

COST Action Progress Report at 24 months (16/10/2018 to 16/10/2020)

CA17112: Prospective European Drug-Induced Liver Injury Network

The Action was approved by the Committee of Senior Officials (CSO) on 13-4-2018 and has the MoU reference COST 023/18.

This report shows the data entered into e-COST to enable the Action Chair to verify the completeness and accuracy of the report with the MC prior to submitting the report via e-COST in fulfilment of the rules for COST Action Management, Monitoring and Final Assessment.

Action leadership and participants

Leadership positions

Position	Name	Contact details	Country*
Chair	Prof Raul Andrade	andrade@uma.es +34951440260	Spain

Position	Name	Contact details	Country*
Vice Chair	Prof Guruprasad Aithal	guru.aithal@nottingham.ac.uk +01158231074	United Kingdom

Working groups

#	WG Title	# of participants	WG Leader	Country*
1	IN-DEPTH PHENOTYPING IN DILI	8	Prof Helena Cortez-Pinto hlcortezpinto@netcabo.pt	Portugal
2	DILI RISK STRATIFICATION	8	Prof Gerd A. Kullak-Ublick gerd.kullak@usz.ch	Switzerland
3	PRECLINICAL EVALUATION OF DILI	10	Prof Jose Fernandez-Checa checa229@yahoo.com	Spain
4	DESIGN AND ENDPOINTS IN CLINICAL DILI INVESTIGATIONS AND TRIALS	8	Prof Einar Bjornsson einarsb@landspitali.is	Iceland
5	KNOWLEDGE DISSEMINATION, COMMUNICATION, TRAINING PLAN AND EXTERNAL RELATIONSHIPS WITH STAKEHOLDERS	4	Ms Simona Stankeviciute stanksim@gmail.com	Lithuania

Other key leadership positions

Position	Name	Contact details	Country*
STSM Coordinator	Dr Francisco Javier Cubero	fcubero@ucm.es	Spain
Science Communication Manager	Ms Simona Stankeviciute	stanksim@gmail.com	Lithuania
GH Scientific Representative	Prof M Isabel Lucena	lucena@uma.es	Spain

* The country displayed is:

- for the Action Chair, the country that nominated that person to the Management Committee before they were elected Action Chair;
- for the Vice Chair the country that nominated the person as a Management Committee Member,
- for all other leadership positions, if the person is a MC Member the country displayed is the country of nomination, otherwise it is the country of the person's primary work affiliation.

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Participants

COST members having accepted the MoU

BE	01/02/2019	BA	18/06/2018	HR	11/05/2018	CZ	01/10/2018	EE	13/09/2018
FR	15/06/2018	DE	23/05/2018	EL	09/10/2018	IS	17/09/2018	IE	03/11/2020
IL	03/05/2018	IT	31/07/2018	LT	09/07/2018	MD	05/03/2020	NL	11/12/2019
MK	26/02/2019	NO	24/08/2018	PT	01/06/2018	RO	14/06/2018	RS	28/01/2019
SK	08/03/2019	SI	07/05/2020	ES	23/05/2018	SE	11/02/2020	CH	03/05/2018
TR	31/10/2018	UK	03/05/2018						

Other participants

Institution Name	Country
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Summary

The main aim and objective of the Action is to

To create a unique, co-operative, interdisciplinary European-based DILI network of stakeholders to coordinate 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

During its first two years the Action progressed the achievement of this as described below

During the first 2 years of activities, the COST-DILI Action (CA17112) has incorporated 12 new member countries with a wide range of competencies - from an initial 16 (6 ITC, 37.5%) to 28 (13 ITC, 46%), encompassing academic and industry stakeholder groups, including 3 new SMEs. This has permitted an increased focus on important neglected areas such as DILI in Pediatrics, and NAFLD-DILI. Furthermore, we have reached out to the International Autoimmune Hepatitis Group (IAIHG) to agree upon areas of common interest related to DILI. Also, a collaboration with the European Liver Patient Association has been established in order to underline the relevance of patient's perspectives of DILI. This will pave the way to an Information Day on DILI. In collaboration with partner centres in Europe through the COST action activities, an e-database has been setup. This resource uniquely enables an efficient and methodical collection of phenotypic data and. Currently there are 68 users across 20 European centres. This facilitates data and sample sharing and central biobanking for collaborative research projects.

In parallel, the CA 17112 has secured partnership with an ongoing, major European IMI scientific project TransBioLine (Translational Safety Biomarker Pipeline). This important initiative will enable discovery, development, validation, regulatory qualification and application of safety biomarkers, with the goal of generating a fundamental change in the way drug hepatic safety is monitored in clinical trials, and how toxicities are diagnosed and managed in clinical practice. To provide further harmonization in research activities between academia, pharmaceutical and regulatory agencies, significant pro-active efforts will be made to integrate recent H2020 initiatives aimed at progressing beyond-state-of-art, areas highly-relevant to COST-DILI (eg Next generation organ-on-chip (RIA-LS) technologies; & Advancing the safety assessment of chemicals). Other important scientific and educational activities have been developed with CIOMS-WHO, and produced with CA17112 members an International White Consensus Paper on DILI. The Chair and Vice chair of this CA-17112 appointed by EASL (European Association for the Study of the Liver) have elaborated a Clinical Practice Guidelines on DILI for the translation of knowledge gained in DILI to improve decision making and clinical outcomes. A position paper outlining current and beyond-state-of-art in vitro/in silico technologies has been drafted. Beyond better representation of organ level function and DILI prediction, organotypic human-based 2D-3D multicellular-cultures offer enhancement cellular biomarker discovery – essential for detecting early signals of hepatotoxicity and in better defining mechanisms DILI. Addressing the basic sciences in tandem with both clinical and parallel Pharma, SMEs and academic consortia perspectives provides much needed cohesion and synergy in the DILI field and impetus for a constructive way forward. The multidisciplinary collaborative approach of ProEuroDILINet provides an ideal environment for innovation.

COST's support for networking has led to important beneficial effects at the level of individual researchers and their institutions, including trust-building and promotion of interdisciplinary partnerships and STSMs, and fostering high-impact international publications that would provide synergy for further joint international collaborative research projects. Actions to further support ECIs/trainees, increase leadership training, provide mentorship and engagement in DILI, are underway.

The Action will implement the following measures in the coming two years to overcome any issues identified in this report as potentially endangering the achievement of the objectives of the Action

The exceptional situation of COVID 19 pandemic represents a major scientific challenge that have clearly

hampered the full intended achievements and objectives of EU COST Actions. Since lockdown commenced across Europe, scheduled events (March-Nov 2020) have been cancelled, postponed, or the format modified. To mitigate impact on the COST Action goals we have organized virtual meetings – across the COST-DILI Action as well as individual/Working-Group meetings continuing and between individuals within the Action. To facilitate this, we have, for example acquired through the COST budget a Zoom platform; whereby the next Core Group meeting (26th Nov 2020) will be entirely virtual. Other meetings have been moved to 2021 and we hope to have them face-to-face. The vast majority of activities in COST require international travel (cross-country mobility). Travelling is restricted and this CA will not be able to execute the proposed activities, especially STSMs, ITC conference grants and training schools under a face-to-face events premise. This will affect disproportionately the junior researchers for which networking COST activities make most sense.

We think that we may need to expand the deadline of this Cost Action depending on the evolution of the pandemic.

Action website

<https://proeurodilinet.eu/>

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Achievement of MoU objectives, deliverables and additional outputs/ achievements

MoU objectives

Please self-assess and describe the level of achievement of each MoU objective. For any MoU objective that is 25% or less achieved, please add an explanation.

Mou objective	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
Type of objective	1.b Coordination of information seeking, identification, collection and/or data curation 1.e Development of knowledge needing international coordination, pertaining to a new or improved theory, model, methodology, technology or technique
Level of progress	26 - 50%
Description of progress with achieving the MoU objective	<p>An improved understanding of key signals of hepatotoxicity is considered a critical feature and route to better DILI predictivity. Parallel developments are proposed describing improved alternative human-based in vitro preclinical models and experiments which can address broadly, knowledge gaps of mechanistic toxicological features in recognized (intrinsic DILI) and unknowns in extrinsic (mainly idiosyncratic) DILI. Such models are described in detail in a review article, a major deliverable and output of WG3 (preclinical DILI). To achieve such ambitious goals, it is evident that a rapid evolution in toxicology approaches - from 'traditional' phenomenological toxicology to in vitro plus in silico-based systems - is urgently required. Important intermediate steps and considerations are considered and discussed, such as utilizing the mode of action (MoA) concept which embraces mechanistic toxicology and pathway approaches (e.g. the Adverse Outcome Pathway (AOP) approach). Aspects relating to the latter are presented which exemplify the complexity of DILI – using paracetamol as a paradigm. Beyond better representation of organ level function and DILI prediction, organotypic human-based 2D-3D co-cultures offer enhancement of the discovery of cellular biomarkers – essential for detecting early signals of hepatotoxicity. Emerging areas in mechanistic DILI provide highly promising opportunities as potential biomarkers, such as circulating extracellular vesicles with specific proteome and liver microRNAs; whilst novel high-throughput compatible in vivo zebrafish models may detect liver injury through transferrin mRNA levels. Engaging with and gaining regulatory acceptance through validation of such biomarkers is key – including more familiar liver safety serum protein biomarkers (cytokeratin 18 (CK-18), high mobility group protein B1 (HMGB1), and osteopontin; requires close interaction with major regulatory authorities such as FDA, EMA, OECD and cross-cutting agencies including the C-Path/ Predictive Safety Testing Consortium.</p> <p>A major review is near completion which embodies the COST-DILI themes 'Realistic in vitro/in silico models in hepatotoxicity; non-invasive optical chemical imaging techniques', with the collaboration of members of WG3. This consensus review article is an important Milestone for WG3 as it is both a deliverable and represents a COST-DILI consortium position paper on applying beyond-state-of-art basic science to DILI. We have strategically aligned this article with two recent and associated high-impact reviews (involving COST-DILI members) which illuminate state-of-art aspects of DILI, including clinical DILI, as well as a proposed general scientific roadmap for DILI, suggesting a useful tiered framework for cell-based technologies for drug development.</p> <p>Benefits of analysing signal detection of potentially DILI in children using electronic health records are being revised. There is no CPG on DILI in pediatrics possible due to the lack of data. A gap of knowledge has been identified that needs an international collaborative approach to understand risk factors, outcome and management. Efforts on this topic are ongoing. Also to advance in the harmonization of definitions to</p>

	<p>differentiate DILI with an autoimmune phenotype from idiopathic Autoimmune hepatitis.</p> <p>The multidisciplinary collaborative approach of ProEuroDILI Net provides an ideal environment for innovation.</p>
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Mou objective	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
Type of objective	<p>1.e Development of knowledge needing international coordination, pertaining to a new or improved theory, model, methodology, technology or technique</p> <p>1.f Achievement of a specific tangible output that cannot be achieved without international coordination (e.g. due to practical issues such as database availability, language barriers, availability of infrastructure or know-how, etc.)</p> <p>1.h Input for future market applications (including cooperation with private enterprises)</p>
Level of progress	26 - 50%
Description of progress with achieving the MoU objective	<p>A STSM by Cristiana Freixo in Nottingham has addressed this specifically, the potential risk factors associated with hepatotoxicity and biomarkers indicating DILI throughout the life course of a drug- leading to manuscript on 'Biomarkers for DILI' jointly between European centres by E.Atallah, C.Freixo, I.Alvarez, F.J Cubero, G.P.Aithal in partnership with Transbioline consortium– final draft in preparation will be made available to members of COST.</p> <p>A systematic review of risk factors of DILI in paediatric population considering the different definition of paediatrics across countries, which is already included in the PROSPERO (international prospective register of systematic reviews database) and is led by CA 17112 members, is currently underway.</p> <p>Using the prospective Spanish DILI Registry database, members of the CA 17112 in collaboration with the University of Duke (Ayako Suzuki, IPC) and the NCTR (National Centre of Toxicology Research) are exploring the role of host and drug factors in both the biochemical expression (type) of liver injury and the time to resolution of the liver injury. Two manuscripts have been drafted and will be submitted shortly.</p> <p>A Systematic review with meta-analysis on the prevention and management of drug-induced liver injury in randomised clinical trials", is being sent for consideration for publication in Pharmacological Research (D1). In recent years, prevention and management of idiosyncratic drug-induced liver injury (DILI) have received growing attention due to its increasing public health burden. However, owing to the complexity and low prevalence of DILI, performance of randomised clinical trials faces multi-layered challenges.</p> <p>In this systematic review with meta-analysis, we summarised the design and findings of 22 randomised clinical trials in prevention and management of DILI and non-acetaminophen DILI-related acute liver failure. This is the first systematic review that illustrates the difficulties and deficiencies of clinical research on DILI according to the heterogeneity of DILI case qualification, inclusion and exclusion criteria, efficacy criteria and methodological design. In addition, we evidenced, based on the scarce number of trials available and flawed methodology, that tested agents did not show efficacy on DILI prevention and management.</p> <p>An important implication derived from this novel study is the need to plan and set up an international multicentre research network to investigate the effectiveness of known and novel interventions that could improve clinical outcomes of DILI in the setting of adaptive clinical trials design with defined threshold criteria for patient inclusion, monitoring plans, stopping rules and precise endpoints.</p> <p>Short-term scientific missions (STSMs) with the Regulatory Agencies. We plan to work with The European Clinical Research Infrastructural Network (www.ecrin.org), in order to plan and design clinical studies to test treatments for DILI. According to</p>

	Jacques Demotes MD PhD who is the director general ECRIN, the application will take approximately 1 year (November 2022), ethical and other approval another year (November 2023) and with their support the trial could start in early 2024. The period from November 2020 to November 2021 will be used to come up with a study design, with adequate endpoints to assess effect of an intervention on clinical outcomes.
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Mou objective	To establish standardized prospective data collection procedures and to develop an infrastructure for heterogeneous data and sample sharing
Type of objective	1.b Coordination of information seeking, identification, collection and/or data curation 1.e Development of knowledge needing international coordination, pertaining to a new or improved theory, model, methodology, technology or technique 1.f Achievement of a specific tangible output that cannot be achieved without international coordination (e.g. due to practical issues such as database availability, language barriers, availability of infrastructure or know-how, etc.)
Level of progress	76 - 100%
Description of progress with achieving the MoU objective	The Pro-Euro DILI registry has been revised in collaboration with partner centres in Europe through the COST action activities and e-database (https://www.proeurodili.eu/) now enables efficient, methodical collection of phenotypic data and coordination of monthly case Review sessions. Currently there are 68 users across 20 European centres (corresponding to 7 countries). This facilitates data and sample sharing and central biobanking for collaborative research projects (e.g. Transbioline Consortium)

Mou objective	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
Type of objective	1.a Development of a common understanding/definition of the subject matter 1.e Development of knowledge needing international coordination, pertaining to a new or improved theory, model, methodology, technology or technique 1.j Dissemination of research results to stakeholders (excluding specific input in view of knowledge application)
Level of progress	51 - 75%
Description of progress with achieving the MoU objective	<p>A European Clinical Practice Guidelines on DILI appointed by the EASL and intended to be a major guidance for clinicians, regulators and pharmaceutical industry with regard to detection, diagnosis and prevention of DILI has been finished during the grant period (2019). The expert panel of this CPG included 5 CA 17112 members: Raul J. Andrade (Chair), Guruprasad P Aithal, Einar Bjornsson, Gerd Kulak-Ublick and Dominique Larrey.</p> <p>Several CA-17112 members have been actively involved in the CIOMS Working Group on DILI, which is part of the WHO, after a work on this OPUS over a 3-year period have recently published an updated Guidance on DILI for use by physicians, regulators, and drug developers in the pre-market and post-Market space worldwide. The plan is for it to be a living document with periodic updates. The CIOMS forms are used worldwide to report Adverse events in Clinical Trials and in post-marketing surveillance. The forms that they previously used had not been updated since the 1990's. IN that vain, we anticipate that Table 7 and Appendix 2 will be of particular value to help standardize DILI assessment and case adjudication across the world.</p> <p>Another European Clinical Practice Guidelines on Occupational Liver Diseases appointed by the EASL was also finished during the grant period (2019). In this CPG a CA 17112 member (M. Isabel Lucena) has been a member of the expert panel.</p> <p>A collaboration of CA 17112 with the Interactive Safety Graphics Taskforce of the DIA-</p>

	<p>ASA Biopharma Working Group (USA) has been setup. The aim of this project is by using the Spanish DILI Registry database to develop and validate an open-source tool for identifying and investigating signals of hepatotoxicity during clinical development.</p> <p>Addition to the COST-DILI network of major SMEs, eg Biopredic International, who are involved in hepatic models/ reagents/ products for DILI and the world licensing holder for the human HepaRG cell line; and have extensive collaborations and reach in the Pharma and regulatory communities.</p>
Mou objective	<p>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</p>
Type of objective	<p>1.g Input to stakeholders (e.g. standardization body, policy-makers, regulators, users), excluding commercial applications</p> <p>1.i Dissemination of research results to the general public</p>
Level of progress	<p>26 - 50%</p>
Description of progress with achieving the MoU objective	<p>WG1 has address issues regarding the criteria for DILI case definition, characterization and classification of phenotypic sub-groups in DILI; 2. harmonize efforts for in-depth DILI phenotyping and bio-sample repository; and 3. coordinate funded database/repository studies to aggregate a large number of DILI cases in a standardized manner. Right from the beginning it was agreed that one important mission would be to harmonize clinical measurements, definitions, classifications and outcomes related to DILI. Activities:</p> <ul style="list-style-type: none"> • It was requested to registry holders to send the type of information recorded in local databases, since registries are different among groups, this would facilitate us to create an aligned database registry appropriate for all centres. • Breakout Group Meeting (March 2019) – collating of ideas/expertise on data collection, data recording, data interpretation. <p>Development of new Pro Euro DILI Registry in three steps: collate existing database variables, discuss requirements & limitations; and final output ProEuroDILI Registry, now available to any researcher.</p> <p>Addressing the basic sciences in tandem with both clinical and parallel Pharma, SMEs and academic consortia perspectives provides much needed cohesion and synergy in the DILI field and impetus for a constructive way forward. Addition to the COST-DILI network of major SMEs and the contact with Regulatory bodies through the Lol for safety biomarkers in DILI represent an important move forward. Extensive collaborations and reach in the Pharma and regulatory communities have been set up.</p> <p>The EU Innovative Medicines Initiative Consortium TransBioLine (Translational Biomarker Pipeline) was initiated in February 2019 (https://www.imi.europa.eu/projects-results/project-factsheets/transbioline). The Vice Chair of the COST action, Prof. Guru Aithal, and the Leader of WG2, Prof. Gerd Kullak-Ublick, are the two leaders of the DILI work package (WP2) in the TransBioLine Consortium. The DILI work package uses the existing infrastructure of the Pro-Euro DILI Network to recruit DILI patients. The recruiting centres comprise the academic hospitals of the Universities of Nottingham, Malaga, Munich, Reykjavik, Paris and Zurich. Patient data are entered into the existing Pro-Euro DILI eCRF, for subsequent export to the TransBioLine database. Patient samples are shipped to the central biobank at the Charité Hospital in Berlin. The aim of the Consortium is to qualify new safety biomarkers of DILI measured in plasma. As an IMI consortium, TransBioLine is a</p>

	<p>public-private partnership that involves 27 partners in total, comprising 12 academic partners, 7 EFPIA companies, 7 SMEs (small and medium-sized enterprises) and 1 patient organization. The planned duration of TransBioLine is 5 years, ending in January 2024. Nine members of the CA are involved in this international collaboration.</p> <p>We intend to discuss the preparation of large-scale European projects in the next Working Group meeting, to be held in Nottingham April 2021. We intend to identify topics of interest suitable for applying to the H2020, 9 EU Framework Programme, alongside other funding programmes.</p> <p>Activities performed by the WGs through the first half of the project have already started identifying and strategizing a roadmap to DILI research, but this work will formally be commenced at the next WGs meeting in Nottingham, April 2021.</p>
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Mou objective	Create a mutual strategy to optimize the training capacities related to DILI currently available at different cross-border stakeholders via exchange programmes
Type of objective	<p>2.a Building a community around a topic of scientific and/or socio-economic relevance, allowing for knowledge exchange and the development of a joint research agenda</p> <p>2.c Bridging separate fields of science/disciplines to achieve breakthroughs that require an interdisciplinary approach</p> <p>2.e Building capacity in the demographic inclusiveness of networks in science and technology, including representation of newly established research groups, Early-Career Investigators, the under-represented gender and teams from countries/regions with less capacity in the field of the Action</p>
Level of progress	51 - 75%
Description of progress with achieving the MoU objective	<p>23 countries hosting STSMs both clinical and basic have been proposed. ITC representing 34%; women 26%, ECI hosting 26%. Up to now, six STSMs have been enjoyed. In the 2nd GP there were 6 ECIs who profit from their stay at other research centers located in a different country. Other ten new STSMs have been launched in this 3rd GP. Furthermore, students exchanges between the laboratories are envisioned once the STSM has finalized as a result of collaborative projects and synergistic outcomes as join publications.</p> <p>1st ITC Conference Grant has been awarded to the PhD Student, Ms. Joana Saraiva (Portugal, ITC)</p> <p>This Cost Action has further responded to the policy on COST Excellence and Inclusiveness because has created a robust cross-border networking of researchers. There are also 5 COST International Partner Countries (Chile , China , India , United States , Uruguay) and we have incorporated Malaysia as the first IPCR country.</p>

Mou objective	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
Type of objective	<p>2.a Building a community around a topic of scientific and/or socio-economic relevance, allowing for knowledge exchange and the development of a joint research agenda</p> <p>2.e Building capacity in the demographic inclusiveness of networks in science and technology, including representation of newly established research groups, Early-Career Investigators, the under-represented gender and teams from countries/regions with less capacity in the field of the Action</p>
Level of progress	51 - 75%
Description of progress with achieving the MoU objective	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

	The CA 17112 has set forward the rules and a rigorous application process that set minimum standards for the laboratories at the Hosting institution and the planning of work for the STSM needs to be approved
Mou objective	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
Type of objective	2.a Building a community around a topic of scientific and/or socio-economic relevance, allowing for knowledge exchange and the development of a joint research agenda 2.c Bridging separate fields of science/disciplines to achieve breakthroughs that require an interdisciplinary approach 2.e Building capacity in the demographic inclusiveness of networks in science and technology, including representation of newly established research groups, Early-Career Investigators, the under-represented gender and teams from countries/regions with less capacity in the field of the Action
Level of progress	26 - 50%
Description of progress with achieving the MoU objective	Annual European DILI conference are planned for this GP and until the end of the Cost Action. A monothematic conference in DILI along with the Eurotox Conference was postponed until sept 2021. This conference will bring together researchers from Academia, Pharmaceutical Industry, SMEs and Regulatory bodies to integrate knowledge and anticipate needs at the different institutions
Mou objective	Facilitate exchange of professional expertise, research material/ data between experienced researchers and ECIs through workshops and training summer schools
Type of objective	2.a Building a community around a topic of scientific and/or socio-economic relevance, allowing for knowledge exchange and the development of a joint research agenda
Level of progress	51 - 75%
Description of progress with achieving the MoU objective	This CA has already run 2 Training Schools and is planning a 3 rd one for early 2021. 1st Training School (TS) Assessment of Drug-Induced Liver Injury: Key Rules and Common Pitfalls. How To Make a Clinical Narrative: 10 Trainees reimbursed: 50% from ITC countries; 70% Women; 80% ECI The 2nd TS Recent Advances on Stem Cell Research and Cell Therapies, organized by a woman in Lisbon (ITC). 13 trainees reimbursed: 38% from ITC countries, 67% females; 92% ECI Measures taken for quality: The recognition by EUROTOX of the 1st Training School as a continuing professional development course of 11 teaching hours. The application was made by ECIs. The course will be re-run in Slovakia. http://www.eurotox.com/courses-for-ert/ert-courses/ . ECIs feedback concerning the quality and benefit achieved by these activities and their suggestions have been adopted in future activities. EASL School of Hepatology Thematic Workshop. WG3 propose to apply to EASL in 2021-2022 to establish a high-profile hybrid (taught/ practical) workshop on DILI focussing on basic liver cell science. Major sponsors will be sought such as Gilead and Biopredic International to provide financial/ in-kind support.
Mou objective	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

Type of objective	<p>2.a Building a community around a topic of scientific and/or socio-economic relevance, allowing for knowledge exchange and the development of a joint research agenda</p> <p>2.e Building capacity in the demographic inclusiveness of networks in science and technology, including representation of newly established research groups, Early-Career Investigators, the under-represented gender and teams from countries/regions with less capacity in the field of the Action</p>
Level of progress	51 - 75%
Description of progress with achieving the MoU objective	<p>Very close supervision and mentorship has been done to ECIs and a set of measures have been taken into the CA17112 in order to increase their leadership, to assist in their development through education and capacity building, organizing activities primarily organized by ECIs and ensuring their representation and gender balance on all committees, conferences and WGs.</p> <p>And the networking activities have stimulated a high number of follow-up proposals for further research projects. Support and partnership to translate breakthrough ideas into tangible impact; Help ECIs to grow professionally and Create learning opportunities and exchange of knowledge.</p>

Mou objective	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.
Type of objective	2.b Building a community around a new or emerging field of research
Level of progress	51 - 75%
Description of progress with achieving the MoU objective	<p>There are organized two Info days on DILI during the next Grant Periods. Progress has been made establishing a collaboration with EASL (European Association for the Study of the Liver) and ELPA (European Liver Patients Association). Presentation by Dr H. Glasová (serves as a member of ELPA and is member of CA17 112) of a COST DILI CA-17112 project and proposal of collaboration of ELPA with the COST DILI at the ELPA Stakeholders', Scientific Committee and Advisory Board meetings and Extraordinary General Assembly, Barcelona, Spain, on the 1.12.-5.12. 2019</p> <p>An Info Day on DILI is being projected for next GP</p> <p>COST Action CA 17112 has website (https://proeurodilinet.eu), social media accounts (i.e. Twitter and LinkedIn), where all the information about the Action and its progress is being shared.</p> <p>The website was created in 2018. The website ensures a 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). It also includes a section with all the dissemination activities done (newsletters, scientific publications...).</p>

Deliverables

This section covers only deliverables that were foreseen for the Action, not additional outputs that were generated during the Action (these additional outputs will be added in the following section). Please select and comment on the progress with achieving each deliverable.

For deliverables that are:

- Delivered, please provide proof to enable the Action Rapporteur to confirm the delivery
- Not delivered but delivery is foreseen within 2 years please explain how the delivery will be achieved
- Not foreseen to be delivered please explain why not

Deliverable	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		
Progress with achieving deliverable	Delivered	Month deliverable due	12
Proof of progress with achieving the deliverable	https://www.proeurodili.uma.es/login		

Deliverable	WG1-Coordination of the development of pre-funded database of DILI patients providing a framework for the access to patient cohorts from different EU countries		
Progress with achieving deliverable	Delivered	Month deliverable due	12
Proof of progress with achieving the deliverable	https://proeurodilinet.eu/wp-content/uploads/2020/11/COST-WG1-101019-J-Grove-v2.pdf		

Deliverable	WG1-Conduct a systematic review of published data on DILI diagnosis and management		
Progress with achieving deliverable	Delivered	Month deliverable due	15
Proof of progress with achieving the deliverable	https://uma365-my.sharepoint.com/:b:g/personal/lucena_uma_es/EYqlvRClicJBo_iP945CmDEBrKXzOePo3nagX0nWhw0M-g?e=ao0sWt		

Deliverable	WG1- Development of a classification system for HDS which may increase HDS induced-liver injury recognition, improve causality assessment and foster research in this area		
Progress with achieving deliverable	Not delivered, but expected within 2 years after the end of the Action	Month deliverable due	33
Explanation	We will take advantage of the comprehensive global data that we are analyzing to create a DILI database and build a new classification based on the three elements: evidence, frequency and severity. A classification system for HDS is very much needed which harmonizes nomenclature, composition and quality of the products. This would improve herbals related liver injury causality assessment. We need to set up a global collaboration on herbals induced liver injury categorization including China where the use of Traditional Chinese Medicine is deeply rooted in Chinese clinical practice. A listing of Herbal and Dietary supplements have been made.		

Deliverable	WG1- 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		
Progress with achieving deliverable	Delivered	Month deliverable due	48
Proof of progress with achieving the deliverable	https://proeurodilinet.eu/wp-content/uploads/2019/06/2019-Andrade-EASL-CPG-in-DILI-J-Hepatol.pdf		

Deliverable	WG2-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		
Progress with achieving deliverable	Not delivered, but expected before end of Action	Month deliverable due	18
Explanation	As part of the TransBioLine mission to qualify new safety biomarkers of DILI, an SME called MetaHeps is being supported in its development of a DILI causality assay. This assay uses MH cells (monocyte-derived hepatocytes) to confirm the causal role of a suspected DILI-causing drug in individual patients. The assay is being commercialized primarily for use in drug development. The company MetaHeps is a spin-off of the University Hospital Munich (https://metaheps.com/). Samples collected through the Pro-EuroDILI Registry will be fully characterized with respect to new safety biomarkers, allowing validation of the MetaHeps assay on a wide set of clinical samples.		

Deliverable	WG2-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		
Progress with achieving deliverable	Not delivered, but expected before end of Action	Month deliverable due	21
Explanation	Members of the CA 17112 in collaboration with the University of Duke (Ayako Suzuki, IPC) and the NTRC (National Centre Toxicology Research) are exploring the role of host and drug factors in both the biochemical expression (type) of liver injury and the time to resolution of the liver injury. Two manuscripts have been drafted and will be submitted shortly.		

Deliverable	WG2-Written input to one or more commercial enterprises necessary for Future Market Exploitation of biomarkers		
Progress with achieving deliverable	Not delivered, but expected before end of Action	Month deliverable due	42
Explanation	A detailed beyond-state-of-art COST-DILI Action 'position paper' on preclinical human-based models for improved DILI prediction is underway. Addressing the basic sciences in tandem with both clinical and parallel Pharma, SMEs and academic consortia perspectives provides much needed cohesion and synergy in the DILI field and impetus for a constructive way forward. Addition to the COST-DILI network of major SMEs and LoI for safety biomarkers in DILI have been presented to Regulatory agencies. Extensive collaborations and reach in the Pharma and regulatory communities have been set up		

Deliverable	WG2- Scientific publication to summarize the current knowledge on 1) Drug properties		
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	associated with hepatotoxicity		
Progress with achieving deliverable	Not delivered, but expected before end of Action	Month deliverable due	48
Explanation	Using the prospective Spanish DILI Registry database and other prospective registries, members of the CA 17112 in collaboration with the University of Duke US (Ayako Suzuki, IPC) and the NTRC (National Centre Toxicology Research Centre, FDA) and Nottingham University (GP Aithal) aimed to evaluate the drug categorization system developed and based on published DILI cases in literature, making a critical appraisal of The LiverTox categorization of drug hepatotoxic potential. Categorization of drugs according to the documented evidence of DILI associated with individual drugs should use integrative information (frequency, severity and causality attribution), including data from established registries and databases.		

Deliverable	WG3- A review of current and potential in vitro and in silico models of hepatotoxicity		
Progress with achieving deliverable	Not delivered, but expected before end of Action	Month deliverable due	18
Explanation	A Review titled Realistic in vitro/in silico models in hepatotoxicity; non-invasive optical chemical imaging techniques, with the collaboration of all members at WG3 is underway. This consensus review article is an important Milestone for WG3. We propose to submit this manuscript to Nature Reviews Gastroenterology & Hepatology . Deliverable is near completion and expected before the end of 2020		

Deliverable	WG3- Identify and list the most appropriate control compounds for testing new in vitro models		
Progress with achieving deliverable	Not delivered, but expected before end of Action	Month deliverable due	42
Explanation	This activity is due 2022. Progress towards achieving this: Once the review is delivered the members of the WG3 in the next WGs meeting will address this issue and organize the most effective way to move forward.		

Deliverable	WG3- Define a roadmap for the development of in silico, in vitro and experimental models incorporating host determinants of DILI		
Progress with achieving deliverable	Not delivered, but expected before end of Action	Month deliverable due	48
Explanation	Due 2020. Progress towards achieving this: Once the review is delivered the members of the WG3 in the next WGs meeting will address this issue and organize the most effective way to move forward.		

Deliverable	WG4- To standardize procedures and remove bottlenecks at each participating centre that would facilitate the future conduct of a multicentre clinical trial in DILI		
Progress with achieving deliverable	Not delivered, but expected before end of Action	Month deliverable due	42
Explanation	This deliverable is expected right at the end of the cost action. Collaboration with eligible centres is ongoing in order to remove hurdles and pave the way to the achievement of these objectives		

Deliverable	WG4- A proposal for study design for risk or biomarker evaluation, pathway for		
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	evaluating of diagnostics and appropriate statistical methods		
Progress with achieving deliverable	Not delivered, but expected before end of Action	Month deliverable due	36
Explanation	One of the most important goals of the Pro-Euro-DILI registry study as a part of the Transbioline is to validate new biomarkers in DILI. There is a medical need for a biological marker of DILI that could distinguish DILI from other etiologies. It is conceivable that new data from the Transbioline study will emerge in 2021 which might help choosing the optimal biomarkers which should be included as a part of therapeutic clinical trial in DILI. This trial will include validation of new biomarkers for early diagnosis, mechanistics assessment and risk of progression of DILI.		

Deliverable	WG4- Design of clinical trials in DILI to assess the effect of an intervention on disease course or clinical outcomes		
Progress with achieving deliverable	Not delivered, but expected before end of Action	Month deliverable due	48
Explanation	Prerequisites for standardizations of procedures requires scrutinization the literature to find out the most common targets for pharmacotherapy that have previously been used for the treatment of DILI. The members of the WG 4 has divided the search for studies of drugs tried as a therapy for DILI. Firstly, a paper was written on Current management on DILI by Iceland & Turkey. Further studies on the use of corticosteroids, NAC, UDCA and novel therapies have been addressed by members from Iceland, Palermo-Italy, PhDs, Malaga-Spain, Bosnia&Herzegovina, Croatia and Romania.		

Deliverable	WG5-Set up a Website and social networks to translate scientific efforts into public dissemination and regulatory bodies		
Progress with achieving deliverable	Delivered	Month deliverable due	6
Proof of progress with achieving the deliverable	https://proeurodilinet.eu		

Deliverable	WG5- Write a Quality Plan and Good Practice Policies that apply to all COST partners		
Progress with achieving deliverable	Not delivered, but expected before end of Action	Month deliverable due	9
Explanation	This plan has not been delivered yet, however we follow the quality standards and Good Practice Policies that apply at each institution. Besides, we recommend to follow the Code of Conduct and applying the ENCePP guidelines in the conduct of drug safety studies. Systematic research reviews have been registered in the PROSPERO database. We plan to put a CA document together for members to sign and return, stipulating that they would act with honesty and integrity.		

Deliverable	WG5- Mid-term review of the COST Action proposal with the Management Committee (MC) to implement corrective measures		
Progress with achieving deliverable	Delivered	Month deliverable due	24
Proof of progress with achieving the deliverable	https://proeurodilinet.eu/wp-content/uploads/2020/11/CA17112_eMFA.PR_.2.OT_.1.pdf		

Deliverable	WG5- Preparation of large-scale European projects, searching topics of interest at		
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	H2020, 9 EU Framework Programme and other funding programmes		
Progress with achieving deliverable	Not delivered, but expected before end of Action	Month deliverable due	45
Explanation	We intend to discuss the preparation of large-scale European projects in the next Working Group meeting, to be held in Nottingham April 2021. We intend to identify topics of interest suitable for applying to the H2020, 9 EU Framework Programme, alongside other funding programmes and we will appoint those members who will take the lead of these strategies.		

Deliverable	WG5- Organise the Closing meeting and Final Report in which a roadmap to DILI research in Europe will be presented		
Progress with achieving deliverable	Not delivered, but expected before end of Action	Month deliverable due	48
Explanation	In the next Working Groups meeting (held in Nottingham April 2021), we intend to discuss strategy for delivering this activity and appoint individuals to lead our Road Map to DILI research in Europe. Activities performed by the WGs through the first half of the project have already started identifying and strategizing a roadmap to DILI research, but this work will formally be commenced at the next WGs meeting in Nottingham, April 2021. The works that were done by the WGs throughout the first half of the project has already laid down the principles of the roadmap to DILI research.		

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Additional outputs / achievements

Co-authored Action publications

Please enter below ONLY publications (including publications that are submitted but not yet accepted):

- that are on the topic of the Action, and
- that are co-authored by at least two Action participants from two countries participating in the Action, and
- for which the Action networking was necessary.

Please pay special attention to representatives of Inclusiveness Target Countries (ITCs) in each publication. If there are more than 20 publications you *may* choose to enter only the most 20 significant (in terms of Inclusiveness, Excellence and the MoU Objectives).

	Bibliographic data	Countries participating in the Action among authors	Open Access	COST cited?	COST funds?	Relevance to H2020 Societal challenge	Peer Reviewed?
1	<p>doi:10.1016/j.jhep.2019.02.014</p> <p>Title EASL Clinical Practice Guidelines: Drug-induced liver injury</p> <p>Authors Raúl J. Andrade; Guruprasad P. Aithal; Einar S. Björnsson; Neil Kaplowitz; Gerd A. Kullak-Ublick; Dominique Larrey; Tom H. Karlsen</p> <p>DOI doi:10.1016/j.jhep.2019.02.014</p> <p>Type Journal article</p> <p>Published in Journal of Hepatology</p> <p>Published by Elsevier BV</p> <p>ISSN 0168-8278</p> <p>Subject Hepatology</p> <p>Links https://api.elsevier.com/content/article/PII:S0168827819301291?httpAccept=text/xml; https://api.elsevier.com/content/article/PII:S0168827819301291?httpAccept=text/plain</p>	FR, IS, ES, SE, CH, UK	Y	Y	N	Health, demographic change and wellbeing	Y
2	<p>doi:10.1053/j.gastro.2019.02.002</p> <p>Title Incidence and Etiology of Drug-Induced Liver Injury in Mainland China</p>	ES, UK	Y	N	N	Health, demographic change and wellbeing	Y

	<p>Authors</p> <p>DOI</p> <p>Type</p> <p>Published in</p> <p>Published by</p> <p>ISSN</p> <p>Subject</p> <p>Links</p>	<p>Tao Shen; Yingxia Liu; Jia Shang; Qing Xie; Jun Li; Ming Yan; Jianming Xu; Junqi Niu; Jiajun Liu; Paul B. Watkins; Guruprasad P. Aithal; Raúl J. Andrade; Xiaoguang Dou; Lvfang Yao; Fangfang Lv; Qi Wang; Yongguo Li; Xinmin Zhou; Yuexin Zhang; Peilan Zong; Bin Wan; Zhengsheng Zou; Dongliang Yang; Yuqiang Nie; Dongliang Li; Yuya Wang; Xi'an Han; Hui Zhuang; Yimin Mao; Chengwei Chen</p> <p>doi:10.1053/j.gastro.2019.02.002</p> <p>Journal article</p> <p>Gastroenterology</p> <p>Elsevier BV</p> <p>0016-5085</p> <p>Gastroenterology</p> <p>https://api.elsevier.com/content/article/PII:S0016508519303646?httpAccept=text/xml;</p> <p>https://api.elsevier.com/content/article/PII:S0016508519303646?httpAccept=text/plain</p>						
3	<p>doi:10.1038/s41572-019-0105-0</p> <p>Title</p> <p>Authors</p> <p>DOI</p> <p>Type</p> <p>Published in</p> <p>Published by</p> <p>ISSN</p> <p>Links</p>	<p>Drug-induced liver injury</p> <p>Raul J. Andrade; Naga Chalasani; Einar S. Björnsson; Ayako Suzuki; Gerd A. Kullak-Ublick; Paul B. Watkins; Harshad Devarbhavi; Michael Merz; M. Isabel Lucena; Neil Kaplowitz; Guruprasad P. Aithal</p> <p>doi:10.1038/s41572-019-0105-0</p> <p>Journal article</p> <p>Nature Reviews Disease Primers</p> <p>Springer Science and Business Media LLC</p> <p>2056-676X</p> <p>http://www.nature.com/articles/s41572-019-0105-0.pdf;</p> <p>http://www.nature.com/articles/s41572-019-0105-0</p>	IS, ES, CH, UK	Y	Y	N	Health, demographic change and wellbeing	Y

4	<p>doi:10.2174/1381612825666191107161912</p> <p>Title Drug-Induced liver Injury Associated with Severe Cutaneous Hypersensitivity Reactions: A Complex Entity in Need of a Multidisciplinary Approach</p> <p>Authors Judith Sanabria-Cabrera; Inmaculada Medina-Cáliz; Simona Stankevičiūtė; Antonio Rodríguez-Nicolás; Marina Almarza-Torres; M. Isabel Lucena; Raúl J. Andrade</p> <p>DOI doi:10.2174/1381612825666191107161912</p> <p>Type Journal article</p> <p>Published in Current Pharmaceutical Design</p> <p>Published by Bentham Science Publishers Ltd.</p> <p>ISSN 1381-6128</p> <p>Subjects Pharmacology; Drug Discovery</p> <p>Link http://eurekaselect.com/article/download/176495</p>	LT, ES	N	Y	N	Health, demographic change and wellbeing	Y
5	<p>Drug-induced liver injury (DILI): Current status and future directions for drug development and the post-market setting.</p> <p>A consensus by a CIOMS Working Group Council for International Organizations of Medical Sciences (CIOMS)</p> <p>ISBN: 978-929036099-5</p> <p>Year of publication: 2020</p> <p>The report was produced by leading DILI experts from drug regulation, industry and research globally. DILI is a growing challenge because of the ever-increasing number of products used in medical care. DILI is rare but can be serious and is largely unpredictable. The CIOMS consensus report provides a critical framework and essential set of tools to detect, diagnose and manage DILI during drug</p>	EE, FR, DE, IS, IL, ES, CH, UK	Y	N	N	Health, demographic change and wellbeing	N

	<p>development and post-marketing.</p> <p>Several number of COST Action 17-112 PRO-EURO DILI NETWORK members contributed to it.</p> <p>The report in PDF format is freely available here: https://cioms.ch/wp-content/uploads/2020/06/CIOMS_DILI_Web_16Jun2020.pdf</p> <p>978-929036099-5</p>							
6	<p>doi:10.1002/cpt.1493</p> <p>Title</p> <p>Authors</p> <p>DOI</p> <p>Type</p> <p>Published in</p> <p>Published by</p> <p>ISSNs</p> <p>Subjects</p> <p>Links</p>	<p>Shared Genetic Risk Factors Across Carbamazepine-Induced Hypersensitivity Reactions</p> <p>Paola Nicoletti; Sarah Barrett; Laurence McEvoy; Ann K. Daly; Guruprasad Aithal; M. Isabel Lucena; Raul J. Andrade; Mia Wadelius; Pär Hallberg; Camilla Stephens; Einar S. Bjornsson; Peter Friedmann; Kati Kainu; Tarja Laitinen; Anthony Marson; Mariam Molokhia; Elizabeth Phillips; Werner Pichler; Antonino Romano; Neil Shear; Graeme Sills; Luciana K. Tanno; Ashley Swale; Aris Floratos; Yufeng Shen; Matthew R. Nelson; Paul B. Watkins; Mark J. Daly; Andrew P. Morris; Ana Alfirevic; Munir Pirmohamed</p> <p>doi:10.1002/cpt.1493</p> <p>Journal article</p> <p>Clinical Pharmacology & Therapeutics</p> <p>Wiley</p> <p>0009-9236; 1532-6535</p> <p>Pharmacology (medical); Pharmacology</p> <p>https://api.wiley.com/onlinelibrary/tdm/v1/articles/10.1002%2Fcpt.1493;</p> <p>https://onlinelibrary.wiley.com/doi/pdf/10.1002/cpt.1493;</p> <p>https://onlinelibrary.wiley.com/doi/full-xml/10.1002/cpt.1493</p>	IS, ES, UK	Y	N	N	Health, demographic change and wellbeing	Y

7	<p>doi:10.1111/liv.13952</p> <p>Title</p> <p>Authors</p> <p>DOI</p> <p>Type</p> <p>Published in</p> <p>Published by</p> <p>ISSNs</p> <p>Subject</p> <p>Links</p>	<p>The influence of drug properties and host factors on delayed onset of symptoms in drug-induced liver injury</p> <p>Andres Gonzalez Jimenez; Kristin McEuen; Minjun Chen; Ayako Suzuki; Mercedes Robles Diaz; Inmaculada Medina Caliz; Fernando Bessone; Nelia Hernandez; Marco Arrese; Raymundo Parana; M. Isabel Lucena; Camilla Stephens; Raúl J. Andrade</p> <p>doi:10.1111/liv.13952</p> <p>Journal article</p> <p>Liver International</p> <p>Wiley</p> <p>1478-3223; 1478-3231</p> <p>Hepatology</p> <p>https://api.wiley.com/onlinelibrary/tdm/v1/articles/10.1111%2Fliv.13952;</p> <p>https://onlinelibrary.wiley.com/doi/pdf/10.1111/liv.13952;</p> <p>https://onlinelibrary.wiley.com/doi/full-xml/10.1111/liv.13952</p>		Other	Y	Y		Y
8	<p>doi:10.1002/hep.29802</p> <p>Title</p> <p>Authors</p> <p>DOI</p> <p>Type</p>	<p>Candidate biomarkers for the diagnosis and prognosis of drug-induced liver injury: An international collaborative effort</p> <p>Rachel J. Church; Gerd A. Kullak-Ublick; Jiri Aubrecht; Herbert L. Bonkovsky; Naga Chalasani; Robert J. Fontana; Jens C. Goepfert; Frances Hackman; Nicholas M. P. King; Simon Kirby; Patrick Kirby; John Marcinko; Sif Ormarsdottir; Shelli J. Schomaker; Ina Schuppe Koistinen; Francis Wolenski; Nadir Arber; Michael Merz; John Michael Sauer; Raul J. Andrade; Florian van Bömmel; Thierry Poynard; Paul B. Watkins</p> <p>doi:10.1002/hep.29802</p> <p>Journal article</p>	ES, CH	Y	N	N	Health, demographic change and wellbeing	Y

		<p>]; https://api.elsevier.com/content/article/PII:S0016508519300940?httpAccept=text/plain</p>						
10	<p>doi:10.1002/cpt.1375 Title Authors DOI Type Published in Published by ISSNs Subjects Links</p>	<p>Drug-induced Liver Injury due to Flucloxacillin: Relevance of Multiple Human Leukocyte Antigen Alleles Paola Nicoletti; Guruprasad P. Aithal; Thomas C. Chamberlain; Sally Coulthard; Mohammad Alshabeeb; Jane I. Grove; Raul J. Andrade; Einar Bjornsson; John F. Dillon; Par Hallberg; M. Isabel Lucena; Anke H. Maitland-van der Zee; Jennifer H. Martin; Mariam Molokhia; Munir Pirmohamed; Mia Wadelius; Yufeng Shen; Matthew R. Nelson; Ann K. Daly doi:10.1002/cpt.1375 Journal article Clinical Pharmacology & Therapeutics Wiley 0009-9236; 1532-6535 Pharmacology (medical); Pharmacology https://api.wiley.com/onlinelibrary/tdm/v1/articles/10.1002/cpt.1375; https://onlinelibrary.wiley.com/doi/pdf/10.1002/cpt.1375; https://onlinelibrary.wiley.com/doi/full-text/10.1002/cpt.1375</p>	IS, ES, UK	N	N	N	Health, demographic change and wellbeing	Y
11	<p>doi:10.1016/j.jhep.2019.08.008 Title Authors DOI Type Published in</p>	<p>EASL Clinical Practice Guideline: Occupational liver diseases Massimo Colombo; Carlo La Vecchia; Marcello Lotti; M. Isabel Lucena; Christophe Stove; Valérie Paradis; Philip Newsome doi:10.1016/j.jhep.2019.08.008 Journal article Journal of Hepatology</p>	FR, IT, ES	Y	Y	N	Health, demographic change and wellbeing	Y

	<p>Published by Elsevier BV ISSN 0168-8278 Subject Hepatology Links https://api.elsevier.com/content/article/PII:S016882781930474X?httpAccept=text/xml; https://api.elsevier.com/content/article/PII:S016882781930474X?httpAccept=text/plain</p>						
12	<p>Hao Niu, Judith Sanabria-Cabrera, Ismael Alvarez-Alvarez, Mercedes Robles-Diaz, Simona Stankevičiūtė, Guruprasad P Aithal, Einar S Björnsson, Raul J Andrade, M Isabel Lucena. Systematic review with meta-analysis: prevention and management of drug-induced liver injury in randomised clinical trials</p> <p>Sent to Pharmacological Research.</p> <p>ECIs: Judith Sanabria-Cabrera, Ismael Alvarez-Alvarez, Simona Stankevičiūtė, Hao Niu.</p>	IS, LT, ES, UK	Y	Y	Y	Health, demographic change and wellbeing	Y
13	<p>E.Atallah, C.Freixo, I.Alvarez, F.J Cubero, G.P.Aithal. Biomarkers for drug-induced liver injury (DILI). Clinical Pharmacology & Therapeutics.</p> <p>ECIs: E.Atallah, C.Freixo, I.Alvarez.</p> <p>It is a deliverable of the TransBioline Consortium. Expected to publish.</p>	PT, ES, UK	N	Y	N	Health, demographic change and wellbeing	Y
14	<p>Rianne A. Weersink, Ismael Alvarez-Alvarez, Inmaculada Medina-Cáliz, Judith Sanabria-Cabrera, Mercedes Robles-Díaz, Aida Ortega-Alonso, Miren García-Cortés, Elvira Bonilla, Hao Niu, German Soriano, Miguel Jimenez-Perez, Hacibe</p>	NL, ES	Y	Y	N	Health, demographic change and wellbeing	Y

	<p>Hallal, Sonia Blanco, Neil Kaplowitz, M Isabel Lucena, Raúl J. Andrade. Clinical characteristics and outcome of drug-induced liver injury in the older patients: from the young-old to the oldest-old. <i>Clinical Gastroenterology and Hepatology</i> 2020. IN PRESS</p> <p>ECIs: Rianne A. Weersink, Ismael Alvarez-Alvarez, Judith Sanabria-Cabrera, Hao Niu.</p>						
15	<p>doi:10.3390/ijms21051651</p> <p>Title Reclassifying Hepatic Cell Death during Liver Damage: Ferroptosis—A Novel Form of Non-Apoptotic Cell Death?</p> <p>Authors Ricardo U. Macías-Rodríguez; María Eugenia Inzaugarat; Astrid Ruiz-Margáin; Leonard J. Nelson; Christian Trautwein; Francisco Javier Cubero</p> <p>DOI doi:10.3390/ijms21051651</p> <p>Type Journal article</p> <p>Published in International Journal of Molecular Sciences</p> <p>Published by MDPI AG</p> <p>ISSN 1422-0067</p> <p>Subjects Physical and Theoretical Chemistry; Inorganic Chemistry; Organic Chemistry; Spectroscopy; Molecular Biology; Catalysis; General Medicine; Computer Science Applications</p> <p>Link https://www.mdpi.com/1422-0067/21/5/1651/pdf</p>	DE, ES, UK	Y	Y	N	Health, demographic change and wellbeing	Y
16	<p>Nuria López-Alcántara, Laura Morán, Marina Villanueva, Cristiana Freixo, Raúl J. Andrade, M. Isabel Lucena, Francisco Javier Cubero.</p>	PT, ES	N	Y	N	Health, demographic change and wellbeing	Y

Idiosyncratic drug-induced liver injury (DILI): Status quo and future challenges					
Biomedicine and Pharmacotherapy (Q1: 32/139) IN PRESS					

Projects resulting from Action activities

Please enter below all the projects on the topic of the Action resulting from Action activities, involving at least one Action participant, and for which the Action networking was necessary.

The Action reported 1 project(s) and 0 proposal(s) resulting from the Action networking.

Key details of the projects are shown below.

#	Title	Countries participating in the Action among proposers	Main proposer name	Funder	Amount	Call identifier	Relevance to H2020 Societal Challenge
1	IMI2- Translational Safety Biomarker Pipeline (TransBioLine): Enabling development and implementation of novel safety biomarkers in clinical trials and diagnosis of disease.	DE, IS, ES, CH, UK	Raúl J. Andrade	H2020	27906492 €	H2020-JTI-IMI2-2017	Health, demographic change and wellbeing

Other outputs / achievements

Please enter below any additional outputs/ achievements on the topic of the Action that contribute to the COST mission: "COST enables break-through scientific developments leading to new concepts and products and thereby contributes to strengthen Europe's research and innovation capacities", and for which the Action networking was necessary (e.g. a patent, standards, white paper).

Output / achievement description	Dependence of achievement on the Action networking
Publications with International Partner Countries (USA, LATIN AMERICAN COUNTRIES): <ul style="list-style-type: none"> • BESSONE F, ROBLES-DIAZ M, HERNANDEZ N, MEDINA-CALIZ I, LUCENA MI, ANDRADE RJ. Review. Assessment of Serious 	High

[Acute and Chronic Idiosyncratic Drug-Induced Liver Injury in Clinical Practice](#). Semin Liver Dis. 2019, 39(3):381-394. doi: 10.1055/s-0039-1685519.

- **GONZALEZ-JIMENEZ A**, MCEUEN K, CHEN M, **SUZUKI A**, **ROBLES-DIAZ M**, **MEDINA-CALIZ I**, BESSONE F, **HERNANDEZ N**, **ARRESE M**, PARANA R, **LUCENA MI**, **STEPHENS C**, **ANDRADE RJ**. [The influence of drug properties and host factors on delayed onset of symptoms in Drug-Induced Liver Injury](#). Liver Int. 2019; 39(2):401-410. doi: 10.1111/liv.13952
- ZOUBEK ME, **GONZÁLEZ-JIMENEZ A**, **MEDINA-CÁLIZ I**, **ROBLES-DÍAZ M**, **HERNANDEZ N**, ROMERO-GÓMEZ M, BESSONE F, HALLAL H, **CUBERO FJ**, **LUCENA MI**, **STEPHENS C**, **ANDRADE RJ**. [High Prevalence of Ibuprofen Drug-Induced Liver Injury in Spanish and Latin-American Registries](#). Clin Gastroenterol Hepatol. 2018; 16 (2):292-294. doi: 10.1016/j.cgh.2017.07.037
- Fernando Bessone; **Miren Garcia-Cortes**; **Inmaculada Medina-Caliz**; **Nelia Hernandez**; Raymundo Parana; Manuel Mendizabal; Maria Isabel Schinoni; Ezequiel Ridruejo; Vinicius Nunes; Mirta Peralta; Genario Santos; Margarita Anders; Daniela Chiodi; Martin Tagle; Pedro Montes; Enrique Carrera; **Marco Arrese**; **Maria Isabel Lizarzabal**; **Ismael Alvarez-Alvarez**; **Estefania Caballano-Infantes**; **Hao Niu**; Jose Pinazo. Herbal And Dietary Supplements-Induced Liver Injury In Latin America: Experience From The Latindili Network. Sent to *Clinical Gastroenterology and Hepatology*.
- F.BESSONE, **N. HERNANDEZ**, M.MENDIZABAL, E.RIDRUEJO, G.GUALANO, E.FASSIO, M.PERALTA, H.FAINBOIM, M.ANDERS, H.TANNO, F.TANNO1, R.PARANA, **I.MEDINA-CALIZ**, **M.ROBLES-DIAZ**, **I. ALVAREZ-ALVAREZ**, **H. NIU**, **C.STEPHENS**, L.COLOMBATO, **M. ARRESE**, MV.REGGIARDO, S. KIOKO ONO, F.CARRILHO, **MI LUCENA**, **RJ ANDRADE**. Serious liver injury induced by Nimesulide: an international collaboration study reporting 57 cases. Sent to *Alimentary Pharmacology & Therapeutics*.

An outstanding collaboration between Japan & UK. which highlight that in DILI discovery science will be patient-base and apply science to cell-culture in the laboratory.

High

MASARU KOIDO, ERI KAWAKAMI, JUNKO FUKUMURA, YUI NOGUCHI, MOMOKO OHORI, YASUNORI NIO, PAOLA NICOLETTI, **GURUPRASAD P. AITHAL**, **ANN K. DALY**, PAUL B. WATKINS, HISASHI ANAYAMA, YVONNE DRAGAN, TADAHIRO SHINOZAWA AND TAKANORI TAKEBE.

[Polygenic Architecture Informs Potential Vulnerability To Drug-Induced Liver Injury](#). *Nature Medicine*, 26,541–1548(2020). doi: 10.1038/s41591-020-1023-0. IF 2019: 36.130 (D1: 1/139)

Drug-induced liver injury (DILI): Current status and future directions for drug development and the post-market setting.

High

A consensus by a CIOMS Working Group Council for International Organizations of Medical Sciences (CIOMS)

ISBN: 978-929036099-5. Year of publication: 2020

The report was produced by leading DILI experts from drug regulation, industry and research globally. DILI is a growing challenge because of

the ever-increasing number of products used in medical care. DILI is rare but can be serious and is largely unpredictable. The CIOMS consensus report provides a critical framework and essential set of tools to detect, diagnose and manage DILI during drug development and post-marketing.

Several number of COST Action 17-112 PRO-EURO DILI NETWORK members contributed to it.

The report in PDF format is freely available here: https://cioms.ch/wp-content/uploads/2020/06/CIOMS_DILI_Web_16Jun2020.pdf

DRAFT

Impacts

Please describe the impacts (the short- to long-term scientific, technological, and / or socioeconomic changes produced by a COST Action, directly or indirectly, intended or unintended) that have resulted, or might result, from the Action in the following table (one impact per line).

Description of the impact, i.e. what will change, and for whom, as a result of what the Action achieved	Type of impact	Timing of impact
<p>Coordination and standardization of processes: a structure protocol for data collection when suspicion of DILI cases, and approaches: a common database across Europe that will improve the quality and consistency of research outputs that will enable accelerating research activities as the partnership within TransBioLine IMI project for the development of novel safety biomarkers that will facilitate a precision medicine.</p> <p>This CA has contributed to the establishment and structuring of new interdisciplinary research fields</p>	<ul style="list-style-type: none"> • Scientific / Technological • Societal 	Achieved
<p>A European Clinical Practice Guidelines on DILI has been published which raises public awareness of this disorder by physicians and empower them to make an accurate diagnosis, early identification of DILI and a better approach to identification of risk factors and management.</p> <p>Building inter-institutional collaboration</p>	<ul style="list-style-type: none"> • Scientific / Technological 	Achieved
<p>Joint research undertaking, and a large number of publications. The networking activities have stimulated a high number of follow-up proposals for further research projects. These activities certainly contribute to the reputation building of the participating researchers and institutions.</p>	<ul style="list-style-type: none"> • Scientific / Technological • Societal 	Achieved
<p>Support and partnership to translate breakthrough ideas into tangible impact; Help ECIs to grow professionally and Create learning opportunities and exchange of knowledge and all these achievements are reached with a limited funding budget</p>	<ul style="list-style-type: none"> • Scientific / Technological 	Achieved
<p>We have established links with EMA that has created a new 'Collaborating Expert Programme', which may be of interest to CA 17112's academic members, particularly PhD students. It is a guest programme where EMA welcome researchers into the Agency to perform research in regulatory science topics of public health interest. it is intended to provide an opportunity for the researchers to gain first-hand experience in a scientific EU Agency and develop new competencies.</p>	<ul style="list-style-type: none"> • Scientific / Technological 	Foreseen within two years of the end of the Action

Please describe how the Action is advancing the careers, skills and network of researchers, including ECIs (for example: joint supervision of graduate and PhD students, research exchanges not funded by the Action, collaborations, Training Schools with ECTS accreditation, joint projects and jobs prospects).

Mentorship of Simona Stankevičiūtė (Lithuanian University of Health Sciences, ITC) for a period of 3 months (01.03.2019-30.04.2019) in the Spanish DILI Registry group (University of Malaga). And of Rianne Weersink (University of Groningen, The Netherlands) (Oct 2019-Dec2019). Several synergistic outcomes resulted from this research exchange. Joint publications have followed and collaborative project is being discussed. Project funding and grants are being sought to concretize this collaboration. These collaborations have enabled these students to join the CA and assume responsibilities. Other collaborative projects as a Doctoral Thesis in co-tutela is ongoing. Training Schools Participation in the training schools was highly productive – accomplishing the main objectives defined for the PRO-EURO-DILI-NET Cost Action, namely a bi-directional exchange of knowledge. All these activities (& STSMs) included appropriate mentoring and pastoral support for the students and ECIs. 23 Trainees reimbursed: 43% from ITC countries; 70% Women; 85% ECI. ECIs feedback concerning the quality and benefit achieved by these activities

and their suggestions have been adopted for future activities. STSMs have enabled further exchange of knowledge between laboratories as well as a collaboration in their respective areas of research in DILI. Besides, several synergistic outcomes resulted from the STSM. Further students' exchanges between the laboratories are envisioned and the setting up of collaborative projects which are being discussed. Project funding and grants are being sought to concretize the collaborations. These STSMs have built up trust within research cooperation. ITC scientists have been involved in these missions which have led to Collaborative research papers. Undoubtedly, the links established even to ITCs have been strengthened and we think they will be long-lasting. This guarantee the sustainability of the networking impact.

The career benefits are mainly to researchers with the following amount of experience after their PhD: ≤ 8 years.

Which of the stakeholders described in the “Plan for involving the most relevant stakeholders” in the Action’s MoU have been engaged and how? What additional stakeholders have been, or will be, engaged and how?

Addition to the COST-DILI network of major SMEs, Biopredic International, Rennes, France, involved in hepatic models/ reagents/ products for DILI and the world licensing holder for the human HepaRG cell line; and have extensive collaborations and reach in the Pharma and regulatory communities. Astra-Zeneca and DestiNA Genomics, Edinburg & Granada, Spain. With this SMEs we have presented a EUROSTAR application project 2020. Participation in the TransBioLine IMI project for the qualification of safety biomarkers in clinical drug development and postmarketing. The setting up of meetings with other International Societies (EASL, AASLD, EUROTOX, Slovak Society of Hepatology) that bring together all relevant stakeholders: Academia, Pharmaceutical Industry, SMEs, and Regulatory agencies to integrate efforts within this cross-disciplinary platform. We have established links with EMA for PhD students exchange. Another international consortium that has been reached out is the International Autoimmune Hepatitis Group. Involved in the CIOMS Working Group on DILI (international collaboration with Academia, Pharma and Regulatory agencies), after a work on this OPUS over a 3-year period has recently published an updated Guidance. To guarantee the involvement of patients we have contacted and organized activities in collaboration with EASL (European Association for the Study of the Liver) and ELPA (European Liver Patients Association).

Dissemination and exploitation of Action results (other than co-authored Action publications listed previously)

Please describe the Action's dissemination and exploitation approach as well as all activities undertaken to ensure dissemination and exploitation of the Action results and the effectiveness of these activities.

Dissemination and exploitation approach of the Action

To ensure dissemination and exploitation of Action results and the effectiveness of these activities this following poster will be presented by Raúl J. Andrade at the Liver Meeting Digital Experience next 23-25th November 2020. A collaboration of CA 17112 with the Interactive Safety Graphics Taskforce of the DIA-ASA Biopharma Working Group (USA) has been setup. The aim of this project is by using the Spanish DILI Registry database to develop and validate an open-source tool for identifying and investigating signals of hepatotoxicity during clinical development.
https://uma365-my.sharepoint.com/:b:/g/personal/lucena_uma_es/EXkTOg_gdA5Mgm1tOWALEUEBzdwwrwmSuyAgTuS6OanKSw?e=Yx8m7X

Dissemination

Dissemination meetings funded by the Action

Title of Dissemination meeting	Meeting date	Meeting country	Action participant	Event name and hyperlink to the website	Title of presentation	Description of added value to the Action
N/A						

Other dissemination activities

E.g. participation to non-Action meetings, e.g. EU Parliament, meetings with policy makers, experts in the field, regional authorities.

Item/activity	Target audience	Outcome	Hyperlink
Dissemination Meetings: Ann Daly (European DILI Consortium and Newcastle University, UK) appointed by the COST-ACTION CA-17112 as a speaker in the 23rd Symposium on Microsomes and Drug Oxidations. Prague, 30 Aug-03 Sept 2020 in representation of the Pro-Euro DILI network. Title: "Pharmacogenomics in Mechanisms of Idiosyncratic DILI in Man"	Academic and Research communities, clinicians and healthcare professionals. Early carrier investigators in the field of Microsomes and Drug oxidations. Liver Networks on Drug metabolism.	To disseminate the aim and objectives of the Pro-Euro DILI Network, its scientific and technological activities at European level and the main networking activities at this international conference. The potential to reach out this important society which will allow to establish new collaborations that will contribute positively to the network quality and the improvement of knowledge.	https://mdoprague2021.cz/speakers/

<p>in the session "Metabolizing enzymes in drug-induced toxicity" Re-scheduled due to COVID-19. September 5 - 9, 2021</p>			
<p>An important scientific and educational activity has been developed with CIOMS (Council of International Organizations of Medical Sciences), which is under the umbrella of WHO-UNESCO (https://cioms.ch/working-groups/dili/) and produced an International White Consensus Paper on Drug-Induced Liver Injury (DILI): Current status and future directions for drug development and the postmarketing setting. The Chair and Vice chair of this CA-17112 appointed by EASL (European Association for the Study of the Liver) have elaborated a Clinical Practice Guidelines on DILI for the translation of knowledge gained in DILI to improve decision making and clinical outcomes. Reference to the CA-17112 activities were given at the following CIOMS WG DILI meetings that was attended by 3rd CIOMS Working Group meeting held on 8–9 May 2018 in Reykjavík, Iceland 4th CIOMS Working Group meeting held on 27–28 November 2018 in Aix-en-Provence, France 5th CIOMS Working Group meeting held on 15–16 May 2019 in Tallinn, Estonia</p>	<p>Academic & research communities. All key stakeholders: regulators, industry and practising physicians. Thus, the CIOMS Meeting will need to have a broad scope in order to be useful to regulatory agencies, clinicians & pharmaceutical industry. CA-17112 members were involved in this working group meeting. Regulators (U.S. FDA; EMA, BfArM Germany; PMDA Japan; ANVISA Brazil; SAHPRA / Medicines Control Council South Africa; Teikyo University, consultant of MHLW, Japan; MPA Sweden Academia (University of Nottingham, United Kingdom; University of Málaga, Spain; National University of Iceland; International Union of Basic and Clinical Pharmacology (IUPHAR); University Hospital Zurich, Switzerland Industry (Eisai, Novartis, Takeda, Sanofi, MSD, Fibrogen, Bayer Consortia (C-Path Predictive Safety Testing Consortium)</p>	<p>The results of the COST action were disseminated at these international conferences. During the 3rd CIOMS WG meeting on DILI (2018, Iceland), a brief description was provided about what this COST Action is about, its mission and strategy, policies and tools. During the 4th CIOMS WG meeting (2018, France), Raul J Andrade presented an update from the Pro-Euro DILI Network, which he is chairing with Guruprasad Aithal as Vice-Chair. This multidisciplinary network of experts is part of the European Cooperation in Science and Technology (COST). Its aims are to pre-empt and prevent DILI, to improve clinical care and outcomes, and to foster translational research, public awareness and education. Current working group topics are: phenotyping in DILI, risk stratification, preclinical evaluation, clinical trial and investigation design, and dissemination/communication. During the 5th CIOMS WG meeting (May 2019, Estonia), Raul J Andrade presented an update from the Pro-Euro DILI Network. This network, which has five Working Groups, does not conduct its own research, instead it provides a platform for scientific and technical cooperation. The 1st WG Groups, 2nd CG & MC meetings and the 1st Training Course in Malaga on 14-15 March 2019 were announced.</p>	<p>https://cioms.ch/working-groups/dili</p>
<p>1st Working Groups Meeting, 2nd Core Group & Management Committee Meeting. Málaga, 14-15 March 2019. Attended by 70 members of the CA-17112 and 25 countries including USA (Dr Ayako Suzuki)</p>	<p>Academic and Research communities, clinicians and healthcare professionals, patients and public health organizations, general public, pharmaceutical and biotechnology companies, in addition to</p>	<p>It allowed members of the Working Group to get to know each other, to share the different point of view and advance the tasks and deliverables and consider future perspectives. The possibility to combine</p>	<p>https://proeurodilinet.eu/wp-content/uploads/2018/11/COST-press-release.pdf</p>

<p>and China (Yimin Mao).</p>	<p>national and European regulatory bodies and policy makers. ECIs & 6th years medicine students.</p>	<p>this WG meeting foster the interdisciplinarity and scientific changes. Press release: To disseminate the COST ACTION Meeting organized in Malaga through the medias. This is the first COST international activity organized in Drug-Induced Liver Injury (DILI) being led by Prof. Raul J. Andrade who is full professor of Medicine in this University. To increase our understanding on DILI disorder and to make interactions between researchers from different background to be able to build up future collaborations of this intriguing disorder which have important consequences in Public Health.</p>	
<p>American Association for the Study of the Liver (AASLD) Special Interest Group (SIG) Hepatotoxicity Group. Raúl J. Andrade: member of the steering committee.</p>	<p>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.</p>	<p>To Disseminate the results of the Pro-Euro DILI Network. To promote research and education to the clinicians and researchers. To design an educational program to advance knowledges for the understanding of mechanisms underline DILI.</p>	<p>https://www.aasld.org/membership/member-resources/special-interest-groups/hepatotoxicity</p>
<p>DILI CA-17112 meeting @ EASL Digital ILC 2020. 29th August 2020. 09:30-11:10 am Pro-Euro DILI Net COST-ACTION DILI MEETING. This virtual meeting was held within the EASL Digital ILC 2020. It was focused on updating important gap of knowledge in this CA. Lecture: Marko Korenjak, President of the European Liver Patient Association (ELPA); Teresa Casanovas, President of the ASSCAT - Spanish liver patient organization, Barcelona Collaboration with ELPA: the relevance of a patient perspective in DILI Lecture: Prof. Diego Vergani, Prof. Giorgina Vergani, UK The International Autoimmune Hepatitis Group (IAIHG): opportunities for mutual collaboration Lecture: Prof. Dr. Çigdem Arikan, Turkey DILI in Pediatric population</p>	<p>Pro-Euro DILI Network's stakeholders researchers, clinicians and academics. Patients society.</p>	<p>NEW SCENARIOS OF COLLABORATIONS HAVE BEEN OPENED AND AGREED ON BOTH SIDES: Collaboration with ELPA; The International Autoimmune Hepatitis Group (IAIHG): opportunities for mutual collaboration; the setting-up a working group on pediatrics. ANNOUNCEMENTS: Next WG meeting in Montpellier (France), hosted by Dr. Dominique Larrey In December 2020. Probably virtual. Monothematic conference on DILI along the EUROTOX meeting. September 26-28, 2021. Next WGs meeting in Vilnius (Lithuania). Pending to fix a new date. Next MC meeting to be held in Nottingham (UK) in January 2021.</p>	<p>https://proeurodilinet.eu/dili-ca-17112-meeting-easl-2020-london-17th-april-2020</p>

<p>Prof. Raul Andrade. University of Malaga/UMA- Spain. Speaker @1st Core Group Meeting Lisbon 9 January 2019. Portugal. DRUG-INDUCED LIVER INJURY – When to suspect? How to confirm?</p>	<p>Researchers, clinicians and academics. Medical staff of the University Hospital Santa María, Lisboa & CA-17112 members.</p>	<p>To Disseminate the results of the CA-17112 group. This lecture allowed Clinical pharmacology physician to become a member of this CA (Cristina Freixo, ECIs).</p>	<p>https://proeurodilinet.eu/1st-core-group-meeting-ca17112-lisboa-09-january-2019</p>
<p>XiX Hepatology Meeting, Malaga 08-09 October 2020. Organizer & Chair: Raúl J. Andrade. Lecture: Clinical trials in drug-induced liver injury. VIRTUAL Einar S Björnsson (Landspítali, The National University Hospital of Iceland. Iceland). Leader of the CA-17112. WG4: in Dili Clinical Trials for the Design & establishing meaningful endpoints in clinical DILI investigations This meeting brings together well-known international experts in hepatology from Spain and also outstanding European speakers .</p>	<p>Academic and Research communities, clinicians and healthcare professionals, patients and public health organizations, general public, pharmaceutical and biotechnology companies, in addition to national and University hospital of Malaga.</p>	<p>There is a medical need to treat patients with symptomatic and biochemically advanced DILI in order to improve their prognosis. International consensus of clinical trials in DILI is necessary and the speaker mentioned the different approaches followed at the CA17112 Working Group 4 in Dili Clinical Trials for the Design & establishing meaningful endpoints in clinical DILI investigations A Systematic review with meta-analysis: prevention and management of drug-induced liver injury and non-acetaminophen acute liver failure in randomised clinical trials has been done.</p>	<p>https://www.jornadasavancehepatologia.u.ma.es</p>
<p>WEBSITE & SOCIAL MEDIAS The website was created in 2018 and it is composed of 6 tabs: About us, Members, Events, Working groups, Documents, News as well as a direct link to the Social medias (Twitter, LinkedIn) There is also an exclusive section for the members of the CA-17112. They can access to the content through a password.</p>	<p>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.</p>	<p>The website ensures a 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). It also includes a section with all the dissemination activities done (newsletters, scientific publications...). The social media platforms serve as a tool to provide wider outreach. In every Twitter post, if it is relevant, we provide a link to our website, and we tag relevant people, so that their followers can also see the message. So far, the “Prospective European Drug-Induced Liver Injury Net” has 36 tweets and 66 followers. The LinkedIn platform ensures the possibility to share more content, we post more pictures and longer information posts here. The growth of LinkedIn followers is slower compared to Twitter. We believe some of</p>	<p>https://proeurodilinet.eu</p>

		this could be attributed to the different natures of the platforms, and also that planned dissemination of our events through LinkedIn was not expansive due to event cancellations due to COVID.	
Newsletters. Issued every month. Sent through emailing and published on the website.	CA-17112 members and other members and institutions that are collaborating with us.	To disseminate the last activities and upcoming actions taken in the CA-17112	https://proeurodilinet.eu/documents
Dissemination Meetings: Raúl J. Andrade (Spain), speaker in the World Drug Safety Congress 2020 in representation of the Pro-Euro DILI network. 01-02 September 2020. Panel discussion: Liver Toxicity Predictive Safety.	Academic and Research communities, clinicians and healthcare professionals. Safety scientists. Pharmacovigilance experts. Industry.	To disseminate the aim and objectives of the Pro-Euro DILI Network CA-17112, its scientific and technological activities at European level and the main networking activities at this international conference.	https://www.terrapinn.com/conference/world-drug-safety-us/2020-speakers.stm
Dr. Helena Glasová (Slovakia), COST Action member proposed a collaboration between COST DILI and European Association for Clinical Pharmacology and Therapeutics (EACPT) with regard to the future EACPT Congress (Athens, 26-29 June 2021) at the joint meeting of the EACPT Executive Committee and of the Congress Organizing Committee.	Clinical pharmacologists, clinicians, healthcare professionals, industry. COST ACTION CA-17112 members	To disseminate the aim and objectives of the Pro-Euro DILI Network CA-17112, its scientific and technological activities at European level and the main networking activities at this international conference.	http://eacpt2021.com/
Setting-up of a working group on pediatrics. Prof. Cigdem Arıkan, Turkey	Pro-Euro DILI Network COST ACTION CA-17112 members, researchers, clinicians and pediatricians	To harmonize definitions, causes needed to be excluded on DILI in children taking advantage of what we have learnt from adults. To set-up a data-base to include cases of DILI in Pediatrics. To perform a systematic review on DILI in pediatrics population. In collaboration with the University of Málaga, University of Nottingham and Koc University School of Medicine; Pediatric Hepatology & GI and Liver transplantation, KUTTAM Liver Immunology Laboratory, TIREX, Istanbul, Turkey.	https://proeurodilinet.eu/wp-content/uploads/2020/11/MINUTE1.pdf
Upcoming collaboration between The International Autoimmune Hepatitis Group (IAIHG) Led by Diego Vergani and the Pro-	Pro-Euro DILI Network COST Action CA-17112 members, researchers, clinicians, IAIHG experts...	A Consensus Conference proposed by Prof Andrade between IAIHG experts and the CA members to agree upon definition	https://proeurodilinet.eu/wp-content/uploads/2020/11/MINUTE1.pdf

Euro DILI Network CA-17112.		and diagnostic criteria in DILI-AIH	
Collaboration with the European Liver Patient Association (ELPA): the relevance of a patient perspective in DILI	Pro-Euro DILI Network COST Action CA-17112, researchers, clinicians, scientific societies, patient association	Dr. Marko Korenjak, President of the European Liver Patient Association (ELPA) and Dr. Teresa Casanovas, President of the ASSCAT (Spanish liver patient organization). Dr. Korenjak presented the work of the ELPA, the role of patient's associations in informing liver patients and the involvement of these associations in training patients. On the other hand, Dr. Casanovas focused her presentation on DILI from the point of view of a patient's association by presenting a case report of probable autoimmune hepatitis caused by a herbal and dietary supplement Helena Glasova (CA-17112 member) is member of the scientific committee of ELPA and will help us to organize an info day on DILI to increase awareness among the general public.	https://proeurodilinet.eu/wp-content/uploads/2020/11/MINUTE1.pdf
Dissemination Meetings: Raúl J. Andrade (Spain), speaker in the The FDA Toxicology/Liver Toxicity Work Groups. November 13, 2019 White Oak, Silver Spring, MD in representation of the Pro-Euro DILI network. Title: "Drug Induced Liver Injury Guideline & Clinical Studies: The European Perspective"	Academic and Research communities, clinicians and healthcare professionals. FDA Toxicology/Liver Toxicity Work Groups	To disseminate the aim and objectives of the Pro-Euro DILI Network CA-17112, its scientific and technological activities at European level and the main networking activities at this international conference.	https://uma365-my.sharepoint.com/:b:/g/personal/lucena_uma_es/EX_WiWRhANhNIhL5lxHuSrEBu-Mv0QZvcXRzpK7FmgQL5g?e=PnF3Yq
Publication of an updated Guidance on DILI for use by physicians, regulators, and drug developers in the pre-market and post-Market space worldwide.	COST ACTION CA-17112 members, clinician, academics, pharmaceutical industry, experts i DILI.	Several CA-17112 members (RJ Andrade, GP Aithal, E Bjornsson, M Merk, G Kullak-Ublick, Yimin Mao, H Le Louet) have been actively involved in the CIOMS Working Group on DILI, which is part of the WHO. After a work on this OPUS over a 3-year period have recently published an updated Guidance on DILI for use by physicians, regulators, and drug developers in the pre-market and post-Market space worldwide. You can access a FREE version from the CIOMS website, by clicking HERE (https://	https://cioms.ch/publications/product/drug-induced-liver-injury

		<p>cioms.ch/publications/product/drug-induced-liver-injury). The plan is for it to be a living document with periodic updates. The CIOMS forms are used worldwide to report Adverse events in Clinical Trials and in post-marketing surveillance. The forms that they previously used had not been updated since the 1990's. IN that vain, we anticipate that Table 7 and Appendix 2 will be of particular value to help standardize DILI assessment and case adjudication across the world. The members are planning to provide a synopsis of the report at the April 2021 FDA-AASLD DILI Conference.</p>	
<p>Transbioline Data Analysis Workshop 24th-25th February 2020. Liverpool, UK. Jane Grove (Co-leader WG1 COST Action CA-17112)</p>	<p>Pro-Euro DILI Network CA-17112 members, clinicians, academics, industry, healthcare professionals.</p>	<p>To support networking activities arising from the COST Action CA-17112.</p>	<p>https://uma365-my.sharepoint.com/:b/g/personal/lucena_uma_es/ET4s1jj1_VNmwpZUkKktMEBmC5AsS_u-jl6t3ZhxQva-Q?e=FnYxYZ</p>
<p>Dr. Helena Glasová (Slovakia), COST Action member, presented the plan of activities of the COST CA-17112 project at the Board Meetings of Slovak Society of Hepatology (SSH), the Slovak Society of Clinical Pharmacology (SSCP).</p>	<p>Slovak Society of Hepatology (SSH), Slovak Society of Clinical Pharmacology (SSCP), European Liver Patient Association (ELPA)</p>	<p>Slovak Society of Hepatology (SSH). This was a structured verbal presentation with a ppt presentation where for the introduction of the COST Action. She used the information from the COST website & presented it to the SSH Board members. As the Board of SSH is the body overseeing and guaranteeing the scientific standards of hepatology care in Slovakia, it was of a direct practical importance. If not for Covid-19 situation, we would probably have had proceeded with a national, or at least a pilot project on DILI. The SSH Board Meeting took place on the 22nd of May 2019 at Donovaly, Slovakia. It was part of the Annual Conference of SSH – 47th Days of Hepatology. • Website of the SSH is here: https://www.slovhep.sk • link to the programme on the website here: https://www.slovhep.sk/en/podujatia/show-archiv-events/1 Slovak Society of Clinical Pharmacology (SSCP). Similarly the</p>	<p>https://www.slovhep.sk/en/podujatia/show-event/38</p>

	<p>presentation about the COST Action project happened during the Board Meeting of the SSCP. It was held on 17th of December 2019 in Bratislava, Slovakia. Similarly, she presented the COST Action for the ELPA (European Liver Patient Association).</p>	
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Exploitation activities

Please describe below any activities undertaken to ensure exploitation (use, in particular in a commercial context) of the Action's achievements.

Item/activity	Target audience	Outcome
<p>Presentation of the Poster entitled "An open-source tool for identifying and investigating signals of hepatotoxicity during clinical development". during the THE LIVER MEETING DIGITAL EXPERIENCE to be held next 23-26th November 2020. By Raúl J. Andrade.</p>	<p>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.</p>	<p>To present creative free tools in order to improve safety monitoring.</p>

Other matters

This section is confidential to the Management Committee, the Action Rapporteur and the COST Association, and is not included in the version of the report that is published on the COST website.

COST Members with pending intention to accept the MoU

The following COST Members have the status “intention to accept the MoU”: DK. Please comment.

Ireland approved its inclusion by the MC last 22th July 2020. Represented by Davide Tiana. Denmark has accepted the Memorandum of Understanding of the COST Action CA17112. The MC candidate from Denmark is Prof. Lise L. Gluud (University of Copenhagen, Denmark), inclusion of Denmark as a member country is pending approval by the MC deadline 19/11/2020. She is consultant Gastroenterologist and Professor of gastroenterology and hepatology at the University of Copenhagen. Research on DILI and interaction with the consortium: i) undertake a prospective study to including patients with a clinical diagnosis of acute DILI. Subgroup analyses of patients drug induced autoimmune liver disease will be performed. Phenotyping will be performed to characterize the underlying pathophysiology; ii) create a research network and environment with partners in academia and hospital. She will host the upcoming EUROTOX Congress in Copenhagen on September 2021. Malasia (IPCR country) is represented by DR. JUSTIN YEONG YEH LEE. Has accepted the MoU and is being vote in eCost by the Management Committee.

Difficulties in implementing the Action

If any difficulties are experienced in the implementation of the Action (e.g. imbalances of participation across the Working Groups, inactive country representatives) please describe these below. Please also describe the efforts made by the MC to address these.

The COVID-19 pandemic, has highly reduced the mobility and networking possibilities that our COST Action wanted to develop.

Indeed, traveling and the movement of people has been severely affected and is likely to be further hampered. In fact our CA-17112 has already suffered the consequences of the COVID-19 crisis with several activities being canceled or significantly diminished like:

* the 3rd WGs, 3rd MC & 4th CG meeting. CA-17112. Kaunas, Lithuania. Foreseen in MArch 2020 and now postponed till 2021 (no date at that time).

* the Monothematic conference on DILI along the EUROTOX meeting postponed until September 26-28, 2021

* our DILI CA-17112 meeting foreseen among the ILC Liver Meeting of April 2020n in London and finally done during the EASL Digital ILC 2020 in August.

Very hard to organize STSMs as well as dissemination activities. Therefore, full execution of the proposed aims/objectives and activities is compromised.

Hopefully we may resume on-site meetings in the second semester of 2021.

Dissemination meeting funded by the Cost Action had to be postponed to 2021 at the 23rd Symposium on Microsomes and Drug Oxidations. Prague, 30 Aug-03 Sept 2020 in representation of the CA-17112 Pro-Euro DILI network.

Endangerment Measures

Taking into account the issues identified throughout this report, please summarise the measures the Action will implement in the coming two years to overcome any issues identified as potentially endangering the achievement of the objectives of the Action.

The exceptional situation of COVID 19 pandemic represents a major scientific challenge that have clearly hampered the full intended achievements and objectives of EU COST Actions. Since lockdown commenced across Europe, scheduled events (March-Nov 2020) have been cancelled, postponed, or the format modified. To mitigate impact on the COST Action goals we have organized virtual meetings – across the COST-DILI Action as well as

individual/Working-Group meetings continuing and between individuals within the Action. To facilitate this, we have, for example acquired through the COST budget a Zoom platform; whereby the next Core Group meeting (26th Nov 2020) will be entirely virtual. Other meetings have been moved to 2021 and we hope to have them face-to-face. The vast majority of activities in COST require international travel (cross-country mobility). Travelling is restricted and this CA will not be able to execute the proposed activities, especially STSMs, ITC conference grants and training schools under a face-to-face events premise. This will affect disproportionately the junior researchers for which networking COST activities make most sense. We think that we may need to expand the deadline of this Cost Action depending on the evolution of the pandemic.

Suggestions for improvements to COST framework/ procedures

The mandate of the Scientific Committee includes providing advice to the COST Committee of Senior Officials on possible improvements to the COST framework. Please describe below any improvements that you believe should be made to the COST framework.

STSM within countries have been denied by Cost Administrative. However, we must highlight that some funds could and should be allocated to national exchanges (STSMs) which will increase cooperation within the umbrella of the COST. Our WGs and have instigated mitigation methods eg Zoom meetings etc etc; Report writing etc etc. COST needs to be more flexible in finance matters. Currently, the Grant Holder Institution is dealing with a huge amount of work but the current support system to GH through a 15% FSAC that is calculated not on the total allocated budget but on the eventual direct costs spent is clearly a problem that needs to be solved out.

Sustaining the network beyond the Action

Are there any plans to sustain the network beyond the end of the Action?

NO

Emerging topics/ developments in the field of the Action

Please describe any emerging topics or potentially important future developments identified during the Action and that could potentially be addressed by future COST activities such as Actions S&T Conferences or Exploratory Workshops.

Topics in need of research:
 Network of centres for clinical research including Transplant centers for conducting clinical trials in Pediatrics
 Mechanism and management of Immune check points immune mediated DILI
 Harmonization in DILI with autoimmune phenotype
 Synthetic biology approaches to modelling DILI;
 Machine Learning/Artificial Intelligence applications in DILI;
 Advanced technologies for DILI

We plan to prepare a large-scale project under Horizon Europe leveraging the COST-DILI Action network synergies to enable harmonization of basic and clinical DILI research across Europe and provide a roadmap for DILI research and treatment in Europe for the coming decade(s)

Annex 1: Types of objectives

1 - Coordination of scientific and technological activities at a European level

- 1.a - Development of a common understanding/definition of the subject matter
- 1.b - Coordination of information seeking, identification, collection and/or data curation
- 1.c - Coordination of experimentation or testing
- 1.d - Comparison and/or performance assessment of a theory, model, methodology, technology or technique
- 1.e - Development of knowledge needing international coordination, pertaining to a new or improved theory, model, methodology, technology or technique
- 1.f - Achievement of a specific tangible output that cannot be achieved without international coordination (e.g. due to practical issues such as database availability, language barriers, availability of infrastructure or know-how, etc.)
- 1.g - Input to stakeholders (e.g. standardization body, policy-makers, regulators, users), excluding commercial applications
- 1.h - Input for future market applications (including cooperation with private enterprises)
- 1.i - Dissemination of research results to the general public
- 1.j - Dissemination of research results to stakeholders (excluding specific input in view of knowledge application)

2 - Community building

- 2.a - Building a community around a topic of scientific and/or socio-economic relevance, allowing for knowledge exchange and the development of a joint research agenda
- 2.b - Building a community around a new or emerging field of research
- 2.c - Bridging separate fields of science/disciplines to achieve breakthroughs that require an interdisciplinary approach
- 2.d - Acting as a stakeholder platform or trans-national practice community, pertaining to a certain area of socio-economical or societal application, or to a certain market sector
- 2.e - Building capacity in the demographic inclusiveness of networks in science and technology, including representation of newly established research groups, Early-Career Investigators, the under-represented gender and teams from countries/regions with less capacity in the field of the Action

Annex 2: Dimensions of successes

1 - Breakthroughs

- 1.a - Scientific breakthrough
- 1.b - Technological breakthrough
- 1.c - Breakthrough in socio-economic or societal applications

2 - Policy contribution

- 2.a - Contribution to regulatory policy
- 2.b - Contribution to environmental, infrastructural or agricultural policy
- 2.c - Contribution to economic or socio-economic policy
- 2.d - Contribution to social, cultural or legal policy

3 - Capacity building

- 3.a - Building capacity in an existing field of science and technology
- 3.b - Building capacity in bridging separate fields of science and technology
- 3.c - Building capacity in a new or emerging field of science and technology
- 3.d - Building capacity in valorising and implementing advances and applications in science and technology
- 3.e - Building capacity in the demographic inclusiveness of networks in science and technology, including representation of newly established research groups, Early-Career Investigators, the under-represented gender and teams from countries/regions with less capacity in the field of the Action

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