

# **COST Action**

## **Progress Review at 24 months**

### **(16/10/2018 to 16/10/2020)**

## **CA17112: Prospective European Drug-Induced Liver Injury Network**

This report is submitted by the Action Rapporteur in fulfilment of the requirements of the rules for COST Action Management, Monitoring and Final Assessment and is confidential to the COST Association and the Management Committee of the Action.

## Summaries

### **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 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 coordination of monthly case adjudication sessions. 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 Rapporteur summarised the Action's major outcomes, impacts and successes as follows**

This COST Action has made excellent achievements during the first 48 months of activities in terms of global networking, collaborations among universities and industries, high-impact scientific publications, e-

database across European centres, and European IMI scientific project. Based on the achievements, it can be anticipated that the Action will be successfully completed within the 4 years. It is also anticipated that the Action will develop further projects aiming at Horizon Europe.

It is appreciated that the CA members were involved in an International White Consensus Paper on DILI and made a Clinical Practice Guidelines on DILI which has an important impact in clinical practice.

### **The Action Chair has described their plans for addressing issues identified in their report as follows**

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.

### **The Rapporteur summarised the Actions's plans for addressing issues identified in the report**

As the Action has done so impressively within 2 years. It is anticipated that the Action can be successfully completed within the deadline. However, it is understandable that the deadline may be extended depending the evolution of the pandemic.

## Achievement of MoU objectives, deliverables and additional outputs/ achievements

### MoU objectives

The Action reported progress of the following objectives.

MoU objective	Level of progress	Rapporteur assessment
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	26 - 50%	CONFIRMED
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	26 - 50%	CONFIRMED
To establish standardized prospective data collection procedures and to develop an infrastructure for heterogeneous data and sample sharing	76 - 100%	CONFIRMED
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	51 - 75%	CONFIRMED
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	26 - 50%	CONFIRMED
Create a mutual strategy to optimize the training capacities related to DILI currently available at different cross-border stakeholders via exchange programmes	51 - 75%	CONFIRMED
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	51 - 75%	CONFIRMED
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	26 - 50%	CONFIRMED
Facilitate exchange of professional expertise, research material/ data between experienced researchers and ECIs through workshops and training summer schools	51 - 75%	CONFIRMED
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	51 - 75%	CONFIRMED
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	51 - 75%	CONFIRMED

awareness.

### Rapporteur assessment of the level of progress reported by the Action.

The Rapporteur confirmed the level of progress reported by the Action for all objectives.

### Action explanation regarding MoU objectives reported as 25% or less achieved

The table below shows the Action's explanation and the Rapporteur's analysis thereof for any MoU objectives that the Action reported as 25% or less achieved.

MoU Objective that was reported as 25% or less achieved	Action's explanation	Rapporteur's analysis
The Action did not report any objectives as 25% or less achieved.		

### General Assessment of MoU objectives

The level of ambition of the MoU objectives is **High**.  
Overall, **all MoU Objectives are progressing appropriately**.

## Deliverables

The table below shows, for each deliverable, the delivery status reported by the Action and the Rapporteur's comment.

Deliverable	Month deliverable due	Delivery status	Rapporteur Comment
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	12	Delivered	It was apparently that the e-database has been established, i.e. Prospective European drug-induced liver injury registry, although the rapporteur can't make the registration without user name and password.
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	12	Delivered	Excellent ppt presentation summering WG 1 - In-Depth Phenotyping in DILI. It has the following key features: anonymized data set held securely – GDPR compliant; user guidance notes and training provided, printable CRF as editable pdf, data auditing included, stored data remains available and downloadable by owner, can accommodate control groups and expert adjudication findings, facilitates optional data sharing within consortium for academic research where agreed, and compatible with TransBioLine IMI project partnership (automated defined secure data sharing/exports).
WG1-Conduct a systematic review of published data on DILI diagnosis and management	15	Delivered	It was a submission of manuscript for publication in peer reviewed journal. The link at SharePoint has expired during the period of assessment (Troubleshoot issues with Microsoft SharePoint Foundation. Correlation ID: 222d979f-b0db-b000-a239-e17b518cefd8. Date and Time: 12/14/2020 1:46:57. However, it was anticipated that the quality of manuscript would be evaluated by peer reviewers for publication.
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	33	Not delivered, but expected within 2 years after the end of the Action	The Action has planed to set up a global collaboration on herbals in particular with China. It would be better to indicate the collaborators in China regarding listing of herbal and dietary supplements.
WG1- Development of a consensus document on the diagnosis, classification, assessment and treatment of DILI in addition to standardization of nomenclature and	48	Delivered	The paper was submitted by the European Association for the Study of the Liver on 14 February 2019 and accepted for

causality assessment to harmonize the criteria used for DILI diagnosis in clinical practise across Europe			publication on 14 February 2019 in Journal of Hepatology. COST Action CA17112 was stated in the acknowledgement. It was an excellent paper and has been cited for more than 100 times.
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	18	Not delivered, but expected before end of Action	It would be better to show the evidence that the DILI causality assay is being commercialized. Information on <a href="https://metaheps.com/">https://metaheps.com/</a> shows that it was supported by Horizon2020 (SME-grant) and others but not the COST Action, although it was stated on the economic milestones that COST application was successful in April 2018. It is anticipated that the deliverable will be successfully made according to the original plan.
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	21	Not delivered, but expected before end of Action	Based on the information on <a href="https://metaheps.com/news.html">https://metaheps.com/news.html</a> , the group has already published two papers entitled "Early ALT response to corticosteroid treatment distinguishes idiosyncratic drug-induced liver injury from autoimmune hepatitis (Live International, 18 July 2019)" and "Drug-Drug Combinations Can Enhance Toxicity as Shown by Monocyte-Derived Hepatocyte-like Cells From Patients With Idiosyncratic Drug-Induced Liver Injury (Toxicological Science, 12 August 2019)". It is anticipated that additional two papers will be published according to the original plan.
WG2-Written input to one or more commercial enterprises necessary for Future Market Exploitation of biomarkers	42	Not delivered, but expected before end of Action	Based on the activities (and economic milestones), it is anticipated that the deliverables will be made according to the original plan, such as position paper on preclinical human-based models for improved DILI prediction and market exploitation with pharms and regulatory agencies/communities.
WG2- Scientific publication to summarize the current knowledge on 1) Drug properties associated with hepatotoxicity	48	Not delivered, but expected before end of Action	It is likely that the scientific paper(s) will be co-authored between the members of the CA 17112 and the University of Duke US (Ayako Suzuki, IPC) and the NTRC (National Centre Toxicology Research Centre, FDA) and Nottingham University (GP Aithal), which is excellent.
WG3- A review of current and potential in vitro and in silico models of hepatotoxicity	18	Not delivered, but expected before end of Action	It is anticipated the the deliverable will be successfully made and appreciated that the

			targeted journal is Nature Reviews.
WG3- Identify and list the most appropriate control compounds for testing new in vitro models	42	Not delivered, but expected before end of Action	It is anticipated that the deliverable as a list of compounds for testing, will be successfully made after the review has been submitted.
WG3- Define a roadmap for the development of in silico, in vitro and experimental models incorporating host determinants of DILI	48	Not delivered, but expected before end of Action	The development of in silico, in vitro and experimental models incorporating host determinants of DILI is attractive. It is anticipated that it would be achievable by defining the roadmap for it before the end of Action.
WG4- To standardize procedures and remove bottlenecks at each participating centre that would facilitate the future conduct of a multicentre clinical trial in DILI	42	Not delivered, but expected before end of Action	WG4 is responsible for designing multicentre clinical trials, particularly in establishing precise endpoints to assess the efficacy of novel interventions or for exploring novel biomarkers in DILI. It is anticipated that it can be successfully made before the end of Action.
WG4- A proposal for study design for risk or biomarker evaluation, pathway for evaluating of diagnostics and appropriate statistical methods	36	Not delivered, but expected before end of Action	It sounds like that WG4 is collecting new data from the Transbioline study which will emerge in 2021 in order to choose the optimal biomarkers as a part of therapeutic clinical trial in DILI.
WG4- Design of clinical trials in DILI to assess the effect of an intervention on disease course or clinical outcomes	48	Not delivered, but expected before end of Action	It is unclear whether the paper that was written on Current management on DILI by Iceland & Turkey was supported by the Action. It is also unclear whether future studies or multicentre clinical trials will be conducted by the members from Iceland, Palermo-Italy, Malaga-Spain, Bosnia&Herzegovina, Croatia and Romania.
WG5-Set up a Website and social networks to translate scientific efforts into public dissemination and regulatory bodies	6	Delivered	The website looks excellent in every aspect. One concern was that the Action was not mentioned in scientific publication by Shen et al. Gastroenterology 2019.
WG5- Write a Quality Plan and Good Practice Policies that apply to all COST partners	9	Not delivered, but expected before end of Action	It is anticipated that the deliverable will be successfully made before end of Action, e.g. systematic research reviews have been registered in the PROSPERO database.
WG5- Mid-term review of the COST Action proposal with the Management Committee (MC) to implement corrective measures	24	Delivered	It looks professional and excellent. The information and the related materials were appreciated.



WG5- Preparation of large-scale European projects, searching topics of interest at H2020, 9 EU Framework Programme and other funding programmes	45	Not delivered, but expected before end of Action	Based on the achievements of this COST Action so far, it is anticipated that the future research proposals derived from the members of this Action will have good opportunities in targeting Horizon Europe and other major funding programs.
WG5- Organise the Closing meeting and Final Report in which a roadmap to DILI research in Europe will be presented	48	Not delivered, but expected before end of Action	It is anticipated that the closing meeting will be successfully made either in person or online.

## General Assessment of deliverables

The level of ambition of the deliverables is **high**.  
Overall, **all deliverables are progressing appropriately**.

## Additional outputs / achievements

### Co-authored Action publications

The Action reported 16 publications on the topic of the Action, co-authored by at least two Action participants from two countries participating in the Action. The full list of publications appears in Annex I.

The:

- **Quality** of the Action's co-authored publications is **excellent**.  
Publications were impressive, particularly regarding the journals where papers were published.
- **Significance** of the Action's co-authored publications is **excellent**.  
Most reviews were comprehensive and some of them have had high citations (more than 100 times).
- **Relevance** to the Action of the Action's co-authored publications is **very good**.  
Most papers were of relevance but some were neither COST funded nor cited.
- **Quantity** of the Action's co-authored publications is **excellent**.  
It was impressive that so many papers have been published. It can be anticipated that there will be more publications before and after the Action.

### Projects and proposals resulting from Action activities

The Action reported the following projects resulting from Action activities involving at least one Action participant.

Title	Main proposer name	Funder
IMI2- Translational Safety Biomarker Pipeline (TransBioLine): Enabling development and implementation of novel safety biomarkers in clinical trials and diagnosis of disease.	Raúl J. Andrade	H2020

In addition the Action reported 0 proposals resulting from Action activities involving at least one Action participant, and for which the Action networking was necessary.

Relevance of the Action's proposals and/ or projects is **excellent**.

Quantity of the Action's proposals and/ or projects is **excellent**.

### Other outputs / achievements

The table below shows the other outputs / achievements.

Other Output / Achievement reported by Action	Significance of the output
<b>Publications with International Partner Countries (USA, LATIN AMERICAN COUNTRIES):</b> <ul style="list-style-type: none"> <li>• BESSONE F, ROBLES-DIAZ M, HERNANDEZ N, MEDINA-CALIZ I, LUCENA MI, ANDRADE RJ. <a href="#">Review. Assessment of Serious Acute and Chronic Idiosyncratic Drug-Induced Liver Injury in</a></li> </ul>	High

[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.

<p><a href="#">Polygenic Architecture Informs Potential Vulnerability To Drug-Induced Liver Injury</a>. <i>Nature Medicine</i>, 26,541–1548(2020). doi: 10.1038/s41591-020-1023-0. IF 2019: 36.130 (D1: 1/139)</p>	
<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><b>ISBN: 978-929036099-5. Year of publication: 2020</b></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 development and post-marketing.</p> <p>Several number of COST Action 17-112 PRO-EURO DILI NETWORK members contributed to it.</p> <p><b>The report in PDF format is freely available here: <a href="https://cioms.ch/wp-content/uploads/2020/06/CIOMS_DILI_Web_16Jun2020.pdf">https://cioms.ch/wp-content/uploads/2020/06/CIOMS_DILI_Web_16Jun2020.pdf</a></b></p>	<p>High</p>

The quality and quantity of the other outputs/ achievements was assessed as follows.

The Action has already made significant achievements that were highly dependent on the networking globally, which can be reflected by high quality and quantity of publications. It can be anticipated that the Action will be successfully completed according to the MoU.

## Impacts

The Action reported the following 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.

Description of the impact	Type of impact	Timing of impact
<p><b>Coordination and standardization of processes:</b> 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"> <li>• Scientific / Technological</li> <li>• Societal</li> </ul>	Achieved
<p>Validity, relevance and significance (in particular importance and timeliness) of the impact reported by the Action: Data registry across Europe that the Action has made will not only improve the quality and consistency of research outputs within the CA members but also attract more international collaborations in the future.</p>		
<p><b>A European Clinical Practice Guidelines on DILI</b> 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><b>Building inter-institutional collaboration</b></p>	<ul style="list-style-type: none"> <li>• Scientific / Technological</li> </ul>	Achieved
<p>Validity, relevance and significance (in particular importance and timeliness) of the impact reported by the Action: This was highly significant that "A European Clinical Practice Guidelines on DILI" has been published and already been cited for more than 100 times, showing public awareness of this Action.</p>		
<p><b>Joint research undertaking, and a large number of publications.</b> 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"> <li>• Scientific / Technological</li> <li>• Societal</li> </ul>	Achieved
<p>Validity, relevance and significance (in particular importance and timeliness) of the impact reported by the Action: The Action has generated an impressive number of publications. It can be anticipated that the Action will evoke a number of follow-up proposals for further research projects, such as Horizon Europe.</p>		
<p><b>Support and partnership</b> 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"> <li>• Scientific / Technological</li> </ul>	Achieved
<p>Validity, relevance and significance (in particular importance and timeliness) of the impact reported by the Action: This Action was an excellent platform for ECIs to have opportunities and exchange of knowledge with well-established PIs in the field.</p>		
<p>We have <b>established links with EMA</b> 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"> <li>• Scientific / Technological</li> </ul>	Foreseen within two years of the end of the Action
<p>Validity, relevance and significance (in particular importance and timeliness) of the impact reported by the Action: It was understandable that impact foreseen within two years of the end of the Action.</p>		

The extent to which the Action has advanced the careers, skills and networks of researchers including ECIs (as described by the Action) is **excellent**.

#### **Stakeholder engagement**

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).

**The Rapporteur recommended that the following stakeholders should also be engaged by the Action.**

### **General assessment of impacts**

The Action's impacts are best described as follows:

**Multiple highly significant impacts are reasonably foreseen, at least one of which is already observed [Excellent]**

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

### Dissemination

#### Dissemination meetings funded by the Action

#### Action website

<https://proeurodilinet.eu/>

The:

- openness and user-friendliness of the Action website are excellent
- content of the Action website (programmes and minutes of all events present, all outputs/deliverables accessible from website) is excellent

The Action website was an effective means of disseminating the Action.

Rapporteur's comment on the website

#### Other dissemination activities

The following other dissemination activities reported by the Action were effective and added value

<b>Item/activity</b>	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" in the session _Metabolizing enzymes in drug-induced toxicity" Re-scheduled due to COVID-19. September 5 - 9, 2021
<b>Target Audience</b>	Academic and Research communities, clinicians and healthcare professionals. Early carrier investigators in the field of Microsomes and Drug oxidations. Liver Networks on Drug metabolism.
<b>Outcome of the activity</b>	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 potencial 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.
<b>Hyperlink</b>	<a href="https://mdoprague2021.cz/speakers/">https://mdoprague2021.cz/speakers/</a>

<b>Item/activity</b>	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 ( <a href="https://cioms.ch/working-groups/dili/">https://cioms.ch/working-groups/dili/</a> ) 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
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<b>Target Audience</b>	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)
<b>Outcome of the activity</b>	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.
<b>Hyperlink</b>	<a href="https://cioms.ch/working-groups/dili">https://cioms.ch/working-groups/dili</a>

<b>Item/activity</b>	1st Working Groups Meeting, 2nd Core Group & Management Committee Meeting. Málaga, 14-15 March 2019. Attended by 70 members of the CA-17112 from 25 countries including USA (Dr Ayako Suzuki) and China (Yimin Mao).
<b>Target Audience</b>	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. ECIs & 6th years medicine students.
<b>Outcome of the activity</b>	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 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.
<b>Hyperlink</b>	<a href="https://proeurodilinet.eu/wp-content/uploads/2018/11/COST-press-release.pdf">https://proeurodilinet.eu/wp-content/uploads/2018/11/COST-press-release.pdf</a>

<b>Item/activity</b>	American Association for the Study of the Liver (AASLD) Special Interest Group (SIG) Hepatotoxicity Group. Raúl J. Andrade: member of the steering committee.
<b>Target Audience</b>	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.
<b>Outcome of the activity</b>	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.
<b>Hyperlink</b>	<a href="https://www.aasld.org/membership/member-resources/special-interest-groups/hepatotoxicity">https://www.aasld.org/membership/member-resources/special-interest-groups/hepatotoxicity</a>

<b>Item/activity</b>	DILI CA-17112 meeting @ EASL Digital ILC 2020. 29th August 2020. 09:30-11:10 am Pro-
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	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. Giordina Vergani, UK The International Autoimmune Hepatitis Group (IAIHG): opportunities for mutual collaboration Lecture: Prof. Dr. Çigdem Arıkan, Turkey DILI in Pediatric population
<b>Target Audience</b>	Pro-Euro DILI Network's stakeholders researchers, clinicians and academics. Patients society.
<b>Outcome of the activity</b>	NEW SCENARIOS OF COL LABORATIONS 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.
<b>Hyperlink</b>	<a href="https://proeurodilinet.eu/dili-ca-17112-meetingeasl-2020-london-17th-april-2020">https://proeurodilinet.eu/dili-ca-17112-meetingeasl-2020-london-17th-april-2020</a>

<b>Item/activity</b>	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?
<b>Target Audience</b>	Researchers, clinicians and academics. Medical staff of the University Hospital Santa María, Lisboa & CA-17112 members.
<b>Outcome of the activity</b>	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).
<b>Hyperlink</b>	<a href="https://proeurodilinet.eu/1st-core-group-meeting-ca17112-lisboa-09-january-2019">https://proeurodilinet.eu/1st-core-group-meeting-ca17112-lisboa-09-january-2019</a>

<b>Item/activity</b>	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 .
<b>Target Audience</b>	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.
<b>Outcome of the activity</b>	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.
<b>Hyperlink</b>	<a href="https://www.jornadasavancehepatologia.uma.es">https://www.jornadasavancehepatologia.uma.es</a>

<b>Item/activity</b>	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.
<b>Target Audience</b>	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.
<b>Outcome of the</b>	The website ensures a clear presentation of the aims and objectives of the action as well as

<b>activity</b>	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 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.
<b>Hyperlink</b>	<a href="https://proeurodilinet.eu">https://proeurodilinet.eu</a>

<b>Item/activity</b>	Newsletters. Issued every month. Sent through emailing and published on the website.
<b>Target Audience</b>	CA-17112 members and other members and institutions that are collaborating with us.
<b>Outcome of the activity</b>	To disseminate the last activities and upcoming actions taken in the CA-17112
<b>Hyperlink</b>	<a href="https://proeurodilinet.eu/documents">https://proeurodilinet.eu/documents</a>

<b>Item/activity</b>	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.
<b>Target Audience</b>	Academic and Research communities, clinicians and healthcare professionals. Safety scientists. Pharmacovigilance experts. Industry.
<b>Outcome of the activity</b>	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.
<b>Hyperlink</b>	<a href="https://www.terrapinn.com/conference/world-drug-safety-us/2020-speakers.stm">https://www.terrapinn.com/conference/world-drug-safety-us/2020-speakers.stm</a>

<b>Item/activity</b>	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.
<b>Target Audience</b>	Clinical pharmacologists, clinicians, healthcare professionals, industry. COST ACTION CA-17112 members
<b>Outcome of the activity</b>	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.
<b>Hyperlink</b>	<a href="http://eacpt2021.com/">http://eacpt2021.com/</a>

<b>Item/activity</b>	Setting-up of a working group on pediatrics. Prof. Cigdem Arkan, Turkey
<b>Target Audience</b>	Pro-Euro DILI Network COST ACTION CA-17112 members, researchers, clinicians and pediatricians
<b>Outcome of the activity</b>	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.
<b>Hyperlink</b>	<a href="https://proeurodilinet.eu/wp-content/uploads/2020/11/MINUTE1.pdf">https://proeurodilinet.eu/wp-content/uploads/2020/11/MINUTE1.pdf</a>

<b>Item/activity</b>	Upcoming collaboration between The International Autoimmune Hepatitis Group (IAIHG) Led by Diego Vergani and the Pro-Euro DILI Network CA-17112.
<b>Target Audience</b>	Pro-Euro DILI Network COST Action CA-17112 members, researchers, clinicians, IAIHG experts...
<b>Outcome of the activity</b>	A Consensus Conference proposed by Prof Andrade between IAIHG experts and the CA members to agree upon definition and diagnostic criteria in DILI-AIH
<b>Hyperlink</b>	<a href="https://proeurodilinet.eu/wp-content/uploads/2020/11/MINUTE1.pdf">https://proeurodilinet.eu/wp-content/uploads/2020/11/MINUTE1.pdf</a>

<b>Item/activity</b>	Collaboration with the European Liver Patient Association (ELPA): the relevance of a patient perspective in DILI
<b>Target Audience</b>	Pro-Euro DILI Network COST Action CA-17112, researchers, clinicians, scientific societies, patient association
<b>Outcome of the activity</b>	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.
<b>Hyperlink</b>	<a href="https://proeurodilinet.eu/wp-content/uploads/2020/11/MINUTE1.pdf">https://proeurodilinet.eu/wp-content/uploads/2020/11/MINUTE1.pdf</a>

<b>Item/activity</b>	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"
<b>Target Audience</b>	Academic and Research communities, clinicians and healthcare professionals. FDA Toxicology/Liver Toxicity Work Groups
<b>Outcome of the activity</b>	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.
<b>Hyperlink</b>	<a href="https://uma365-my.sharepoint.com/:b:/g/personal/lucena_uma_es/EX_WiWRhANhNihL5lxHuSrEBu-Mv0QZvcXRzpK7FmgQL5g?e=PnF3Yq">https://uma365-my.sharepoint.com/:b:/g/personal/lucena_uma_es/EX_WiWRhANhNihL5lxHuSrEBu-Mv0QZvcXRzpK7FmgQL5g?e=PnF3Yq</a>

<b>Item/activity</b>	Publication of an updated Guidance on DILI for use by physicians, regulators, and drug developers in the pre-market and post-Market space worldwide.
<b>Target Audience</b>	COST ACTION CA-17112 members, clinician, academics, pharmaceutical industry, experts i DILI.
<b>Outcome of the activity</b>	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 <a href="https://cioms.ch/publications/product/drug-induced-liver-injury">HERE</a> (https://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.
<b>Hyperlink</b>	<a href="https://cioms.ch/publications/product/drug-induced-liver-injury">https://cioms.ch/publications/product/drug-induced-liver-injury</a>

<b>Item/activity</b>	Transbioline Data Analysis Workshop 24th-25th February 2020. Liverpool, UK. Jane Grove (Co-leader WG1 COST Action CA-17112)
<b>Target Audience</b>	Pro-Euro DILI Network CA-17112 members, clinicians, academics, industry, healthcare professionals.
<b>Outcome of the activity</b>	To support networking activities arising from the COST Action CA-17112.
<b>Hyperlink</b>	<a href="https://uma365-my.sharepoint.com/:b:/g/personal/lucena_uma_es/ET4s1jJl1_VNmWPzUkKktMEBmC5AsS_u-jl6t3ZhxQva-Q?e=FnYxYZ">https://uma365-my.sharepoint.com/:b:/g/personal/lucena_uma_es/ET4s1jJl1_VNmWPzUkKktMEBmC5AsS_u-jl6t3ZhxQva-Q?e=FnYxYZ</a>

<b>Item/activity</b>	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).
<b>Target Audience</b>	Slovak Society of Hepatology (SSH), Slovak Society of Clinical Pharmacology (SSCP), European Liver Patient Association (ELPA)
<b>Outcome of the activity</b>	Slovak Society of Hepatology (SSH). This was a structured verbal presentation with a ppt presentation where for the introduction of the COST Action. Dr. Glasova 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: <a href="https://www.slovhep.sk">https://www.slovhep.sk</a> • link to the programme on the website here: <a href="https://www.slovhep.sk/en/podujatia/show-archiv-events/1">https://www.slovhep.sk/en/podujatia/show-archiv-events/1</a> Slovak Society of Clinical Pharmacology (SSCP). Similarly the 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).
<b>Hyperlink</b>	<a href="https://www.slovhep.sk/en/podujatia/show-event/38">https://www.slovhep.sk/en/podujatia/show-event/38</a>

## Exploitation activities

The following activities to ensure exploitation (use, in particular in a commercial context) of the Action's achievements reported by the Action were effective and added value

<b>Item/activity</b>	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.
<b>Target Audience</b>	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.
<b>Outcome of the activity</b>	To present creative free tools in order to improve safety monitoring.

## Assessment of Action dissemination and exploitation activities

The effectiveness of the Action's dissemination and exploitation approach (other than co-authored

publications) is assessed as follows

The link was expired. El vínculo ha expirado. Se estableció que este vínculo expirara al transcurrir un determinado periodo de tiempo. Póngase en contacto con quien compartió este vínculo con su usuario. TECHNICAL DETAILS Troubleshoot issues with Microsoft SharePoint Foundation. Correlation ID: 6fe2979f-90f8-b000-a239-e0bd8e091ada  
Date and Time: 16/12/2020 6:35:25

Assessment of Action dissemination and exploitation activities

There were many highly effective Action activities focusing on dissemination of Action results [Excellent]  
There were many highly effective Action activities focusing on exploitation of Action results [Excellent]

## Other matters

### Difficulties in implementing the Action

The Action Rapporteur made the following observations regarding difficulties in implementing the Action:

The concerns were understandable and rearrangements were appreciated.

### Emerging topics / developments in the field of the Action

The Action reported the following emerging topics / developments in the field of the Action.

- 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)

The Action Rapporteur made the following comment on the emerging topics / developments in the field reported by the Action.

It is agreeable that the topics in need of research, particularly network for multicentre clinical trials, harmonization in DILI with autoimmune phenotype, and AI applications in DILI. It could be of interest to think about digital twin technology in connection with AI.

It is also appreciated that the Action plans to prepare a large-scale project under Horizon Europe.

### Action Rapporteur

This Second Progress Report was submitted on 2020-12-17 by:

Prof Duan Chen

Norwegian University of Science and Technology

Norway

## Annex 1: List of publications

The Action reported 16 publications on the topic of the Action, co-authored by at least two Action participants from two countries participating in the Action.

### Co-authored Action publications - peer-reviewed

Title	EASL Clinical Practice Guidelines: Drug-induced liver injury
Authors	Raúl J. Andrade; Guruprasad P. Aithal; Einar S. Björnsson; Neil Kaplowitz; Gerd A. Kullak-Ublick; Dominique Larrey; Tom H. Karlsen
DOI	<a href="https://doi.org/10.1016/j.jhep.2019.02.014">doi:10.1016/j.jhep.2019.02.014</a>
Type	Journal article
Published in	Journal of Hepatology
Published by	Elsevier BV
ISSN	<a href="https://www.elsevier.com/issn/0168-8278">0168-8278</a>
Subject	Hepatology
Links	<a href="https://api.elsevier.com/content/article/PII:S0168827819301291?httpAccept=text/xml">https://api.elsevier.com/content/article/PII:S0168827819301291?httpAccept=text/xml</a> ; <a href="https://api.elsevier.com/content/article/PII:S0168827819301291?httpAccept=text/plain">https://api.elsevier.com/content/article/PII:S0168827819301291?httpAccept=text/plain</a>
Title	Incidence and Etiology of Drug-Induced Liver Injury in Mainland China
Authors	Tao Shen; Yingxia Liu; Jia Shang; Qing Xie; <a href="#">Jun Li</a> ; Ming Yan; Jianming Xu; Junqi Niu; Jiajun Liu; Paul B. Watkins; Guruprasad P. Aithal; Raúl J. Andrade; Xiaoguang Dou; Lvfen 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
DOI	<a href="https://doi.org/10.1053/j.gastro.2019.02.002">doi:10.1053/j.gastro.2019.02.002</a>
Type	Journal article
Published in	Gastroenterology
Published by	Elsevier BV
ISSN	<a href="https://www.elsevier.com/issn/0016-5085">0016-5085</a>
Subject	Gastroenterology
Links	<a href="https://api.elsevier.com/content/article/PII:S0016508519303646?httpAccept=text/xml">https://api.elsevier.com/content/article/PII:S0016508519303646?httpAccept=text/xml</a> ; <a href="https://api.elsevier.com/content/article/PII:S0016508519303646?httpAccept=text/plain">https://api.elsevier.com/content/article/PII:S0016508519303646?httpAccept=text/plain</a>
Title	Drug-induced liver injury
Authors	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
DOI	<a href="https://doi.org/10.1038/s41572-019-0105-0">doi:10.1038/s41572-019-0105-0</a>
Type	Journal article
Published in	Nature Reviews Disease Primers
Published by	Springer Science and Business Media LLC
ISSN	<a href="https://www.nature.com/issn/2056-676X">2056-676X</a>
Links	<a href="http://www.nature.com/articles/s41572-019-0105-0">http://www.nature.com/articles/s41572-019-0105-</a>

	<p><a href="#">0.pdf</a>; <a href="http://www.nature.com/articles/s41572-019-0105-0">http://www.nature.com/articles/s41572-019-0105-0</a></p>
Title	Drug-Induced liver Injury Associated with Severe Cutaneous Hypersensitivity Reactions: A Complex Entity in Need of a Multidisciplinary Approach
Authors	<a href="#">Judith Sanabria-Cabrera</a> ; <a href="#">Inmaculada Medina-Cáliz</a> ; <a href="#">Simona Stankevičiūtė</a> ; <a href="#">Antonio Rodríguez-Nicolás</a> ; <a href="#">Marina Almarza-Torres</a> ; <a href="#">M. Isabel Lucena</a> ; <a href="#">Raúl J. Andrade</a>
DOI	<a href="https://doi.org/10.2174/1381612825666191107161912">doi:10.2174/1381612825666191107161912</a>
Type	Journal article
Published in	Current Pharmaceutical Design
Published by	Bentham Science Publishers Ltd.
ISSN	<a href="#">1381-6128</a>
Subjects	Pharmacology; Drug Discovery
Link	<a href="http://eurekaselect.com/article/download/176495">http://eurekaselect.com/article/download/176495</a>
Title	Shared Genetic Risk Factors Across Carbamazepine-Induced Hypersensitivity Reactions
Authors	Paola Nicoletti; Sarah Barrett; <a href="#">Laurence McEvoy</a> ; <a href="#">Ann K. Daly</a> ; Guruprasad Aithal; <a href="#">M. Isabel Lucena</a> ; <a href="#">Raul J. Andrade</a> ; <a href="#">Mia Wadelius</a> ; <a href="#">Pär Hallberg</a> ; Camilla Stephens; Einar S. Bjornsson; Peter Friedmann; Kati Kainu; Tarja Laitinen; Anthony Marson; Mariam Molokhia; Elizabeth Phillips; Werner Pichler; Antonino Romano; <a href="#">Neil Shear</a> ; Graeme Sills; Luciana K. Tanno; <a href="#">Ashley Swale</a> ; Aris Floratos; Yufeng Shen; Matthew R. Nelson; Paul B. Watkins; Mark J. Daly; Andrew P. Morris; Ana Alfirevic; <a href="#">Munir Pirmohamed</a>
DOI	<a href="https://doi.org/10.1002/cpt.1493">doi:10.1002/cpt.1493</a>
Type	Journal article
Published in	Clinical Pharmacology & Therapeutics
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ISSNs	<a href="#">0009-9236</a> ; <a href="#">1532-6535</a>
Subjects	Pharmacology (medical); Pharmacology
Links	<a href="https://api.wiley.com/onlinelibrary/tdm/v1/articles/10.1002%2Fcpt.1493">https://api.wiley.com/onlinelibrary/tdm/v1/articles/10.1002%2Fcpt.1493</a> ; <a href="https://onlinelibrary.wiley.com/doi/pdf/10.1002/cpt.1493">https://onlinelibrary.wiley.com/doi/pdf/10.1002/cpt.1493</a> ; <a href="https://onlinelibrary.wiley.com/doi/full-xml/10.1002/cpt.1493">https://onlinelibrary.wiley.com/doi/full-xml/10.1002/cpt.1493</a>
Title	The influence of drug properties and host factors on delayed onset of symptoms in drug-induced liver injury
Authors	Andres Gonzalez-Jimenez; Kristin McEuen; <a href="#">Minjun Chen</a> ; <a href="#">Ayako Suzuki</a> ; Mercedes Robles-Diaz; Inmaculada Medina-Caliz; Fernando Bessone; Nelia Hernandez; <a href="#">Marco Arrese</a> ; Raymundo Parana; <a href="#">M. Isabel Lucena</a> ; Camilla Stephens; Raúl J. Andrade
DOI	<a href="https://doi.org/10.1111/liv.13952">doi:10.1111/liv.13952</a>
Type	Journal article



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 ISSNs  
 Subject  
 Links

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 Wiley  
[1478-3223](#); [1478-3231](#)  
 Hepatology  
<https://api.wiley.com/onlinelibrary/tdm/v1/articles/10.1111%2Fliv.13952>;  
<https://onlinelibrary.wiley.com/doi/pdf/10.1111/liv.13952>;  
<https://onlinelibrary.wiley.com/doi/full-xml/10.1111/liv.13952>

Title

Candidate biomarkers for the diagnosis and prognosis of drug-induced liver injury: An international collaborative effort

Authors

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 Marcinak; 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  
[doi:10.1002/hep.29802](https://doi.org/10.1002/hep.29802)

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<https://onlinelibrary.wiley.com/doi/pdf/10.1002/hep.29802>; <https://onlinelibrary.wiley.com/doi/full-xml/10.1002/hep.29802>

Title

A Missense Variant in PTPN22 is a Risk Factor for Drug-induced Liver Injury

Authors

Elizabeth T. Cirulli; Paola Nicoletti; Karen Abramson; Raul J. Andrade; Einar S. Bjornsson; Naga Chalasani; Robert J. Fontana; Pär Hallberg; Yi Ju Li; M. Isabel Lucena; Nanye Long; [Mariam Molokhia](#); Matthew R. Nelson; Joseph A. Odin; [Munir Pirmohamed](#); Thorunn Rafnar; Jose Serrano; Kári Stefánsson; Andrew Stolz; Ann K. Daly; Guruprasad P. Aithal; Paul B. Watkins; Guruprasad P. Aithal; Raul J. Andrade; Fernando Bessone; Einar Bjornsson; Ingolf Cascorbi; Ann K. Daly; John F. Dillon; Christopher P. Day; Par Hallberg; Nelia Hernández; Luisa Ibanez; Gerd A. Kullak-Ublick; Tarja Laitinen; Dominique Larrey; M. Isabel Lucena; Anke Maitland-van der Zee; Jennifer H. Martin; Dick Menzies; Mariam Molokhia; Munir Pirmohamed; Shengying Qin; Mia Wadelius  
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Title Drug-Induced Liver Injury due to Flucloxacillin: Relevance of Multiple Human Leukocyte Antigen Alleles

Authors 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

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<https://onlinelibrary.wiley.com/doi/full-xml/10.1002/cpt.1375>

Title EASL Clinical Practice Guideline: Occupational liver diseases

Authors Massimo Colombo; Carlo La Vecchia; Marcello Lotti; M. Isabel Lucena; Christophe Stove; Valérie Paradis; Philip Newsome

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- 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**

Sent to Pharmacological Research.

ECIs: Judith Sanabria-Cabrera, Ismael Alvarez-Alvarez, Simona Stankevičiūtė, Hao Niu.

- E.Atallah, C.Freixo, I.Alvarez, F.J Cubero, G.P.Aithal. Biomarkers for drug-induced liver injury (DILI). Clinical Pharmacology & Therapeutics.

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- 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 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. Clinical Gastroenterology and Hepatology 2020. IN PRESS

ECIs: Rianne A. Weersink, Ismael Alvarez-Alvarez, Judith Sanabria-Cabrera, Hao Niu.

Title	Reclassifying Hepatic Cell Death during Liver Damage: Ferroptosis—A Novel Form of Non-Apoptotic Cell Death?
Authors	<a href="#">Ricardo U. Macías-Rodríguez</a> ; María Eugenia Inzaugarat; Astrid Ruiz-Margáin; <a href="#">Leonard J. Nelson</a> ; Christian Trautwein; <a href="#">Francisco Javier Cubero</a>
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Link	<a href="https://www.mdpi.com/1422-0067/21/5/1651/pdf">https://www.mdpi.com/1422-0067/21/5/1651/pdf</a>

- Nuria López-Alcántara, Laura Morán, Marina Villanueva, Cristiana Freixo, Raúl J. Andrade, M. Isabel Lucena, Francisco Javier Cubero.

#### **Idiosyncratic drug-induced liver injury (DILI): *Status quo* and future challenges**

Biomedicine and Pharmacotherapy (Q1: 32/139) IN PRESS

#### **Co-authored Action publications - other**

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

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

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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](https://cioms.ch/wp-content/uploads/2020/06/CIOMS_DILI_Web_16Jun2020.pdf)