Brussels, 13 April 2018

COST 023/18

DECISION

Subject: **Memorandum of Understanding for the implementation of the COST Action "Prospective European Drug-Induced Liver Injury Network" (PRO-EURO-DILI-NET) CA17112**

The COST Member Countries and/or the COST Cooperating State will find attached the Memorandum of Understanding for the COST Action Prospective European Drug-Induced Liver Injury Network approved by the Committee of Senior Officials through written procedure on 13 April 2018.

MEMORANDUM OF UNDERSTANDING

For the implementation of a COST Action designated as

COST Action CA17112
PROSPECTIVE EUROPEAN DRUG-INDUCED LIVER INJURY NETWORK (PRO-EURO-DILI-NET)

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

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

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

The main aim and objective of the Action is to To create a unique, co-operative, interdisciplinary European-based DILI network of stakeholders to co-ordinate efforts in DILI, to facilitate bidirectional exchange of discovered knowledge and generated hypotheses among different disciplines, and to promote clinically impactful knowledge discovery and its translation into clinical practice. 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 64 million in 2017.

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

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

OVERVIEW

Summary

There is a clear unmet need for a deeper understanding of idiosyncratic drug-induced liver injury (DILI), a multi-layered challenge that spans the life of the drug from pre-clinical development to clinical trials and post-marketing.

The objectives of the PRO-EURO-DILI-NET Cost Action are to create a unique, co-operative, interdisciplinary European-based DILI network of stakeholders to co-ordinate efforts in DILI, to facilitate bi-directional exchange of discovered knowledge and generated hypotheses among different disciplines, and to promote clinically impactful knowledge discovery and its translation into clinical practice.

This Action will: (a) harmonize efforts for in-depth DILI phenotyping and bio-sample repository and coordinate pre-funded database/repository studies to aggregate a large number of DILI cases in a standardized manner (WG1);

(b) Establish a strategy for development, validation and performance of DILI novel biomarkers and explore multifactorial DILI risk modifiers in clinical data sets using novel approaches for future precision medicine (WG2);

(c) Facilitate clinically impactful knowledge discovery by introducing biological variations and the complexity (i.e., multi-cellular/multi-organ systems) into toxicological experiments to assess hepatotoxicity to guide future drug safety testing (WG3).

(d) Define criteria and establish endpoints to measure efficacy on novel interventions in DILI (WG4);

(e) Draft policy recommendations about near-patient testing tools.

The network will promote and coordinate a highly translational and innovative research program in Europe and beyond with the ultimate goal to pre-empt and prevent DILI, develop innovative therapeutic approaches that could improve clinical outcomes and enhance public awareness, while developing a forum for knowledge exchange and training of young European researches.

Areas of Expertise Relevant for the Action	**Keywords**
● Clinical medicine: Gastroenterology and hepatology	● Idiosyncratic Drug-induced liver injury ● Risk stratification ● Liver injury Diagnostics ● Preclinical toxicology ● End-points

Specific Objectives

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

Research Coordination

● To develop a shared understanding of the key issues related to signals of hepatotoxicity in preclinical models/ experiments, clinical trials, and large electronic medical records, methods of detecting these in experimental models and clinical practice in addition to monitoring this for regulatory as well as pharmacovigilance purposes

● To systematically review potential risk factors associated with hepatotoxicity and biomarkers indicating DILI throughout the life course of a drug including pre-clinical development, in vitro investigations, clinical

trials and post-marketing phase
● To establish standardized prospective data collection procedures and to develop an infrastructure for heterogeneous data and sample sharing
● To develop a functional strategy that is adaptable Europe-wide and beyond for an early identification of DILI, evaluate the performance of established and novel near patient DILI diagnostic tools, harmonize the criteria used for DILI diagnosis and its in-depth phenotyping
● To harmonize nationally and internationally funded research activities towards a common goal and providing bench, bedside and population perspectives. Mutual understanding between academia, clinicians, pharmaceutical and regulatory agencies will establish a strong scientific base for European regulatory decision-making processes, public awareness and education

Capacity Building
● Create a mutual strategy to optimize the training capacities related to DILI currently available at different cross-border stakeholders via exchange programmes
● Improve institutional capacities of participating centres by providing support to reach a minimum set of standards that would ensure high-quality research activities through STSMs
● Establish effective channels of communication between preclinical researchers, clinicians, scientists in different disciplines, SMEs, industry representatives and regulatory bodies through annual DILI conferences and joint meetings with regulatory authorities
● Facilitate exchange of professional expertise, research material/ data between experienced researchers and ECIs through workshops and training summer schools
● Provide mentorship to ECIs with the adequate induction into DILI and preparing them to be actively involved in future cross-border multi-centre, multi-disciplinary studies
● Develop strategies to involve patients who have suffered DILI and to provide public education for the purpose of prioritising research questions in DILI field, identifying gaps in clinical service relevant to DILI subjects and improving public awareness.

TECHNICAL ANNEX

1. S&T EXCELLENCE

1.1. CHALLENGE

1.1.1. DESCRIPTION OF THE CHALLENGE (MAIN AIM)

Idiosyncratic drug-induced liver injury (DILI) is an acute adverse hepatic reaction that occurs in only a small proportion of individuals exposed to a drug. It is unexpected from the known pharmacological action of the agent, leading to illness, disability, hospitalization, including life threatening liver failure (10-15%), need for liver transplantation and death. DILI manifests in a variety of clinical presentations with a 13–17% of cases remaining unresolved at 6 months, and 8% at 12-months follow-up leading to transplantation in 2–4% and in 6–8%. DILI represents a major challenge for clinicians, the pharmaceutical industry and regulatory agencies worldwide. DILI due to commonly used drugs continues to be an important clinical problem with a crude annual incidence of 19 per 100,000 individuals and 22% of the cases requiring hospitalization.

Burden of DILI: The concordance between hepatotoxicity in animal and humans is poor which means that adverse hepatic reactions account for attrition of a substantial proportion of drugs during drug development. Hepatotoxicity has been the second most common reason for withdrawal of drugs from the market worldwide accounting for 32% of such cases between 1975 and 2007. Current preclinical toxicological approaches are not able to predict these adverse events. Thus, DILI jeopardizes patients' safety and poses significant economic burden on pharmaceutical companies

DILI is under-recognised with only 1 in 16 cases recorded by the spontaneous reporting system of pharmacovigilance; information when received is often inadequate for robust causality assessment. DILI occurs in association with a large number of drugs. The wide range of manifestation of DILI and the lack of specific diagnostic tests poses a challenge to clinicians in terms of diagnosis. There are currently no European clinical guidelines available on how to suspect and confirm the diagnosis of DILI or how to manage DILI once it has been diagnosed. There are no biomarkers that pre-empt DILI or detect DILI, therefore, we cannot effectively monitor patients on drug therapy and diagnose DILI early. A delay in detecting DILI and consequently prolonged exposure to the causative drug can increase the patient's risk of experiencing severe or life-threatening outcomes. Failure to diagnose DILI accurately risks reexposure to the causative agent with consequent severe reaction. This puts the patient's life at unnecessary risk, which could be avoided with a correct identification of the culprit drug (e.g. acute-on-chronic liver injury).

Like other forms of adverse drug reactions, DILI is a socio-economic burden because of its impact on healthcare costs and expenses related to social security, such as sickness benefit (the EU societal cost of ADRs is around €80 billion /year with an average of 2250 € for one ADR).

Therefore**, the main aim of the PRO-EURO-DILI-NET COST Action** is to set up a European-wide interdisciplinary co-operative network of stakeholders in the DILI field (including scientists, clinicians, regulatory authorities, Small and Medium Enterprises (SMEs) and industry partners). Through workshops, scientific exchanges as well as training schools, this Action will coordinate the efforts aiming to advance our understanding of DILI as well as facilitate the translation of basic research and preclinical findings into clinical practice.

1.1.2. RELEVANCE AND TIMELINESS

The main reason why DILI is still a major problem is the incomplete understanding of the pathogenic processes leading to this adverse reaction. There is a clear unmet need for a deeper understanding of

DILI, a complex and multi-layered challenge that spans the life of the drug from the time of its pre-clinical development, through clinical trials to its post-marketing clinical use. Only a well-coordinated multidisciplinary network involving research groups focusing on each of the areas can accelerate the process of bridging the translational gaps between pre-clinical toxicological evaluation and clinical DILI through the change of routine practices as well as policies.
Despite the improvements achieved in medication safety analysis and toxicological studies, the overall frequency of hepatotoxicity for all drugs has not decreased in the last 15 years. This indicates the fragility of the past efforts in confronting DILI. One of the major reasons for the lack of any breakthroughs is attributed to the lack of coordination between diverse and varied research activities. Furthermore, a number of obstacles encountered at preclinical, clinical, pharmaceutical industry and regulatory levels have limited the progress in this field:

At the preclinical level:
- The incomplete understanding of DILI and the complexity of underlying mechanisms have hampered the efforts to develop reproducible animal models;
- Currently, there is no widely accepted animal model and none of the models is approved by the regulatory agencies in Europe and US;
- Limited predictive value of current preclinical assays.

At the clinical level:
- Limited power of premarketing randomized clinical trials (RCTs) to detect DILI;
- Lack of specific diagnostic tests for DILI; diagnosis currently depends upon subjective causality assessment methods;
- Reliance on retrospective cohorts for research.

At the pharmaceutical industry level:
- Lack of guidance regarding the recognition, diagnosis and management of DILI, particularly in vulnerable populations – such as cancer patients, pre-existent chronic liver disease, and children;
- The need of comprehensive and systematic workflow for liver safety data capture and analysis;
- Lack of consensus on best practice.

At the regulatory level:
- Drug development continues to require conventional toxicity testing which has been unsuccessful in identifying DILI at an early stage;
- Lack of position statements from regulatory authorities as to what the characteristics of biomarkers of DILI are and what the pipeline is for the development and validation of novel biomarkers;
- Lack of evidence-based practice for Pharmacovigilance including guidance for monitoring and management of DILI in preclinical RCTs as well as post-marketing phase.

Timeliness: Magnitude of attrition of up to 80% of new chemical entities during drug development (from phase I to regulatory application) has put an unsurpassable barrier for the clinical translation of new drugs. This has taken the industry to a point where a revision of existing strategy is essential.
In clinical practice, there is a mounting concern in relation to the ongoing burden of DILI and the emergence of DILI related to novel biologics (i.e. ipilimumab, daclizumab) as well as the increasing cost of diagnosis and management. This is compounded by the consequences of DILI in the context of increasing prevalence of chronic liver disease (non-alcoholic fatty liver disease, NAFLD) globally.
The PRO-EURO-DILI-NET COST Action aims to establish a translational highway through the development of a timely multidisciplinary network of top European/ international experts whose objectives will be centred on coordinating the research activities conducted by the distinct, yet complementary research groups. The unique and open nature of COST Actions matches the needs of the PRO-EURO-DILI-NET COST Action which aims to facilitate the exchange of scientific findings and harmonize locally/ nationally funded research activities.

1.2. OBJECTIVES

1.2.1. RESEARCH COORDINATION OBJECTIVES

The aim of this Action cannot be accomplished at an individual country level especially when considering a rare, yet serious adverse drug reactions such as DILI. Inter-disciplinarity of the proposed topic and significance of the expected outcomes require an extended collaboration with multi-directional interactions at the European level and beyond to exploit complementarities.

The main objective of the Action is to create a unique co-operative, interdisciplinary Europe-based DILI network encompassing clinical investigators (e.g., hepatologists, immunologists, pharmacologists, pathologists), epidemiologists, geneticists, mathematical scientists, bioinformaticians, basic scientists (e.g., cell/molecular biologists, physicists, biochemists, chemists, and system biologists), pharmaceutical industry, innovative SMEs and regulatory bodies.

Other objectives of the Cost Action are:

- To develop a shared understanding of the key issues related to signals of hepatotoxicity in preclinical models/ experiments, clinical trials, and large electronic medical records, methods of detecting these in experimental models and clinical practice in addition to monitoring this for regulatory as well as pharmacovigilance purposes;
- To systematically review potential risk factors associated with hepatotoxicity and biomarkers indicating DILI throughout the life course of a drug including pre-clinical development, *in vitro* investigations, clinical trials and post-marketing phase;
- To establish standardized prospective data collection procedures and to develop an infrastructure for heterogeneous data and sample sharing;
- To develop a functional strategy that is adaptable Europe-wide and beyond for an early identification of DILI, evaluate the performance of established and novel near patient DILI diagnostic tools, harmonize the criteria used for DILI diagnosis and its in-depth phenotyping;
- To harmonize nationally and internationally funded research activities towards a common goal and providing bench, bedside and population perspectives. Mutual understanding between academia, clinicians, pharmaceutical and regulatory agencies will establish a strong scientific base for European regulatory decision-making processes, public awareness and education.

1.2.2. CAPACITY-BUILDING OBJECTIVES

The PRO-EURO-DILI-NET COST Action will bring together outstanding, yet currently fragmented, groups from COST countries. Capacity building efforts will focus on improving the infrastructure to carry out high quality research studies. Alongside, the Action will also aim to support the exchange of knowledge and expertise through cross-border interdisciplinary research, training and teaching. Special emphasis will be given to supporting research studies undertaken by Early Career Investigators (ECIs). ECIs will be provided with an intensive framework of cooperation, through focused workshops, Short Term Scientific Missions (STSMs) and training schools in the aim to develop a group of early Career Investigators/Clinicians with interest and skills in DILI research.
Accordingly, the specific capacity-building objectives include:

Train and retain:

- Create a mutual strategy to optimize the training capacities related to DILI currently available at different cross-border stakeholders via exchange programmes.
- Improve institutional capacities of participating centres by providing support to reach a minimum set of standards that would ensure high-quality research activities through STSMs.
- Establish effective channels of communication between preclinical researchers, clinicians, scientists in different disciplines, SMEs, industry representatives and regulatory bodies through annual DILI conferences and joint meetings with regulatory authorities.
- Facilitate exchange of professional expertise, research material/ data between experienced researchers and ECIs through workshops and training summer schools.

Mentoring:

- Provide mentorship to ECIs with the adequate induction into DILI and preparing them to be actively involved in future cross-border multi-centre, multi-disciplinary studies.

Patient and public involvement:

- Develop strategies to involve patients who have suffered DILI and to provide public education for the purpose of prioritising research questions in DILI field, identifying gaps in clinical service relevant to DILI subjects and improving public awareness.

1.3. PROGRESS BEYOND THE STATE-OF-THE-ART AND INNOVATION POTENTIAL

1.3.1. DESCRIPTION OF THE STATE-OF-THE-ART

The relevance of preclinical studies for regulatory purposes has been questioned for their irreproducibility and inability to predict toxicity in humans. Generally speaking, none of the toxicology experiments during drug-development takes into account biological variations such as age, sex,

reproductive status, and other acquired host factors that may at least partly define the heterogeneity of risks and manifestations of human DILI. With the step change in the understanding of key host factors that determine hepatotoxicity in humans, a number of avenues are considered as potential ways forward to overcome the limitation: humanised animal models, in-vitro experiments using human inducible pluripotent stem cells, liver organoids, multi-organ chips. Such individual approaches alone may not be sufficient to inform future drug safety or drug development strategy; instead, a united research partnership integrating individual approaches, together with corroborating clinical associations observed in patients' data, would complementarily inform such strategies.

In the last decade, research groups in Europe advanced our understanding on genetic variants that influence DILI risks. These genetic variants include single nucleotide polymorphisms (SNPs) in genes involved in drug metabolising enzymes and transporters and variants in the major histocompatibility complex class I and II genes. In addition to genetic variants, several host-related factors (e.g., age, gender) and environmental factors have been associated with DILI risk and phenotypes. While these discoveries have improved our understanding of DILI mechanisms, clinical application of these important findings has so far been limited due to the rarity of the events, limited positive predictive values of identified factors, and uncertainty to extrapolate for agents with different drug properties. Combined effects of genetic variants, potential age-/sex-specific genetic effects, potential significance of epigenetic modifications, skewed X-chromosome inactivation, or escape from X- chromosome inactivation remain uncertain. DILI is a multifactorial disorder. Thus, various host factors may exert significant additive, synergetic, or antagonistic effects on individuals' DILI risks and phenotypes as a group, while interacting with specific drug properties (i.e., drug-host interactions), although individual effects may be subtle (i.e., multifactorial risks). Currently, no established investigational approaches to address such multifactorial risks of human DILI.

Due to the rarity of DILI and heterogeneous manifestations, assessment of host factors on agent-specific DILI requires a cohort of substantial number of cases with a specific agent for translational studies. Despite recent advances, phenotyping of DILI is limited to grouping them into hepatocellular and cholestatic, and mixed patterns based on liver enzymes elevations. A poor correlation between biochemical phenotyping and histopathological manifestations in DILI also challenges clinical DILI phenotyping. Lack of specific diagnostic tests for DILI is the main reason behind challenges in early recognition and accurate diagnosis of DILI. For the development and validation of novel biomarkers for DILI, case aggregation with systematic causality assessment, thorough exclusion of alternative causes, in-depth phenotyping, and linked biological samples is essential. The limited availability to access a large prospective cohort of DILI caused by specific agents also limits our ability to conduct RCTs to investigate potential therapeutic agents in patients with agent-specific DILI.

1.3.2. PROGRESS BEYOND THE STATE-OF-THE-ART

To further advance our understanding of human DILI, it is crucial to introduce biological variations into toxicological experiments, implement experimental approaches to assess/screen hepatotoxicity in a multi-cellular/multi-organ system, and implement analytic approaches to explore multifactorial risks associated with specific DILI or phenotypes (i.e., drug properties, genetic variants, sex, age, co-medications, and other acquired host factors). Emerging experimental approaches can potentially introduce host factors and determinants of DILI risks into preclinical studies. To achieve the goal, it is essential to establish close partnership between clinical investigators and basic researchers to exchange experimental discovery and identified clinical associations bi-directionally and collaboratively design *in silico* and *in vitro* systems to address impact of host factors on specific toxicological mechanisms or agent-specific DILI risks. For instance, liver organoids (e.g., HepaRG:KC [immunomodulation], HepaG:ECs [vascular model], HepaRG:Neurons [innervation model], HepaRG-NAFLD model [pre-existing clinical condition]) and multi-organ chips can be used coupled with advanced non-invasive optical and chemical imaging platforms for assessing 3D, while manipulating cell origins or culture conditions (e.g., man- or women-derived, addition of different sex hormones to a culture system). New discoveries can be translated into clinical analysis to test specific associations/ interactions in a clinical data set. Alternatively, clinical associations can be translated into experimental studies to address impact of specific host factors on in-vitro toxicological parameters.

Discovery of biomarkers for DILI is a key to early detection of DILI. For such research efforts, multi-centric collaboration to aggregate well-characterised cases/controls linked to biosamples is a pre-requisite. Multi-disciplinary research partnership is also necessary to translate discoveries into toxicology experiments to investigate mechanisms and potential extrapolation to other agents. Further, investigations across different ADR (i.e., liver, skin) caused by the same agent may enrich our understanding of ADR and common toxicological mechanisms caused by a specific agent.

Other directions for DILI research include (1) refinement of diagnostic algorithms incorporating drug properties, host factors, and novel markers and (2) implementation of novel strategies for risk

assessment, prevention, and early identification as well as therapeutic options. Such efforts can be promoted by a large well-characterised prospective patient cohort with available series of biosamples collected during the couse of on-going DILI.
Stakeholders will actively participate in the harmonized and complementary endeavours addressing the pitfalls of toxicological studies and identify opportunities to progress beyond conventional methods and strategies. This COST Action will not only offer a network to synthesise existing evidence in the field, but also facilitate collection of additional evidence, especially regarding specific national health-system and research.

1.3.3. INNOVATION IN TACKLING THE CHALLENGE

There have been a few national consortia and registries collating DILI cases both prospectively and retrospectively. They remain disconnected with no adequate opportunity for networking. Multidisciplinary involvement is also lacking. Almost all of the existing consortia have relied upon DILI cases identified once the adverse hepatic reaction has resolved or after its peak manifestation. This has inherently limited in-depth phenotyping. In addition, biological samples suitable for discovery of non-genetic markers cannot be collected unless the cases are identified while DILI is ongoing. Moreover, lack of drug-matched control groups has limited the exploration and validation of potential circulating biomarkers of DILI.
PRO-EURO-DILI NET COST Action will pursue an innovative approach in tackling DILI,

- by creating a platform involving multidisciplinary stakeholders under one umbrella, and by systematically focusing on the areas of DILI where consensus and harmonisation are essential to make substantial progress;
- by focusing on developing a strategy for identifying cases prospectively at the time DILI is on-going as well as drug-matched controls and in-depth phenotyping to allow comprehensive analysis of factors linked to DILI. This approach has a potential to improve DILI detection, diagnosis and prevention;
- by developing novel algorithms for risk stratification which take into account drugs, host environmental factors, and their interactions;
- by developing novel preclinical *in vitro* and experimental animal systems incorporating biological variations (e.g., age, gender, reproductive status, pre-existing disease conditions) in multi-cellular/ multi-organ systems not only to better evaluate drug toxicity and predict DILI, but also to identify potential targets for treatment or biomarker development;
- by developing novel strategies to treat DILI to minimize serious consequences of DILI. Gene-specific candidate-driven studies will be replaced by the GWAS and studies utilising other “-omics” technologies. All these studies will benefit from the large database facilitated by the Action. The identification of the exact genetic and non-genetic variants implicated in the development of DILI constitutes the cornerstone for assembling robust preventive measures.

1.4. ADDED VALUE OF NETWORKING

1.4.1. IN RELATION TO THE CHALLENGE

DILI is a rare disease that signals the need for research groups from individual countries to establish an open network to share experiences, cases, data, research questions and solutions to achieve significant progress in this field. Such network will create a critical mass of researchers, larger cohorts, datasets and biorepositories. It will bring both depth and breadth to the research that is conducted.
Consensus regarding different aspects of DILI will allow improvement in the prospective identification and enrolment of DILI cases as well as harmonisation regarding in-depth phenotyping, including pathological sub-classification.
A network involving multidisciplinary teams is essential to identify critical gaps in research and prioritisation of questions for future research programmes. Basic scientists and drug developers will work with clinicians and regulators to identify mutual needs and synchronise their efforts to overcome the current lack of concordance between animal hepatotoxicity and human DILI.
PRO-EURO-DILI-NET COST Action offers the unique opportunity to combine complementary expertise (experienced and young researchers from different backgrounds) and the prospect of exchanging knowledge on a regular basis. Transfer of skills through workshops will expand the pool of next generation researchers in DILI, as well as start-up companies. The network will promote the expansion of DILI educational and research activities as well as its wide dissemination in Europe and beyond. The network of leading experts and opinion leaders will have the credibility to promote the adoption of scientific evidence-based achievements by regulatory authorities and influence policy changes.

1.4.2. IN RELATION TO EXISTING EFFORTS AT EUROPEAN AND/OR INTERNATIONAL LEVEL

Over the past few years, European and international initiatives have focused their efforts on developing cohorts of patients with DILI through registries, networks and consortia. These have led to the identification of host factors as critical determinants of DILI, so networks investigating mechanisms underlying DILI have explored specific pathways seeking potential biomarkers relevant to preclinical settings. However, to maximize the output and prioritise potential areas where concentrated efforts are necessary, it is prudent to create a network to harmonize individual national research groups and other initiatives. To this end, previous and currently ongoing databases will be integrated. This will permit synergism, identification of areas of possible collaboration between ongoing projects and ensure optimal use of resources.
This COST Action will also coordinate activities of research groups from pre-clinical, clinical and regulatory fields, bring expertise from different areas together to create a common understanding and collaborate to maximise impact. It also establishes a collaboration that is capable of developing strong proposals suitable for upcoming funding opportunities where the data obtained will be integrated. This Action is aligned with the EU strategies on Research and Innovation and Public Health in the framework of Horizon 2020, more specifically Research Innovation (DG R&I) and Innovative Medicines Initiative 2 (IMI).

2. IMPACT

2.1. EXPECTED IMPACT

2.1.1. SHORT-TERM AND LONG-TERM SCIENTIFIC, TECHNOLOGICAL, AND/OR SOCIOECONOMIC IMPACTS

This COST Action will set up the first multi-national, multi-disciplinary collaborative network focused on discovery and translational research in DILI; the critical mass with a common goal that this COST Action creates will have a transformative impact on the field in the long term.
Scientific Impact:
Short-term: A collaborative network will reduce redundancy, promote efficient use of resources and increase productivity of European research groups. ECIs, basic scientists and clinicians will benefit from training schools and professional workshops would increase productivity.
Consensus in case definitions, phenotyping, study endpoints among research groups will markedly improve the quality and consistency of research outputs; hot topics in the DILI field will be prioritised, thus accelerating research activities by the network.
The multidisciplinary network will add breadth and depth to research proposals suitable for Horizon 2020 or similar ambitious programmes. Self-sufficient multi-disciplinary network with focused research strategies will attract investment in DILI research.
Long-term: Collaborative research will promote the creation of refined diagnostic algorithm(s) incorporating drug, host genetic and non-genetic factors facilitating “precision medicine”.
The collaborative research network will provide a platform to develop and implement novel DILI markers for early identification, accurate diagnosis, and prediction of poor outcome, and to discover novel therapeutic strategies.
Interaction between industry, academia, scientists, clinicians and regulatory authorities will stimulate the shift of DILI healthcare strategies from a reactive to a proactive practice.

Technological Impact:
Short-term: Partners will develop a common understanding of critical issues related to pre-clinical hepatotoxicity testing and identify potential *in vitro* or *in silico* techniques for evaluation.
The Action will harmonise the case definitions, in depth phenotyping of DILI cases controls linked with biological samples; these will constitute the ideal resources for conducting studies using system biology approaches for biomarker discovery.
Long-term: Development/ adoption by drug developers of innovative *in vitro* / *in silico* models (suitable for pre-clinical development) which incorporate the concepts of genetic factors influencing response to a drug. Generate spin-offs/ start-up SMEs for exploiting such models - and/ or IP/ Patents. Setting up programmes would promote discovery of novel biomarkers that would pre-empt DILI, assist early detection, monitoring and prediction of clinical outcome. These will include extracellular vesicles (DILI/ drug-class) dependant species; lncRNAs/miRNAs from RNAseq data; Metabolomics/ Targeted proteomics readout - biomarkers: Protein adducts' formation; ophthalmate/ oxidative stress markers; Lipidomics: Polyunsaturated fatty acids (PUFAs) as 'damaged lipid' products/ toxins of liver disease.

Socioeconomic impact:
Short-term: PRO-EURO-DILI-NET COST Action will raise public awareness of DILI given the extensive list of products with DILI potentials and the considerable threat this ADR poses on public health. The current COST Action will standardize early identification and diagnosis of DILI, allowing a critical mass of patient recruitment, leading to reduced burden and healthcare costs.
Long-term: Early detection of candidate drugs with hepatotoxic potentials during preclinical toxicology studies would significantly reduce cost associated with later drug attrition due to DILI and improve public drug safety.
This COST Action will provide the scientific basis and a clear frame for common EU-regulatory efforts with regards to DILI. Adoption of consistent and evidence-based policies by regulatory authorities will increase assurance of public drug safety.

2.2. MEASURES TO MAXIMISE IMPACT

2.2.1. PLAN FOR INVOLVING THE MOST RELEVANT STAKEHOLDERS

The Action aims to involve all relevant stakeholders whether being part of the project or not. The outcomes are expected to affect various disciplines (basic research, clinical research and practice, education, training policies, pharmaceutical industry, regulatory bodies and policy makers). Accordingly, the Action will ensure that the outcomes are disseminated to all relevant stakeholders. The main stakeholders include: (1) patient advocacy groups; (2) clinicians (hepatologists, clinical pharmacologists and pathologists); (3) basic researchers (cell / molecular biologists, biophysicists, chemists, system biologists, immunologists, and bioinformatics); (4) Small and Medium Enterprises (SME) and pharmaceutical industry; (5) regulatory bodies. Stakeholders will be encouraged to meet at both focused and general COST events as specified under the management structure in section 3.2 and informed of COST Action progress through regular email communication.
As part of this, meetings with European and National regulatory agencies and policy makers will be held, providing them with updated guidance and position statements generated by this COST Action. A website - including relevant technical sections and an easy to understand 'layperson section' for public understanding of science - will also be set up describing the COST Action and its objectives, where interested stakeholders can contact the Management Committee to express their interest in joining the Action. The Cost Action will be announced at targeted conferences and workshops in Europe.
The Action will also encourage researchers from other international and national networks to integrate their efforts within this cross-disciplinary platform by inviting them to planned Conferences/ Workshops and other relevant activities. It will also work with national and international scientific societies to integrate DILI sessions into their regular conferences with contribution from Pro-Euro-DILI-Net stakeholders.
The involvement of patients and the general public will be assured by contacting specialized patient organizations and public health associations. Organisations involved in the COST action have established patient and public involvement (PPI) infrastructures; we will build on these existing capacity and develop further capabilities that support specific activities of PRO-EURO-DILI-NET COST action.

2.2.2. DISSEMINATION AND/OR EXPLOITATION PLAN

To whom. The dissemination plan will target the multidisciplinary participants of the Action, Academic and Research communities, clinicians and healthcare professionals, patients and public health organizations, general public, pharmaceutical and biotechnology companies, in addition to national and European regulatory bodies and policy makers.
How the Action will do the dissemination? The Action will invest in diverse dissemination methods in order to adequately reach the aforementioned target audiences, including
Website: The website will be designed to ensure clear presentation of the aims and objectives of the action as well as announcements of recent achievements and upcoming events (e.g. public workshops, conferences and training schools). The website will also clearly detail the source and nature of all Action funding and will feature an electronic discussion forum to encourage interaction and foster collaborative dialogue.
Design and development of eDILI mobile application: Developing an application for Android and iPhone operating systems would facilitate communicating our findings to the public, interacting with stakeholders in addition to announcing future events organized by the Action. **Social media**: Different social networking platforms such as Facebook, Linkedin and Twitter will be used to encourage communication with healthcare professionals, researchers and the public.

Announcements: Announcements for public and professionals (reports, press releases, guidelines, alerts, etc) will be facilitated by network partners and calling for support of relevant national stakeholders, in appropriate languages.
Journal Publications: Research findings will be made available to the scientific community through publications in peer-reviewed scientific journals with clear acknowledgement of the COST.
Conferences: The results of the COST Action will also be disseminated at international conferences and workshops.
Media campaigns: National and/or international press agencies and other appropriate agencies will be called upon, as appropriate, throughout the lifetime of the Action. Informative presentations to patients and the general public will be organized as a regular "info day" (refer to section **3.1.2**).

European and National regulatory agencies will be regularly informed about the COST Action and its achievements in order to enhance DILI awareness and management in the EU.

EXPLOITATION PLAN
There will be innovative opportunities in the industry-driven field of biomarkers development. Pharmaceutical companies strive to adopt pre-clinical – *in silico* and *in vitro* - models for DILI prediction and to be involved in developing novel interventions to test for DILI. There will be an opportunity of transfer of knowledge to set the stage for a novel generation of startup-companies in the field.
From the pharmaceutical industry's perspective, key areas that drug development will likely be able to capitalize on include: (1) Expertise and knowledge: the access to a multidisciplinary expert network will help optimize efficiency and ensure completeness of liver safety assessment and management in drug development; (2) Technology: It will facilitate the access to advanced tools supporting mechanistic understanding and improving prediction, diagnosis, and monitoring of DILI via academic sites of excellence as well as SMEs; (3) Education: The current Action will represent a professional mainstay to educating other clinical investigators of different specialities (beyond gastroenterology, hepatology, or immunology specialties, including infectious diseases specialists) on detecting, assessing and monitoring patients with suspected DILI; (4) Data: The network will constitute the foundation for sharing and pooling data necessary to encounter potential DILI signals during clinical development programmes; (5) Alignment: Parallel to US-driven efforts on filling the gaps related to regulatory and scientific guidance on DILI, this network will serve as an exciting opportunity to come up with a balanced, global perspective on DILI best practices.
May also enhance opportunities for Pharma-Academia collaborations/ funding; knowledge exchange; and intellectual property generation.
COST will promote exchange of information/ ideas/ technologies globally with non-European agencies.

2.3. POTENTIAL FOR INNOVATION VERSUS RISK LEVEL

2.3.1. POTENTIAL FOR SCIENTIFIC, TECHNOLOGICAL AND/OR SOCIOECONOMIC INNOVATION BREAKTHROUGHS

This PRO-EURO-DILI-NET COST Action will enable the formation of a structured European Reference Network on DILI. It is potential for innovation lies in its comprehensive approach, providing a framework for accessing large and well-characterized European cohort of DILI cases from different European countries. This will guarantee the implementation of future, robust interdisciplinary, multicentre clinical, observational and interventional studies.

Scientific and technological:
Multidisciplinary nature of the COST Action permits consideration of diverse perspectives on the challenge of DILI with a potential to evolve innovative strategy to answer that. Dissemination of best practice, sharing of skills and harmonization of research methodologies will optimize quality of output from the wide individual national groups.

Socioeconomic:
Breadth and strength of expertise of COST Action members will contribute to substantial influence on professional societies and policy makers. The Action will also provide a concrete procedure to align current clinical practice guidelines governing the management of DILI with the state-of-the-art evidence in cost-effective treatment adherence interventions.
COST Action has considered these potentials while developing the network of participating groups. The experience and knowledge of the internationally distinguished research groups involved in the Action minimize the risks of failure of the scientific objectives. Excellent experimental facilities and theoretical

resources are available at the participating institutions. Risk factors directly related to the research concepts and results will be continuously monitored at regular meetings, frequent e-sessions, and discussions dedicated to specific problems. Great care will be taken to make the results of the involved research groups immediately available to others and “open for discussion” and comparison.

3. IMPLEMENTATION

3.1. DESCRIPTION OF THE WORK PLAN

3.1.1. DESCRIPTION OF WORKING GROUPS

To accomplish the Actions’ objectives, five working groups (WGs) will be formed. Close cooperation and exchange of knowledge between the WGs will be essential.

WG1. IN-DEPTH PHENOTYPING IN DILI

This WG1 will systematically address issues regarding the criteria for DILI case definition, characterisation and classification of phenotypic sub-groups in DILI. This WG1 is essential to support translational research in DILI and will integrate and collaborate closely with the remaining WGs. There has been no consensus regarding DILI in pre-existing liver disease such as NAFLD, with the use of herbal and dietary supplements (HDS), paediatric population and cancer patients on chemotherapy. WG1 will also focus on these areas.

The main tasks of WG1 will be:

- Harmonize nomenclature, clinical measurements, definitions, classification and outcomes;
- Study the rationale to incorporate deep immunophenotype of innate and adaptive immune pathways with CyTOF mass cytometer;
- Standardize forms for prospective multicentre data collection, established and possibly novel and improved causality assessment tools;
- Contribute to the shared understanding between academia, pharma and regulatory agencies on the strengths and weaknesses of available approaches in identifying DILI signals and risk assessment;
- Establish a panel of drugs that have been withdrawn because of DILI; and those which cause intrinsic DILI (APAP) and those causing hepatotoxicity with high vs low potential – for identifying several key protein-domain targets (drug-drug similarity network) and pathways that might be related to the development of DILI and could be worth investigating further to inform drug development in WG2 and for testing preclinical 2D-3D *in vitro* models in WG3
- Translate the scientific evidences into regulatory language, practices and recommendations.

The expected milestones and deliverables are:

- Capitalizing on already existing databases in DILI to develop a standardized approach to diagnosis and to prepare standard operating procedures (SOPs) for the most appropriate collection and storage of all biological samples (liver biopsy, serum, plasma, DNA, urine and stool) related to DILI (Year 1) – for downstream analysis;
- Coordination of the development of pre-funded database of DILI patients providing a framework for the access to patient cohorts from different EU countries (Year 1);
- A workshop on DILI diagnosis, classification and management for developing improved skills in scientific and clinical questions related to DILI (Year 1);
- Conduct a systematic review of published data on DILI diagnosis and management (Year 2);
- A monothematic conference on DILI jointly with European Professional Societies (Year 2);
- Development of a classification system for HDS which may increase HDS induced-liver injury recognition, improve causality assessment and foster research in this area (Year 3);
- Joint meetings with Regulatory agencies and Info Day (Year 3-4) along with all WGs;
- Development of a consensus document on the diagnosis, classification, assessment and treatment of DILI in addition to standardization of nomenclature and causality assessment to harmonize the criteria used for DILI diagnosis in clinical practise across Europe (Year 3-4).

WG2. DILI RISK STRATIFICATION

WG2 will review both existing and potential tools that 1) evaluate the risk of DILI, 2) assess its severity and 3) predict its outcomes. Investigational activities in WG2 will target drug properties, environmental factors, host risk factors (genetic as well as non-genetic), and biomarkers ranging from routine laboratory tests, emerging and novel laboratory techniques, near patient tests as well as refined algorithms for DILI prediction, diagnosis, management and outcome. Products from WG2 will be eventually applied to DILI risk stratification in clinical and pre-clinical phases.

There is a need to characterize drug's potential for hepatotoxicity, individual susceptibility, and their interactions. WG2 will focus on the development of quantitative system toxicology approaches to improve the understanding of liver safety of existing as well as new medicines. More specifically, we will assess influences of various biological variations (e.g., age, sex, reproductive status, and genetic variants), co-morbidities, co-medications, and potential drug-drug/drug-host interactions on DILI risks and phenotypes using clinical data sets (e.g., DILI registry data, electronic medical records). These various factors will be evaluated not only as single factors but also as combinations (multifactorial risks) for their association with specific DILI events and phenotypes. Such investigations will provide theoretical foundation for bi-directional exchange of discovered knowledge and hypotheses with WG3. The accomplishments of WG1 and WG2 will provide the basis for DILI diagnosis, individuals' risk assessment (WG2) and causality assessment (WG1, WG3) and clinical trials definition criteria, and safety signals recognition (WG4).

The main tasks of WG2 will be:

- Systematically review (and develop if needed) techniques and tools to evaluate the risk of DILI, quantify the degree of injury and impairment of function, and model clinical outcomes;
- Diagnostic and prognostic risk stratification based on relevant biological data such as immunology data using blood samples and liver tissue samples;
- Stratification of drugs based on DILI risk defined by evidence-based hepatotoxic potential, evaluating DILI frequency in national DILI registries and addressing risk disparities (e.g., age, gender);
- Explore multifactorial risks of specific DILI events or phenotypes using various clinical data sets;
- Explore the potential of integrating longitudinal patient data with innovative technology platforms such as pharmacogenomics, proteomics, metabolomics, metagenomics systems, biomedicine approaches, network data set analysis, biomedical informatics and computational modelling - to address future stratified or personalised therapeutic interventions based on an individual's risk level.

The expected milestones and deliverables are:

- Focus on the array of existing research techniques and expertise among the Action members in order to come up with an EU Framework translational research plan for biomarker development - as well as cutting edge research techniques tailored to this need (Year 1);
- Scientific publication to summarize the current knowledge on 1) Drug properties associated with hepatotoxicity; 2) Host factors considered to modify an individuals' risk of DILI and clinical phenotypes; and 3) Drug-host interactions to improve risk stratification in patient care (Year 2-3);
- One Conference on biomarker development (Year 3) and a workshop in DILI risk modifiers, and also DILI in special populations: Viral, autoimmune hepatitis, liver transplant recipients, non-alcoholic fatty liver disease (NAFLD) (Year 2-3);
- Set up STSMs for ECIs to learn about systems biology networks and pharmacometrics (Year 2-3-4);
- Coordinating research to develop new predictive models of drug toxicity (Year 4);
- Written input to one or more commercial enterprises necessary for Future Market Exploitation of biomarkers (Year 4).

WG3. PRECLINICAL EVALUATION OF DILI

One of the major limitations of preclinical assessment of DILI has been the lack of correlation between the signals conventionally accepted as markers of hepatotoxicity in animal toxicological studies and clinically significant DILI. These studies will utilize more realistic in-vitro human co-culture systems and be correlated with primary human liver tissue. WG3 aims to review the current knowledge and expertise on preclinical methods and technologies that assess the associated risk of DILI of a given drug. This WG will subsequently contribute to an improved regulatory decision-making concerning DILI.

The main tasks of WG3 will be:

- Review current and potential *in vitro* and *in silico* models of hepatotoxicity including dynamic 3-D culture systems and critically appraise their strengths, limitations and applications in pre-clinical evaluation;
- Understand the relationship between *in vitro* studies/ *in silico* models and DILI in humans by systematic review of existing and potential methodologies/ technologies;
- Deliver a structured training through visits to ECIs with a focus on *in vitro* models
- Develop more realistic 3D multicellular culture systems using clinical-grade hydrogel scaffolds with liver-like compliance for drug safety testing
- Develop best practice guidance concerning preclinical models of hepatotoxicity.
- Conduct workshops exploring the utility of experimental models that simulate underlying host conditions including development of inducible human pluripotent stem cells (iPSCs) and adult hepatic progenitor cells as an accurate and effective tool for pre-clinical evaluation of DILI.

- Produce a library of existing data on phenotypic and genotypic variation of the global population by characterizing hepatocyte-like cells (HLCs) from individuals with SNPs or polymorphisms, this would be invaluable for drug screening.
- Interact with the Multi -OMICS Platform (WG2) to identify modifications of specific targets in iPSCs-HLCs derived from patients with DILI and develop predictive models of DILI using systems biology.

The expected milestones and deliverables are:
- Set up STSMs and research exchange programmes for ECIs between Action institutes to enhance research skills and techniques (Year 1-4);
- A review of current and potential *in vitro* and *in silico* models of hepatotoxicity (Year 2);
- Define a roadmap for the development of in silico, in vitro and experimental models incorporating host determinants of DILI (Year 3);
- Define a suitable methodology for the thorough assessment of physicochemical properties of the DILI drugs (Year 3);
- Identify most appropriate control compounds for testing new *in vitro* models (Year 3-4);
- One workshop on advanced *in vitro*, *in silico* models for DILI detection and evaluation (Year 3).

WG4. DESIGN AND ENDPOINTS IN CLINICAL DILI INVESTIGATIONS AND TRIALS

Considering the lack of consistency and heterogeneity among DILI studies, it is imperative to set standards for clinical trials design and establish precise endpoints to assess the efficacy of novel interventions or for exploring novel biomarkers in DILI. The Action will argue strongly for sharing individual data from clinical trials from the drugs under development as well as post-marketing where DILI has been identified as an issue. This will allow comprehensive identification of risk factors related to DILI and implant the design of future investigations.

The main tasks of WG4 will be:

WGs will work together bringing their respective expertise on shared tasks:
- Define threshold criteria for patient inclusion in special patient populations, monitoring plans, stopping rules, safety signals and outcome parameters to optimally plan future clinical trials;
- Review and evaluate therapeutic options for patients with DILI;
- Attract support for planning, set up and coordinating observational and interventional multicentre clinical trials in DILI, and investigate the effectiveness of known or novel interventions that could improve clinical outcomes of DILI.
- Explore the prognostic value of the biomarkers endorsed by regulatory agencies in clinical trials, and assess the performance of biomarkers in DILI versus other causes of liver injury.

The expected milestones and deliverables are:
- Set up STSMs and exchange programmes for ECIs with the Regulatory Agencies (Year 1-4);
- To standardize procedures and remove bottlenecks at each participating centre that would facilitate the future conduct of a multicentre clinical trial in DILI (Year 2-4);
- A proposal for study design for risk or biomarker evaluation, pathway for evaluating of diagnostics and appropriate statistical methods (Year 3);
- Design of clinical trials in DILI to assess the effect of an intervention on disease course or clinical outcomes (Year 4);
- Conference on design, outcome measures and therapeutic options of clinical interventions in DILI (Year 4).

WG5. KNOWLEDGE DISSEMINATION, COMMUNICATION, TRAINING PLAN AND EXTERNAL RELATIONSHIPS WITH STAKEHOLDERS

The main objective of WG5 will be the development of good practice models to disseminate the knowledge gained throughout the Action. WG5 will focus on delivering enhanced awareness of DILI and on distributing the new insight into this condition that has resulted from this Action. The WG5 will monitor and evaluate the dissemination plan and advise the Core Group (CG) if the approach needs changing.

The main tasks of WG5 will be:
- Coordinate the set-up and maintenance of the Website and social networks promotion of the Action and maintain updated information on recent activities and downloadable resources;
- Organize and coordinate the conferences' agenda, joint meetings with Government Regulatory bodies, educational seminars and workshops for COST members and the public;
- Organize and coordinate the STSMs and Training Summer Schools;
- Raise awareness regarding opportunities to contribute to national and international conferences and meetings outside the Action to widen its influence;

- Establish contacts and collaborations with new potential Action partners, European or International programmes and organisations;
- Coordinate scientific publications and conference communications;
- Identify key investigators (external evaluators) able to measure the impact of the different recommendations generated by this Action.

The expected milestones and deliverables are:

- Set up a Website and social networks to translate scientific efforts into public dissemination and regulatory bodies (Year 1);
- Write a Quality Plan and Good Practice Policies that apply to all COST partners (Year 1);
- Mid-term review of the COST Action proposal with the Management Committee (MC) to implement corrective measures if deemed necessary (Year 2);
- Organise the Annual European DILI Conference and to coordinate the setting up of an ECIs forum in each of these conferences and to prepare the Joint Meetings with regulatory agencies and Info Days on DILI and the workshops (Year 1-4);
- Organise the STSMs in close collaboration with the CG, MC and Coordinators (Year 1-4);
- To coordinate and organise DILI Training Summer Schools in collaboration with the MC, and to coordinate scientific publications and conference communications (Year 1-4).
- Coordinate the integration of WG results and to deliver the COST main documents to an "External audience" for evaluation (Year 1-4);
- Organise the Annual Reports, Closing meeting and Final Report in which a roadmap to DILI research in Europe will be presented (Year 1-4).

3.1.2. GANTT DIAGRAM

The Action will begin with an Inaugural Conference to identify aims that require prioritization and establish the strategic plan to be accomplished. WGs will meet up to twice a year, with all WGs meeting at the annual scientific meetings. MC meetings will take place annually at the scientific conferences. CG will meet face to face up to every 6 months and via teleconference or using other means of communication every 2 months. The Action will be closed with a final Scientific Conference combined with all WGs.

Activity	2018				2019				2020				2021			
	Q1	Q2	Q3	Q4	Q1	Q2	Q3	Q4	Q1	Q2	Q3	Q4	Q1	Q2	Q3	Q4
MC Kick-off & consecutive meetings																
CG Meetings																
WGs initial & consecutive meetings																
Annual European DILI conference																
Short-Term Scientific Missions																
Specific Workshops Proposed by WGs																
DILI Training Summer Schools																
Joint Meeting with Regulatory Agencies																
Info Day on DILI																
Closing Meeting and Final Report																
Deliverables of WG1																
Standardized approach to diagnosis and SOPs for data/samples collection																
Pre-funded database of DILI patients																
Review: DILI diagnosis & management																
Classification system for HDS																
Consensus on nomenclature, diagnosis, classification, assessment & treatment of DILI																
Deliverables of WG2																
EU Framework translational research plan for biomarker development																
Scientific publication on the current knowledge DILI risk modifiers																
Written input to commercial enterprises for Future Market Exploitation of biomarkers																

Publication on predictive models of drug hepatotoxicity																
Deliverables of WG3																
Review: Realistic *in vitro*/*in silico* models in hepatotoxicity; non-invasive optical/ chemical imaging techniques																
List appropriate control compounds for testing new i*n vitro* models																
Roadmap for the development of preclinical models of DILI																
Deliverables of WG4																
SOPs to facilitate the conduct of a multicentre clinical trial in DILI																
Study design for biomarkers evaluation & robust statistical methods																
Design of clinical trials to assess the effect of an intervention on DILI course or outcomes																
Deliverables of WG5																
Website setup, social media & updates																
Quality plan and good practice policies																
Mobile application development & update																
Mid-term review of the COST Action proposal																
Preparation of large-scale European projects																
RoadMap to DILI research in Europe																

3.1.3. PERT CHART (OPTIONAL)

3.1.4. RISK AND CONTINGENCY PLANS

Risk of insufficient quality: Action delivers poor quality findings. The Action will have measures to ensure an internal peer-review process, either through institutional process or as a part of the COST Action, prior to wider sharing of scientific outputs. In addition, all key documents such as guidance position statements and consensus would go through external peer-review process either through professional societies or specialist journals.

Risk of cost overruns: Action costs go over the estimated costs. In case of cost overruns, the consortium will not request additional funding although it may ask for permission to adjust some aspects of the Action deliverables or activities. Members of the network recognize, and have agreed in principle, that unforeseen risks may require contribution from host institutions 'in kind' (e.g. staff time or space for the meetings) to ensure successful completion of the Action's objectives.

Risk of insufficient extent of dissemination: The Action information does not reach the intended target audience. First, the Action will utilize a wide variety of communications channels. Action partners have extensive experience in the dissemination of technical research results and in communication of research ideas to colleagues and external parities. Thus, the use of a wide range of media channels and expert collaborators in the dissemination of the Action will ensure the results reach the largest possible target audience.

Risk of insufficient collaboration: The CG will review on a regular basis the contributions of each collaborator to ensure equivalent and efficient contribution of all participants. Collaborators failing to adhere to the standards will be counselled for potential barriers and a clear follow-up plan will be set to ensure that the collaborator concerned achieves the future assigned tasks.

Risk of failure to attract ECIs: The call for participation in Summer Training Schools and professional workshops will take place 3 months before the planned date of the activity. However, failure to attract the participation of the desired number of ECIs will oblige an extension of the call while revaluating the publicity strategy.

Risk of unsatisfactory training schools and workshops: While the MC will benefit from the vast experience of collaborators to ensure the delivery of high quality training schools and professional workshops, ECIs will be asked for their feedback concerning the quality and the benefit achieved by these activities. The MC, following the evaluation of ECIs' input and future suggestions, will conclude the relevant recommendations that will be adopted in future activities.

Risk of failure to attend meetings: The failure of any collaborator or WGs representatives to physically attend meetings will be compensated by setting teleconferences or similar means of communication.

3.2. MANAGEMENT STRUCTURES AND PROCEDURES

The Action will follow the rules and procedures for implementing COST Actions. The **MC** is responsible for the coordination of the overall strategy, allocation of funds, and the Actions reports, and will coordinate the preparation of a proposal for future EU programmes; meeting at least once every year. The MC will elect the Action Chair, Vice-Chair, WGs leaders and task coordinators (ECIs coordinator, Gender-Balance coordinator, Website coordinator) at their first meeting. Each COST Country will appoint two MC members. The MC appoints a **CG** consisting of the Chair, Vice-Chair, the WG leaders (local organizers as necessary) and Coordinators. The CG will verify and approve all operational and day to day decisions, synchronize scientific and STSMs activities, and will help the Chair in smooth running of the Action. They will establish efficient communication through emails and teleconferences.
WGs: Five WGs will be established with a WG-Lead and a Co-Lead who will report on the progress of the WG in relation to the deliverables achieved and its dissemination, propose modifications and innovations and coordinate with CG and WG5. When necessary, they may maintain virtual meetings through teleconference or similar means of communication. The Action will combine these WG meetings as participants may work on more than one topic or want to be updated and participate in scientific exchange. All WGs will also meet at the annual conference. An annual workshop will be organized to enable scientists and ECIs to present progress, identify bottlenecks and consider future perspectives. When appropriate several WGs may meet together or a WG may hold a workshop with another network with similar interests.
The Action will give particular attention to ensure strong **representation of ECIs and gender balance** on all Committees/WGs. **Coordinators** will pay attention to maintain a minimum number of ECIs and ensure gender balance when selecting speakers and chairs and co-chairs of the Workshops or Conferences sessions, and promoting their participation in the various activities. Furthermore, ECIs are encouraged to become WG leads or co-leads. These items will be included as a standard point on all MC agendas. The annual report from each WG will include a section detailing the participation of ECIs and gender balance in its activities. A network of ECIs shall be created. To integrate scientists with families and young children, the Action will support appropriate childcare and coordinate its meetings to respect main holiday times.
ECIs will be strongly involved in the COST Action through the organization of **STSMs** and Training Summer Schools to develop the next generation of researchers and avoid a generation gap. **STSMs** will be encouraged to extensively exchange scientific data and technical knowledge and skills between institutions, and to support mobility and career progression of ECIs at an international level. These may bring about innovative scientific approaches. This Action will foster at least 14 STSMs. Through the Best poster competition contest at Scientific Conferences or workshops those posters awarded whose first author is a ECI will be offered priority to enjoy a STSM or attend a training school.
Cross-disciplinaryTraining Schools to promote education of ECIs and others. The ECIs Coordinator will seek opportunities for Action members to access existing training activities among partner centres.
Website coordinator will maintain the website and will be responsible for the technical aspects.

3.3. NETWORK AS A WHOLE

The PRO-EURO-DILI-NET COST Action will constitute a large network encompassing a wide array of European experts originating from different scientific backgrounds and possessing a broad range of qualifications necessary to develop mature hypotheses and long-term strategic plans. Widespread geographical coverage will take into account the differences in in diverse race/ethnicity, pharmaceutical and regulatory drug policies, medical and of health systems organizations between the participating countries and it will enable subanalysis of treatment-specific phenotypes as to detect differences between genetically diverse populations.
This COST Action adopts a global approach by bringing together the scientific communities, excellent SMEs and researchers across Europe, Asia and potential transatlantic collaboration with USA-based initiatives, allowing the establishment of liaison and interaction and exchange of knowledge and information with other research programmes. The Action is committed to increase capacity building potential for the Early Career Investigators integrated in the different multidisciplinary groups within the PRO-EURO-DILI-NET as a matter of upmost priority. The Action will respect an appropriate gender balance in all its aims. Indeed, this European multidisciplinay nekwork of experts in DILI set up to pre-empt and prevent DILI, improve clinical care and outcomes, foster translational research, public awareness and education.