countries will be especially encouraged to apply to STSMs.

- Dissemination and communication tools (Action's webpage, Twitter account, Open Access scientific publications, quarterly newsletters, etc.) will be essential to promote the Action both inwards and outwards the network of the stakeholders identified in section 2.2.2.

4.1.2. DESCRIPTION OF DELIVERABLES AND TIMEFRAME

Deliverable	Description	Time (month)
COST tools specific deliverables		
D0.1	BenBedPhar management structures (at the kick-off meeting)	1
D0.2	Quarterly newsletters in the Action website	At 3 months
D0.3	Biannual MC/WG meetings, documented by meeting reports	6,12,18,24, 30,36,42,48
D0.4	Biannual scientific meetings, coupled with MC/WG meetings, documented by meeting reports.	6,12,18,24, 30,36,42,48
D0.5	Reports and training supports from the 3 TSs (all WGs)	18,30,42
D0.6	2 STSM calls/year; 20 STSMs (reports by STSM Coordinator)	12,18,24,30 36,42,48
D0.7	3 MOOCs organized with over 100 expected participants per MOOC (all WGs), documented by reports	12, 24, 36
D0.8	20 grants for ECIs and PhD students at ITC conferences	Date of meeting
D0.9	Annual reports on ECIs activities (the ECI Coach)	12,24,36,48
D0.10	Annual reports of the Gender Equality Officer	12,24,36,48
D0.11	Annual WG progress reports to MC (all WGs)	12,24,36,48
D0.12	Action progress reports to COST (MC)	12,24,36,48
BenBedPhar specific deliverables		
D1.1	Guidelines, standardized procedures and protocols (≥5)	18
D1.2	Toolbox of customized reagents	18
D1.3	Inventory of available NRF2-relevant biologic samples in biobanks	18, 48
D1.4	Technologic platform with NRF2-related databases, advanced technologies and bioinformatic tools	18, 48
D2.1	Inventory of new and repurposed NRF2-targeted drugs	12, 48
D2.2	Registry of superior NRF2-related animal models of NCDs (≥10)	24, 48
D2.3	Reports on biochemical NRF2 biomarkers in preclinical models and ~10 new preclinical studies initiated	24, 48
D3.1	Database of genetic biomarker profiles related to NRF2 in NCDs	24, 48
D3.2	Panel of somatic mutations in the KEAP1/NRF2 system in non-small lung cancer detected by cfDNA	24
D3.3	Documented NRF2-related genetic variants/endophenotypes and drug response/resistance phenotypes in NCDs	48
D3.4	Panel of blood-based biomarkers (~20) for clinical monitoring of NCDs and the response of NCD patients to NRF2-targeted therapy and design of a clinically-relevant biochip	36
D3.5	Documentation for future clinical trials on NRF2-targeted therapeutics in selected NCDs (~4 clinical trials designed)	36,48

D4.1	Public desclosure of procedures and guidelines (≥5), lead drugs, biomarkers, other technologic outcomes that will be advertised	18, 48
D4.2	Report on the engagement of new SMEs including consulting and Biopharma collaborations	24, 48
D4.3	Reports on the progress of economical exploitation of BenBedPhar outcomes (panel of NRF2-related biomarkers, mutations, etc).	12,24,36,48
D5.1	Project-dedicated webpage (www.benbedphar.eu) & Updates	Continuous
D5.2	Reports on participation in social media and other events (including the number of accessions)	12,24,36,48
D5.3	Reports on the organization of the yearly "BenBedPhar Open day" (including the nº of participants)	12,24,36,48
D5.4	Collaborative articles on NRF2 concepts, drugs, tools, etc	24,36,48

4.1.3. RISK ANALYSIS AND CONTINGENCY PLANS

1) COVID-19. If a solution for this problem is not timely found, it will pose a significant risk factor suspending face-to-face networking activities. Risk level: unknown yet as it will depend on the evolution of treatments, vaccines and general immunization. Contingency plan: We will follow the recommendations published on the COST portal. Fortunately, during the worst months of the pandemic situation, universities and research centres have invested huge efforts in providing online communication tools (Microsoft Teams, Zoom, Moodle). If necessary, face-to-face networking activities will be transformed into virtual activities, from meetings to conferences, workshops, and training schools. In such case, we will prioritize as much as possible the organization of small groups of interaction to increase participation, and some large meetings to provide general information and increase the sense of belonging to the Action. TSs will be organized using the excellent academic tools that have been widely implemented at our Universities. These decisions will be the responsibility of the MC in compliance with COST directives.

2) Achieving the estimated measurable outcomes. The measurable outcomes of the objectives are provided in a transparent manner, despite it is not always possible or desirable to use simple metrics. Risk level: if the measurable outcomes are taken as an estimation, then the risk level is very low. Contingency plan: during the course of the Action WG5 will monitor and will ensure the fulfilment of the indicated outcomes, and increase their impact whenever possible.

3) Poor participation and involvement of Action Participants. Action participants might not have enough time or energy to assure the proper progress of the Action. Risk level: low, considering the commitment of the Action participants. Contingency plan: promoting leadership roles in the Action management structure, especially to women, young scientists and ITC representatives, who will benefit most from having immediate access to cutting-edge knowledge and career opportunities.

4) Translate the NRF2-related knowledge into innovative therapies. Drug development is a costly and long process, and only a small number of candidates reach the market successfully after being clinically validated. Risk level: medium, considering that BenBedPhar is precisely designed to build a functional framework for interdisciplinary cooperation aimed at efficiently translating current knowledge on NRF2 towards clinical and therapeutic applications. Contingency plan: several biopharmaceutical companies engaged in this Action have ongoing phase 2 and 3 clinical trials, which greatly reduces the risk of not finding new NRF2 modulators. Additionally, the Action will implement a network pharmacology approach for drug repurposing within the cluster of NRF2-related NCDs.

5) Biotech/Pharma companies might be reluctant to participate in the Action due to IPR issues. Risk level: low, considering that **several biopharmaceutical companies** with pipelines in NRF2 modulators participate in the Action. Contingency plan: a) Confidentiality agreements will be signed under the guidance of specialized offices; b) several Action participants have experience in joint projects with the industry, as contract researchers or consultants.

6) Management coordination and access to databases might be difficult due to the diversity of data, resources and formats. Risk level: medium, considering that the data compiled and generated within BenBedPhar are intended to be made available to participants through specific free software tools and platforms for data retrieval and analysis such as openBIS. Contingency plan: to achieve a high degree of interoperability, allowing data exchange and re-use according to standard formats and facilitating re-combinations with different datasets from different origins.

4.1.4. GANTT DIAGRAM

	YEAR 1				YEAR 2				YEAR 3				YEAR 4			
Kick-off meeting and report	∘															
Quarterly newsletter	∘	∘	∘	∘	∘	∘	∘	∘	∘	∘	∘	∘	∘	∘	∘	∘
MC Meetings and reports		∘		∘		∘		∘		∘		∘		∘		∘
WG Meetings and reports		∘		∘		∘		∘		∘		∘		∘		∘
Scientific Conferences		∘		∘		∘		∘		∘		∘		∘		∘
TSs and reports							∘				∘				∘	
MOOCs and reports				∘				∘				∘				
Launch calls for STSMs (bi-annual reports)				∘		∘		∘		∘		∘		∘		∘
Gender Equality Officer & ECI Coach reports				∘				∘				∘				∘
WG1.1 Standardized procedures/protocols.						∘										
WG1.2 Toolbox of customized reagents. Updates:						∘										
WG1.3 Biobanks data and updates:						∘										∘
WG1.4 Technology platform and updates:						∘										∘
WG2.1 Inventory of repurposing/new NRF2 drugs				∘												∘
WG2.2 Registry of animal models and updates.								∘								∘
WG2.3 Biomarkers in animal models								∘								∘
WG3.1 Genetic & biochemical biomarker profiles								∘								∘
WG3.2 Panel of somatic KEAP1/NRF2 mutations				∘				∘								
WG3.3 Genetic variants. Drug endophenotypes																∘
WG3.4 Panel of blood-based biomarkers												∘				
WG3.5 Directions for future clinical trials												∘				∘
WG4.1 Database on NRF2 drugs,						∘										∘
WG4.2 Recruitment of more Biopharma Co.								∘								∘
WG4.3 Consulting and Biopharma collaborations				∘				∘				∘				∘
WG5.1 Webpage www.benbedphar.eu & updates		∘	∘	∘	∘	∘	∘	∘	∘	∘	∘	∘	∘	∘	∘	∘
WG5.2 Participation in social media & events				∘				∘				∘				∘
WG5.3 BenBedPhar Open days and social media				∘				∘				∘				∘
WG5.4 Joint publications and communications								∘				∘				∘

Colored squares indicate working quarters.
∘ indicates deliveries.