10th October 2019 Palermo

COST Activity Update

WG 1: In-Depth Phenotyping in DILI

Jane Grove

cost
EUROPEAN COOPERATION IN SCIENCE & TECHNOLOGY

Funded by the Horizon 2020 Framework Programme of the European Union

PRO-EURO DILI NETWORK
Prospective European Drug-induced Liver Injury Network

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Prospective European Drug-induced Liver Injury Network

WG 1: In-Depth phenotyping in DILI: Purpose

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

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WG 1: In-Depth phenotyping – Proposed Actions

1. **address issues regarding the criteria for DILI case definition, characterisation and classification of phenotypic sub-groups in DILI.**
2. **harmonize efforts for in-depth DILI phenotyping and bio-sample repository**
3. **coordinate funded database/repository studies to aggregate a large number of DILI cases in a standardized manner**

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WG 1: In-Depth phenotyping - Harmonization

At the first meeting, it was agreed that one important mission would be to harmonize clinical measurements, definitions, classifications and outcomes related to DILI.

Activities:

- We requested registry holders to send the type of information recorded in local databases (Feb 2019), since registries are different among groups, this will 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.

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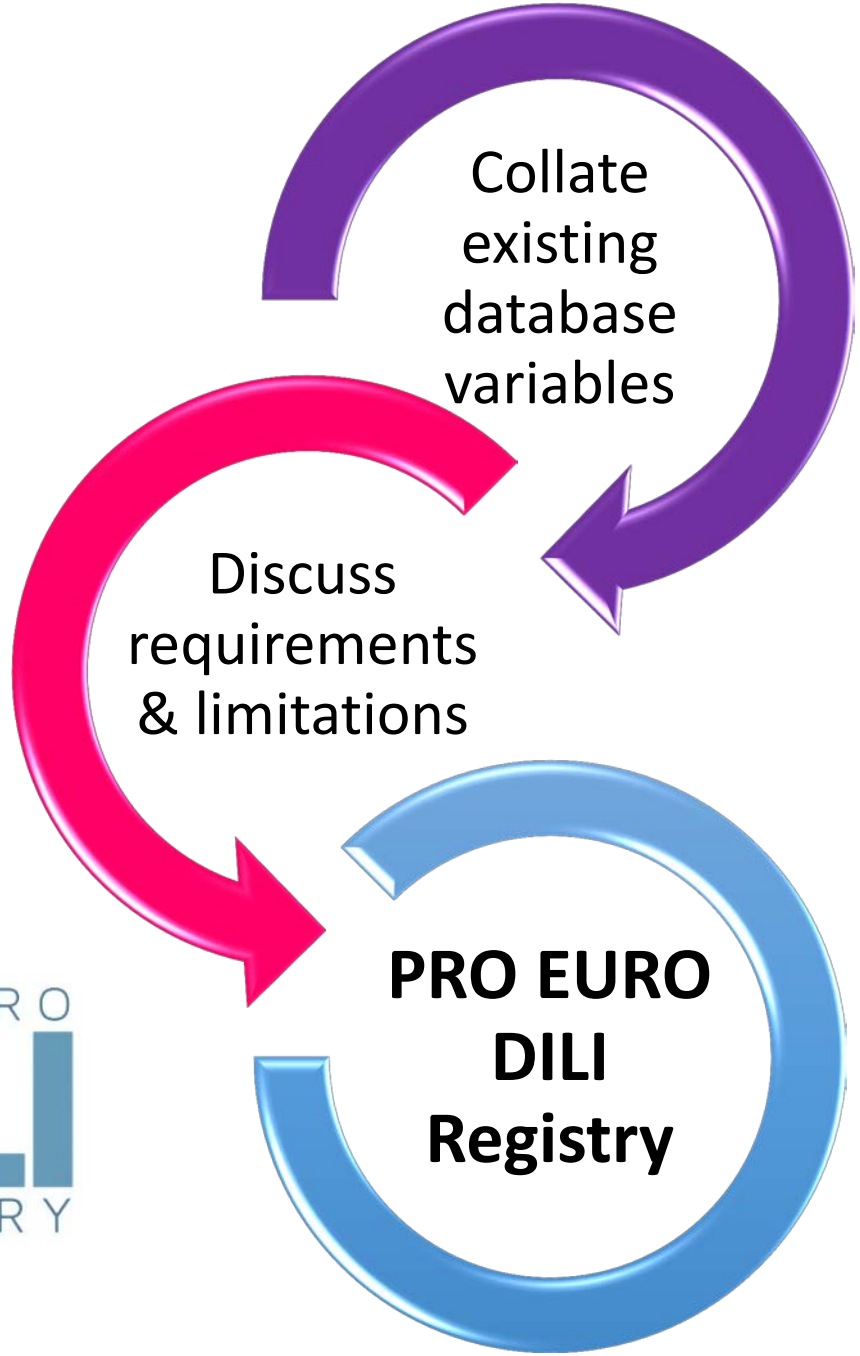
WG 1: Development of DILI Registry

- Dataset from Lisbon
- Dataset from Malaga/Nottingham
- Dataset from SAFE-T/ DILICIN project
- Scoring systems (RUCAM/CIOMS)
- Example cases
- Testing – Data dictionary
- Discussion/Debate/Refinement
- Trouble shooting
- Roll-out
- Training Users

PRO-EURO DILI REGISTRY



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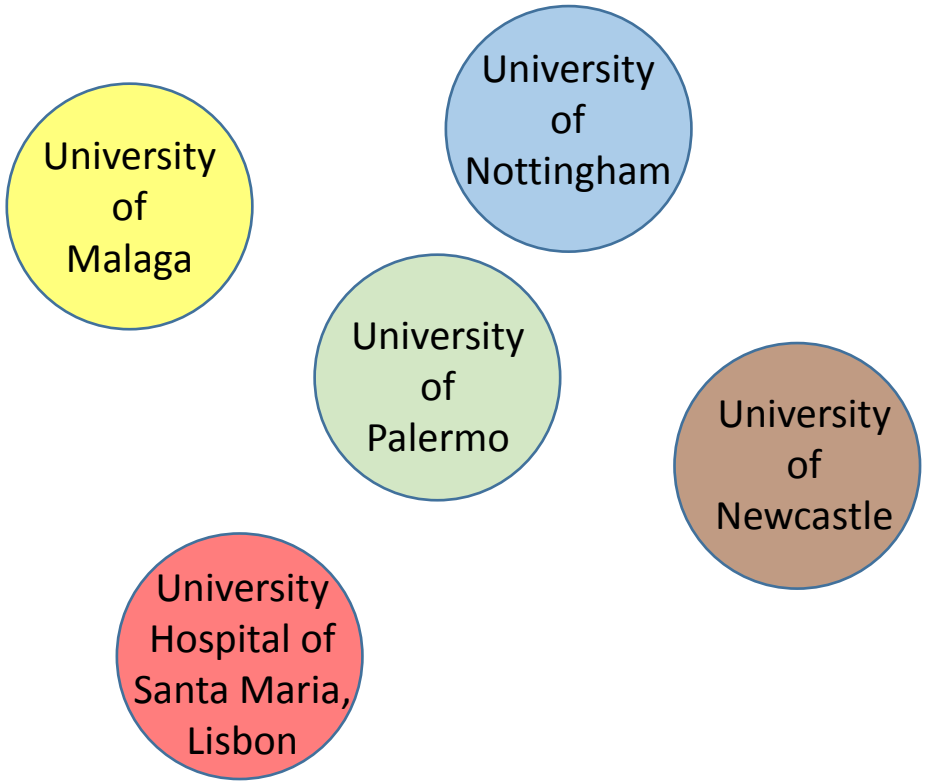
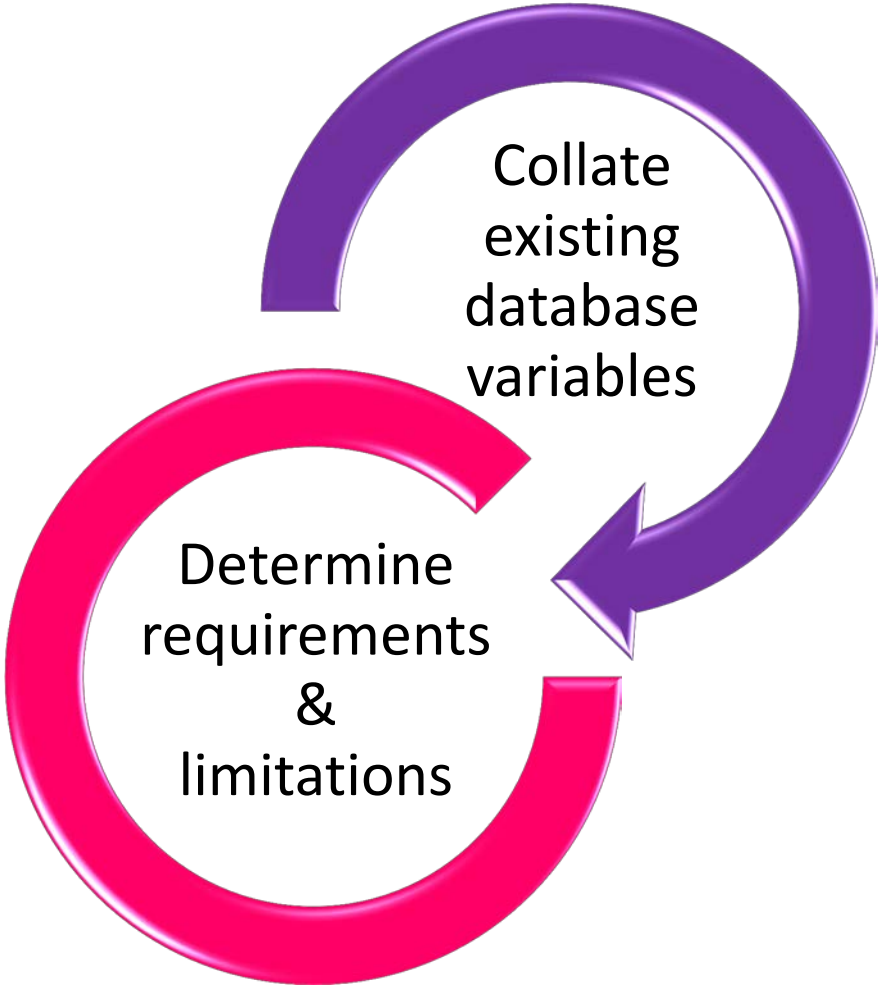
WG 1: Development of New Registry

Interaction Network





WG 1: Development of Registry

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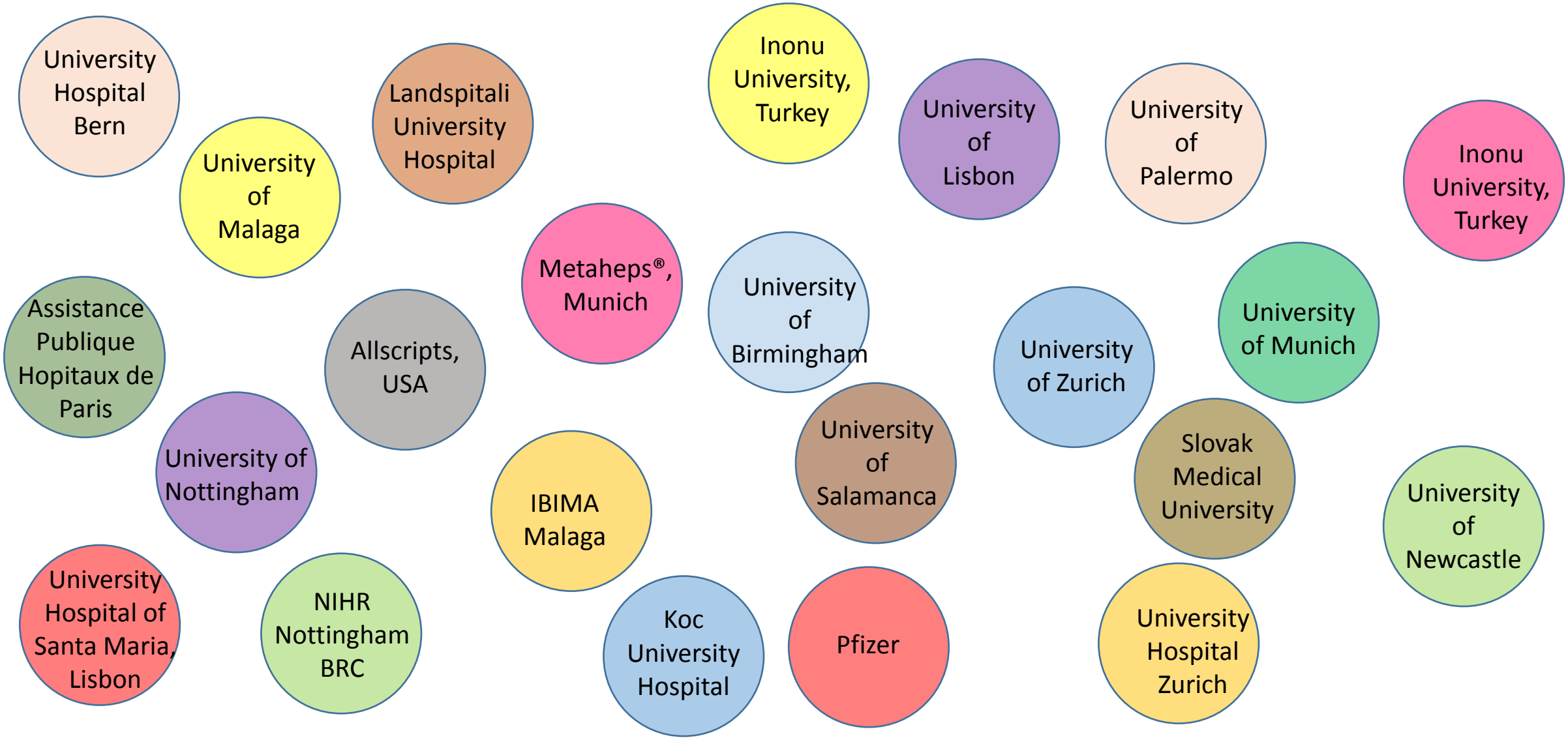
Interaction Network



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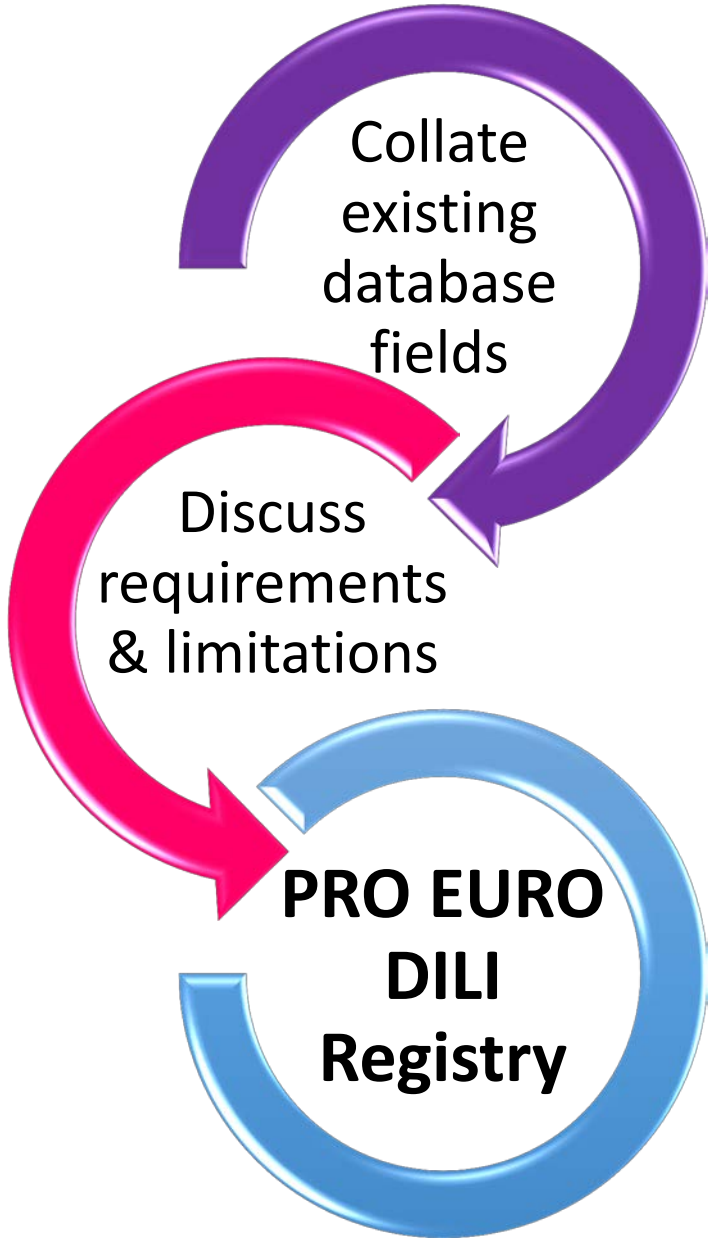
WG 1: Development of New Registry

PRO-EURO DILI REGISTRY

http://www.proeurodili.eu/



ibima Instituto de Investigación Biomédica de Málaga

University of Nottingham UK | CHINA | MALAYSIA

TransBioLine Translational Safety Biomarker Pipeline

PRO-EURO DILI REGISTRY

http://www.proeurodili.eu/

Now available to any researchers

For access contact:
cstephens@uma.es

Secure data storage at University of Malaga

Formal Data transfer / collaboration agreements

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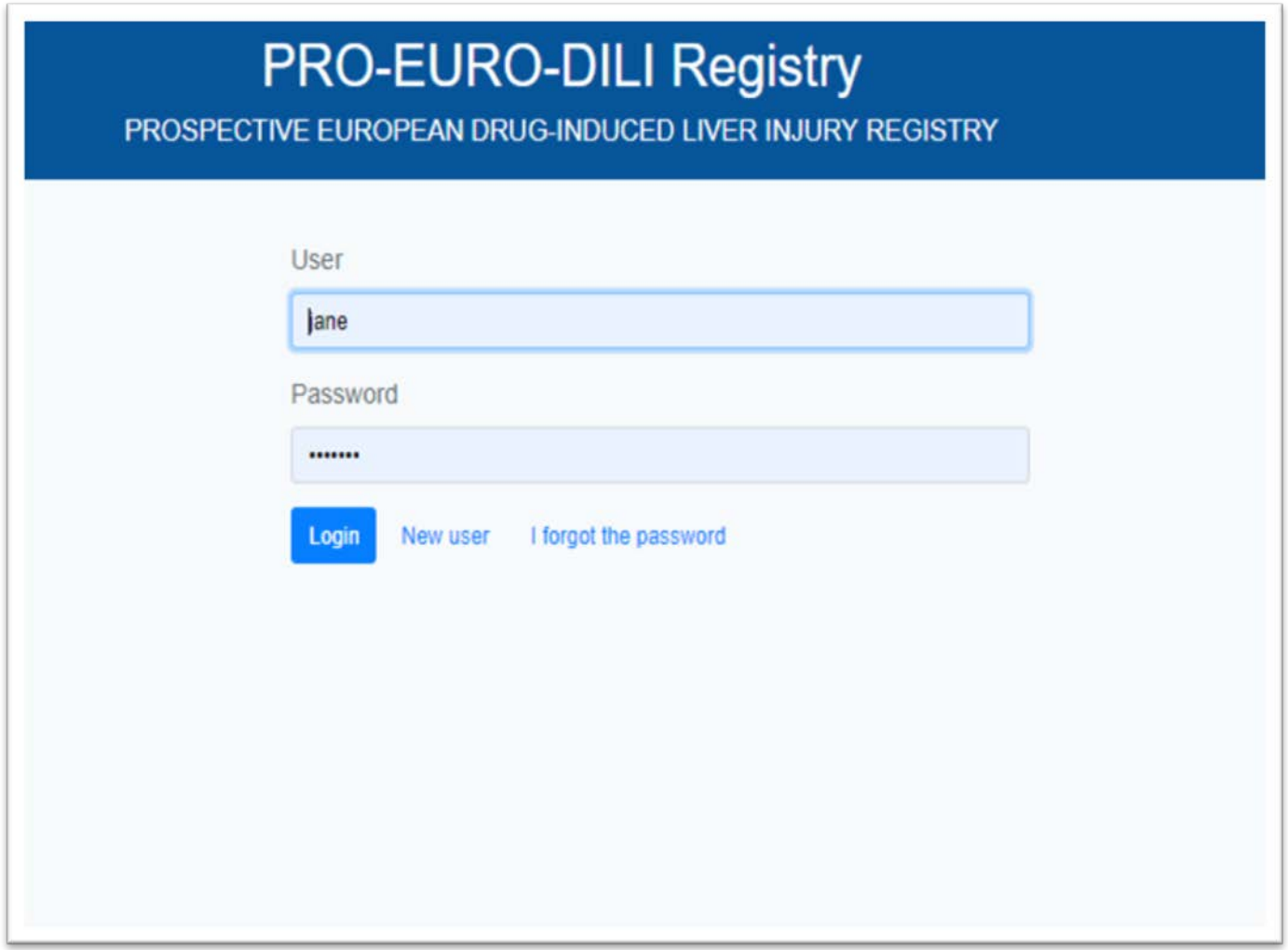

PRO-EURO DILI REGISTRY

https://www.proeurodili.uma.es/login

Key Features:

- Anonymised 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.
- Compatible with TransBioLine IMI project partnership (automated defined secure data sharing/exports)

PRO-EURO DILI REGISTRY

https://www.proeurodili.uma.es/login

In Addition:

- Defined adjudication process by expert panel (via teleconference) to assess inclusion/exclusion as DILI case after clinical investigation
- Collaboration opportunities to strengthen research power of DILI network

(e.g. resource open to industrial partnership projects on individual basis)

- Samples can be transferred to Nottingham for storage (MTA)

Central, searchable, comprehensive core defined-data repository linked to premium quality bio-samples

PRO-EURO DILI REGISTRY

- Individual research studies — Biomarkers
- TransBioLine IMI Consortium — TransBioLine Translational Safety Biomarker Pipeline — www.transbioline.com
- Industry research partnerships — MetaHeps®
- New collaborative projects — NH DestiNA — Genyo

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WG1 Deliverables:

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1. Registry Database: enable harmonized data collection – data dictionary available
2. Registry Biobank: facilitate development of accompanying high-quality bioresource
   - Based on 'user stories' of work flow processes in different centres
   - Standardise sample processing/recording - Biosample SOPs available/in refinement
   - Sample logs in development
3. Case definition, characterisation and classification
   - Link to WG2 (DILI risk stratification)
   - Systematic Adjudication Process
   - Test/evaluate scoring systems
   - Systematic review of diagnosis & management
   - Application to clinical practice
4. Extend Research Network and Research Capabilities – link to WG5 (communication)
   - Establish Legal Framework for collaboration and sharing
   - Enable/Underpin IMI TransBioLine Consortium DILI work package

Break-out sessions:

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1. Pro-Euro DILI Registry Database – consensus - variables, eCRF, 'how it works'
2. Sample Processing standardisation
   – Sample logs Biosample SOPs available/in development
   – create 'User Stories' to capture existing processes- develop work flow plans
3. Adjudication & Scoring – DILI Case Classification – link to WG2
4. Dissemination and use – link to WG5
   - Strategy for collaborative access to cohort samples/data
5. Next steps: Systematic review of diagnosis & management
6. Translation - Explore future possibilities:

- applying established expertise to improve DILI identification by testing use of clinical algorithms to electronic health datasets to give possible clinical decision alert to flag up possible diagnosis/tests to clinical teams across specialities.
- pharmacovigilance as route to identify DILI cases and identify causal drugs.

Pro-Euro DILI Registry Data Dictionary

Database unique identifier
Site Study identifier
year of birth
consent date
Consent by consultee
Genetic analysis consent
Future studies consent
weight
height
gender
Adverse reaction during pregnancy
ethnicity
Diabetes T1/T2
Hypertension
Waist circum >94/80cm
Dyslipidemia
Allergies
Alcohol current/past unit/g
smoking current/past cig/week
psoriasis
Rheumatoid arthritis
Cancer past/present/type
comorbidities
Free text notes

Suspective causative agent (s)
Active ingredient
Brand name
indication
Dose/interval
route
Treatment period
SPC hepatotoxicity reported
Published hepatotox
Adverse reaction date
Symptoms (biochem/jaud/chol)
Disappear?
Hospitalised?
Acute hypotension/cardiogenic shock
Complications withpre-existing liver conditions
Reaction Description
Disease Progression
Outcome
Last 10 medications taken

Imaging tests
Imaging date
Imaging findings
Biopsy date
Biopsy findings

SODIUM level in blood
Potassium level in blood
Urea level in blood
CREATININE level in blood
BILIRUBIN level in blood
ALBUMIN level in blood
ALT - Alanine transaminase
AST- Aspartate Aminotransferase
ALP Alkaline Phosphatase
GGT - Gamma-Glutamyltransferase
Iron in blood
hemoglobin level in blood
PLATELETS level in blood
WBC - white blood cells
MCH
MCHC
RBC
HCT
MCV
Triglycerides
Cholesterol in blood
HDL - high density lipoprotein
LDL - low density lipoprotein
PT
INR
fasting glucose level in blood
HbA1C1
CK-MB
Lactate dehydrogenase
Thyroid-stimulating hormone
Creatinine kinase
eosinophils
basophils
ESR

CRP1
total protein
AFP
Ferritin
Trasferrin_Saturation
Alpha_1_Antitrypsin
Caeruloplasmin
HOMA-IR
Insulin
Cpeptide
Viral serology tests
Hep B
HBe_Ag
Hep C
Clinical Impression CMV/EBV/HSV-1/HSV-2
IgG
IgM
IgA
Mitrochrondrial_Studies
Gastric_pariental_cells
Liver_kidney_microsomal
Smooth_muscle_antibodies
LKM-1
ANA
ANAC

Total BILirubin ULN
Conj bilirubin ULN
ALT ULN
AST ULN
ALP ULN
GGT ULN

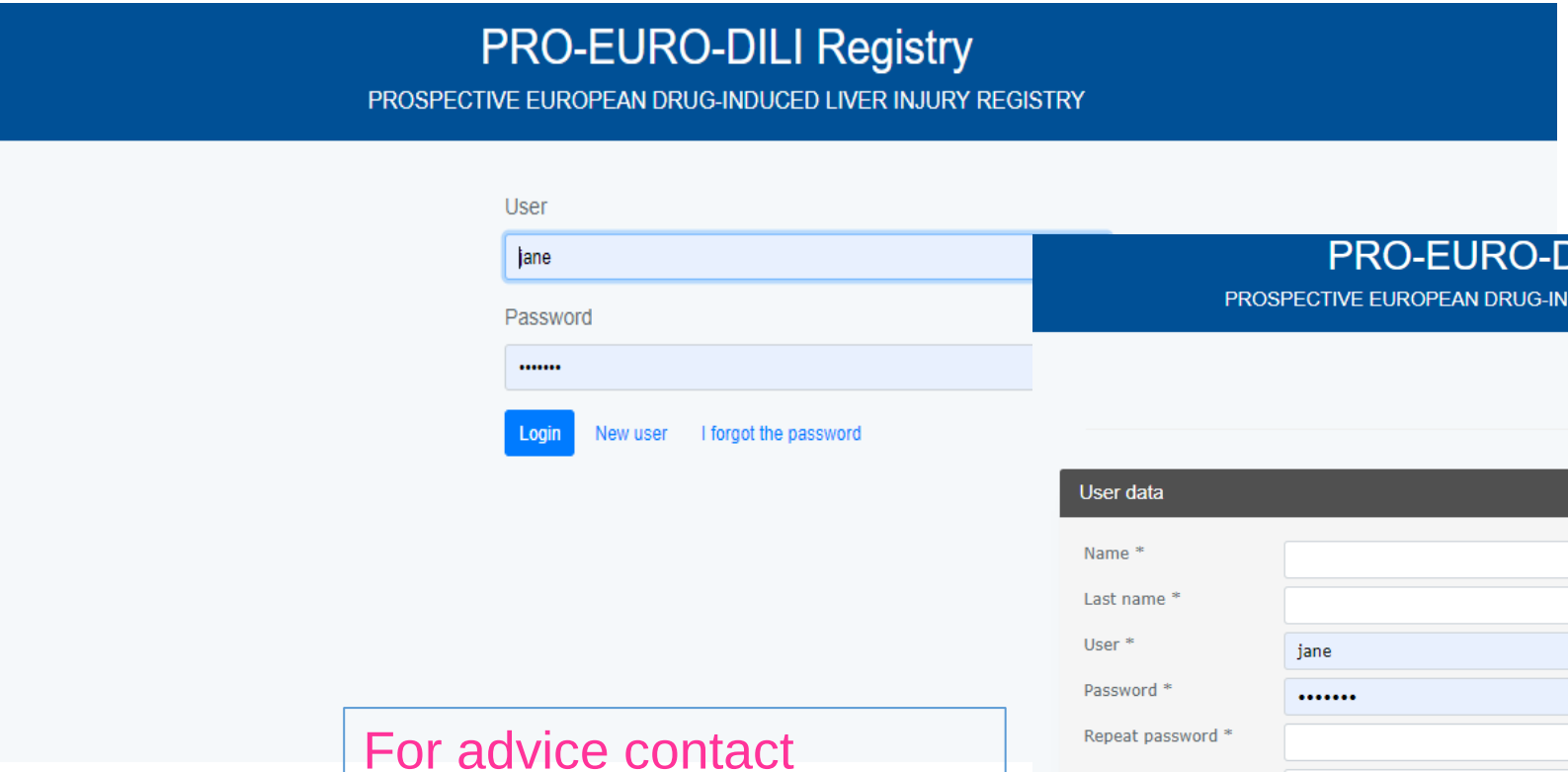
Clinical Blood Tests

Prior; first that fulfil DILI criteria; follow-up

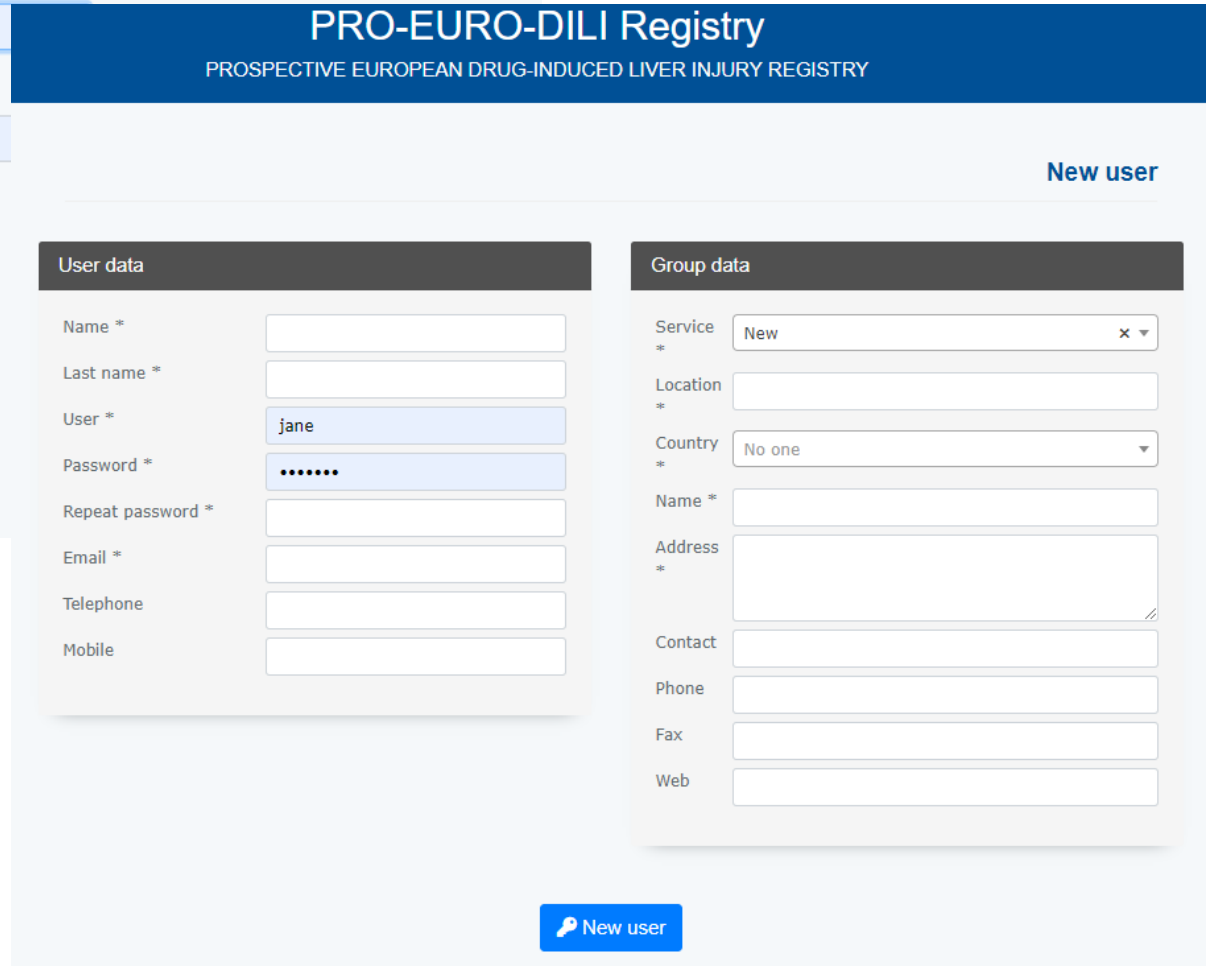
Database

Collation of Patient Data on web-based database

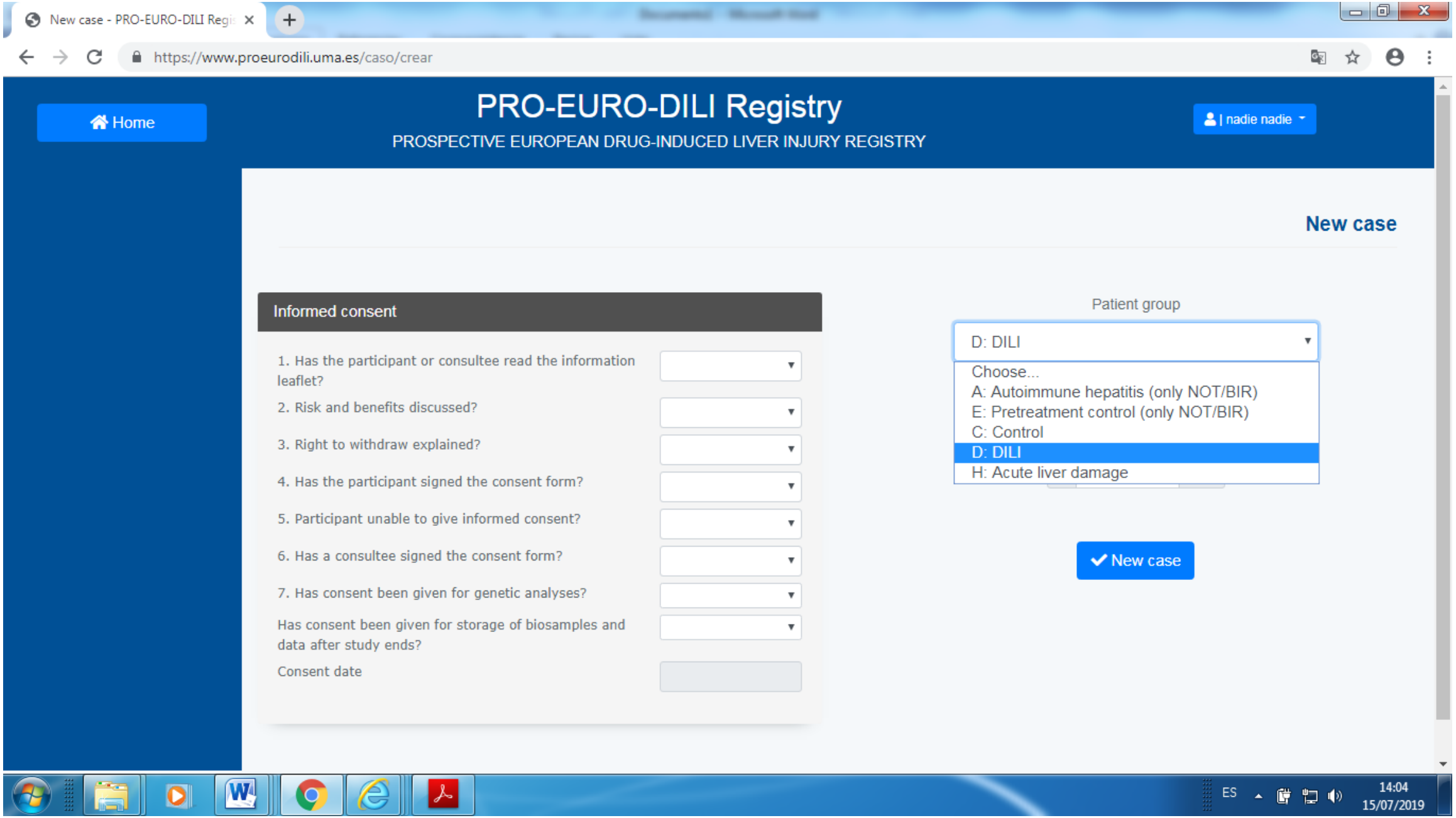
http://www.proeurodili.eu/



Request access:
New user



For advice contact
cstephens@uma.es

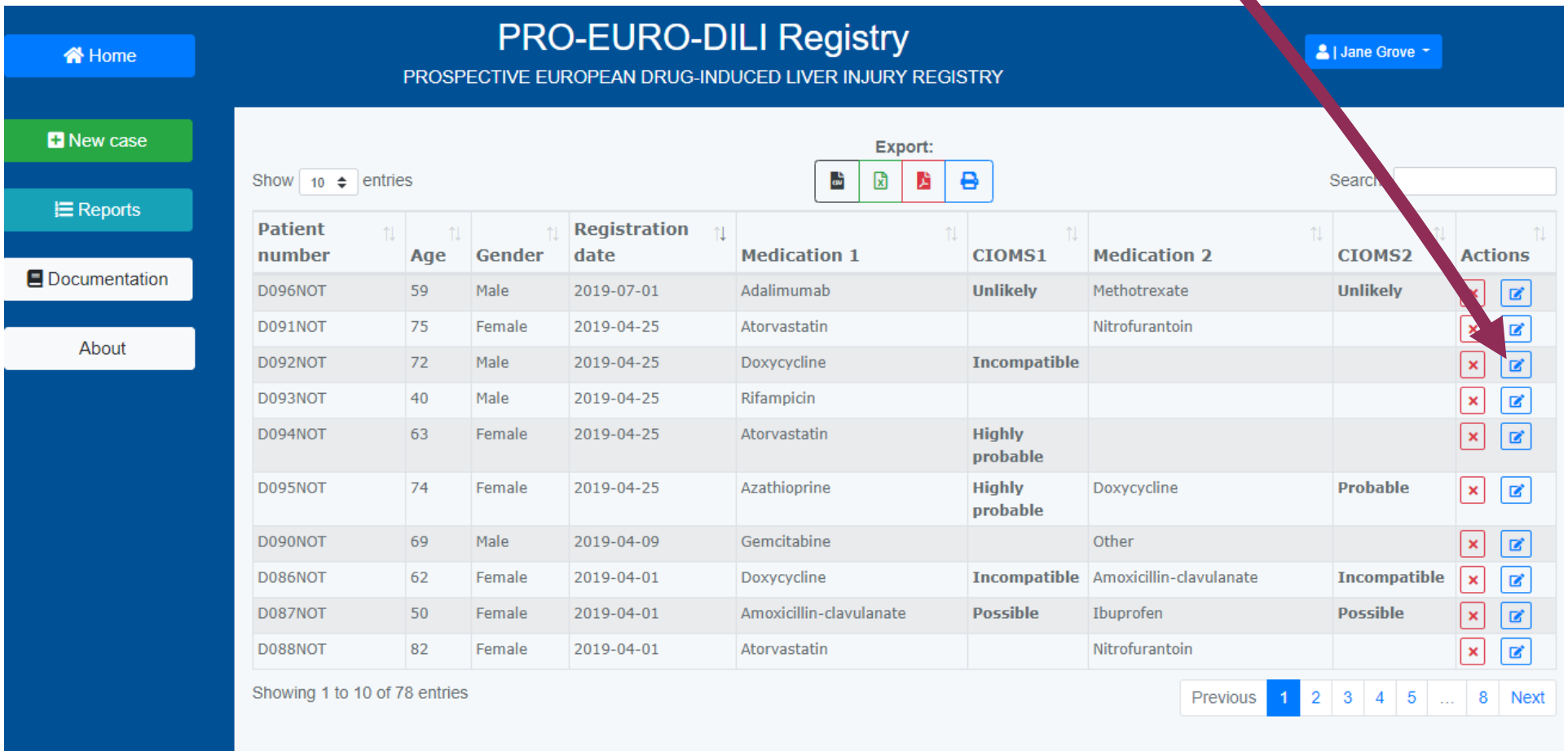

New case - PRO-EURO-DILI Regis
https://www.proeurodili.uma.es/caso/crear
Home
PRO-EURO-DILI Registry
PROSPECTIVE EUROPEAN DRUG-INDUCED LIVER INJURY REGISTRY
nadie nadie
New case
Informed consent
1. Has the participant or consultee read the information leaflet?
2. Risk and benefits discussed?
3. Right to withdraw explained?
4. Has the participant signed the consent form?
5. Participant unable to give informed consent?
6. Has a consultee signed the consent form?
7. Has consent been given for genetic analyses?
Has consent been given for storage of biosamples and data after study ends?
Consent date
Patient group
D: DILI
Choose...
A: Autoimmune hepatitis (only NOT/BIR)
E: Pretreatment control (only NOT/BIR)
C: Control
D: DILI
H: Acute liver damage
New case
ES
14:04
15/07/2019

http://www.proeurodili.eu/

Database

Home: shows patients from your site

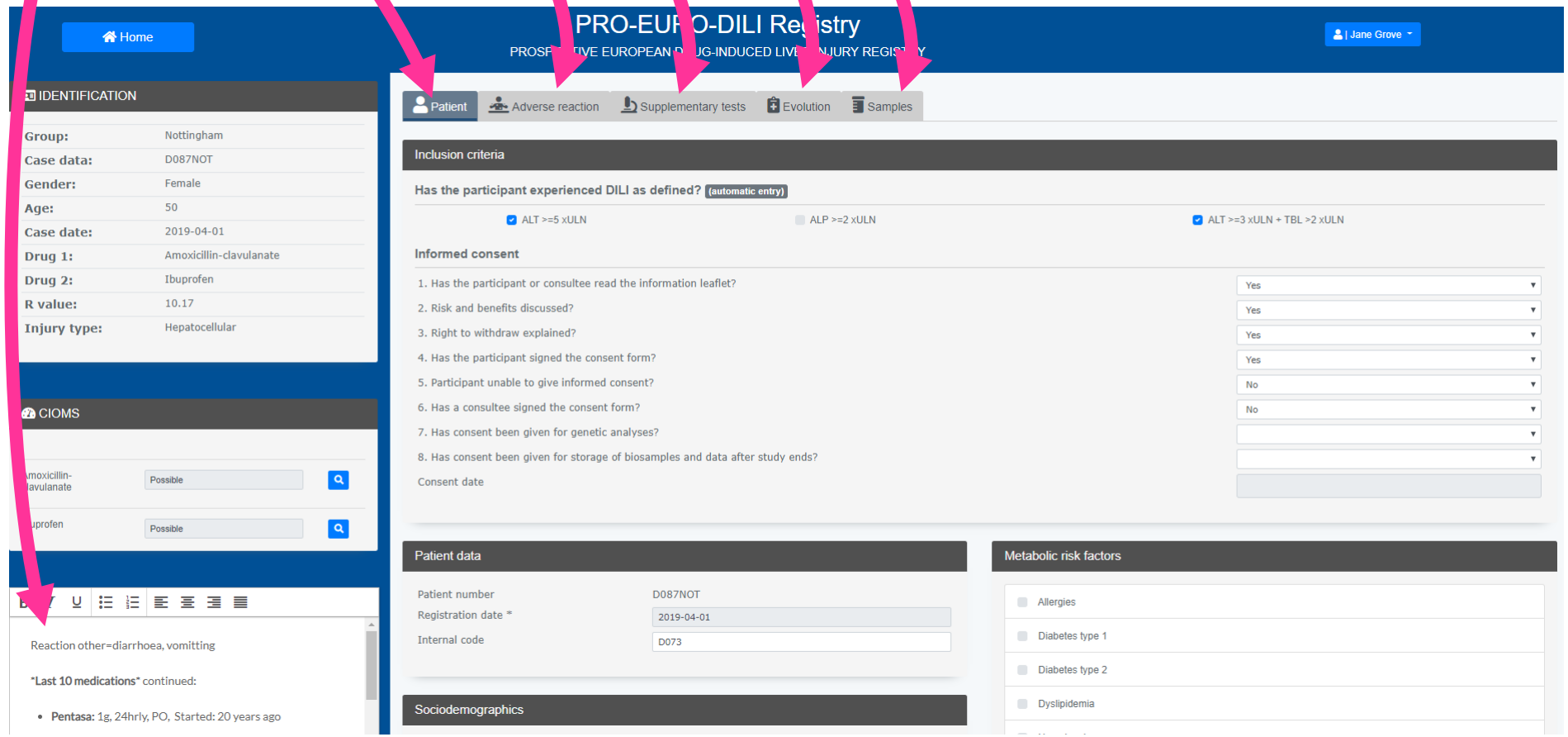
To edit case



Patient info collected ‘Patient Tab’

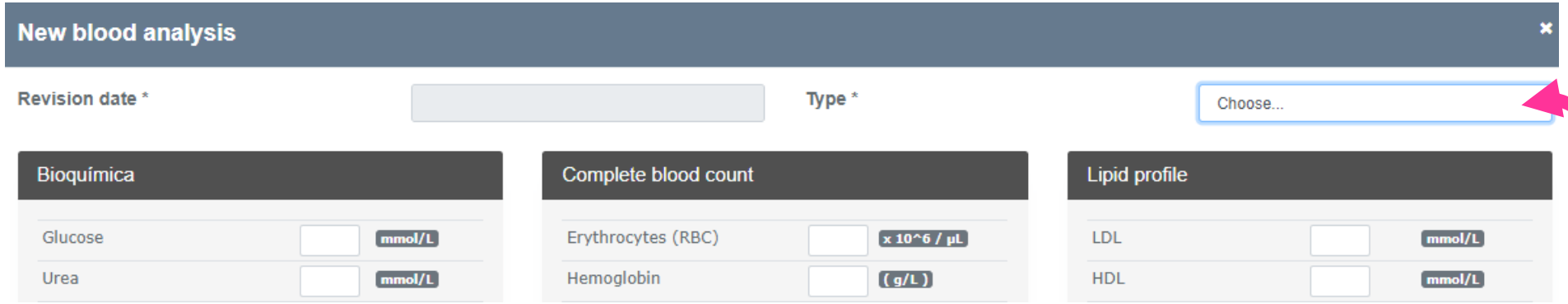
Add info / notes

Complete each tab



Add a new case or edit

‘Supplementary Tests’ Tab – for clinical test results
Can add new blood analysis data etc



Add a date and visit type

If you do not have any blood analysis prior to the first sample collection date and the first analysis in which the liver values fulfil the DILI criteria is in fact the first blood sample collection date, then it is very important to call this new blood analysis type “First that fulfil DILI criteria”, NOT “Recruitment visit 1”.
The second visit will then be called Follow-up visit 1b, or 2 depending on the timing of this visit.
Hence, note that in this situation there will be no analysis named “Recruitment visit 1”.
‘Recruitment visit 1’ will only occur when you have an earlier blood analysis dataset that fulfils DILI criteria when research samples were not collected (which is often the case).

You must have an entry for ‘first that fulfil’ as needed for CIOMS.

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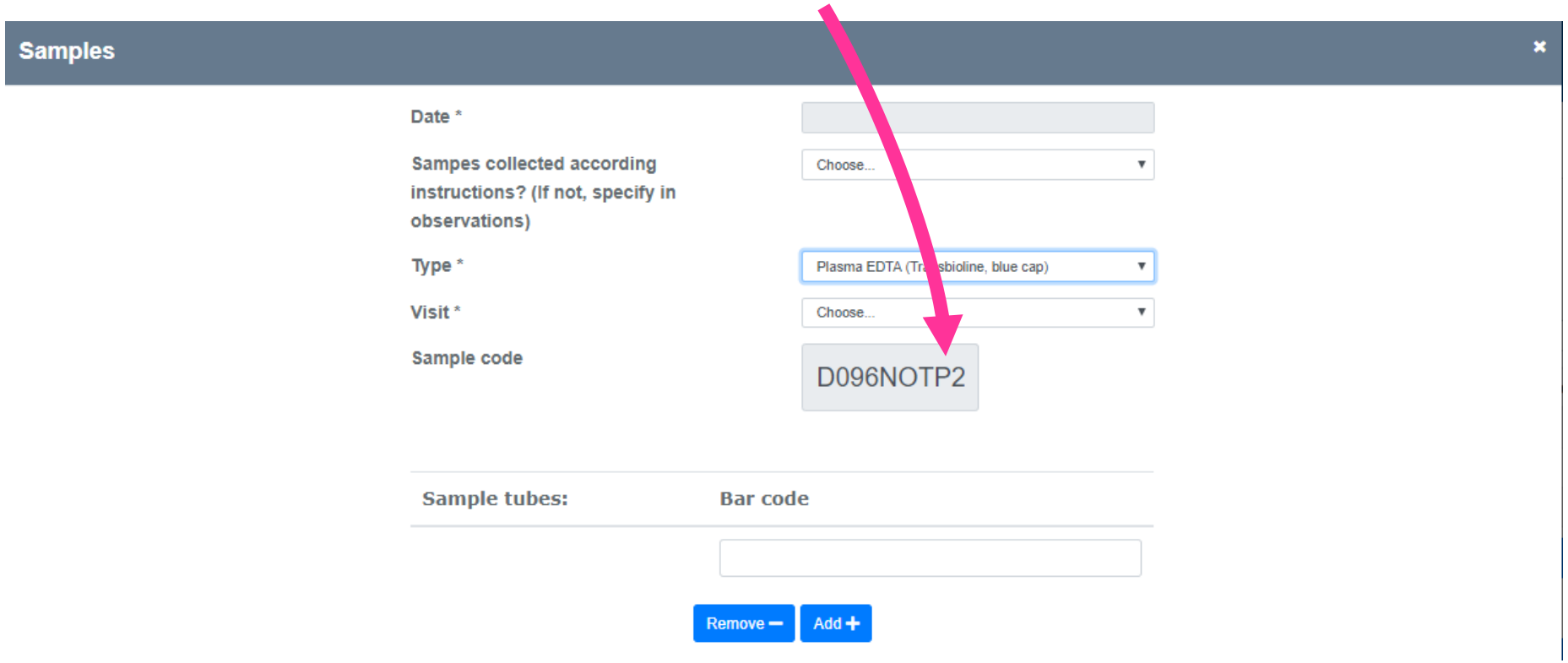
‘Samples’ Tab – for recording sample cryovial barcodes and additional tubes

On Pro Dili database ‘P2’ is platelet free plasma PFP (EDTA).
‘P1’ is EDTA plasma.
Label ‘barcode’ as aliquot 1, 2, 3, 4 etc
So we can track what additional samples are available for Pro Euro DILI projects.



Adjudication Committee Case Presentation

Case number

Center name and code

August 31st, 2016

Title: Case number

- Case description:
  - Ethnicity, gender, age
  - Comorbid conditions, BMI
  - Alcohol consumption
  - Risk factors
  - **Suspected medication(s)/start and stop dates**
  - Concomitant medications/ start and stop dates

Case Number

- Time to onset: when did symptoms suggestive of DILI appear?
  - Please specify date …… type of symptoms ……
- Did the patient experience hypotension, bradycardia, sepsis, etc. suggestive of ischemic hepatitis?

- Liver parameters at DILI recognition (normal laboratory range): AST, ALT, ALP and TBL
  - Are baseline (prior to DILI) liver parameters available for the subject? Please report AST, ALT, ALP and TBL

Case Number

Serological tests

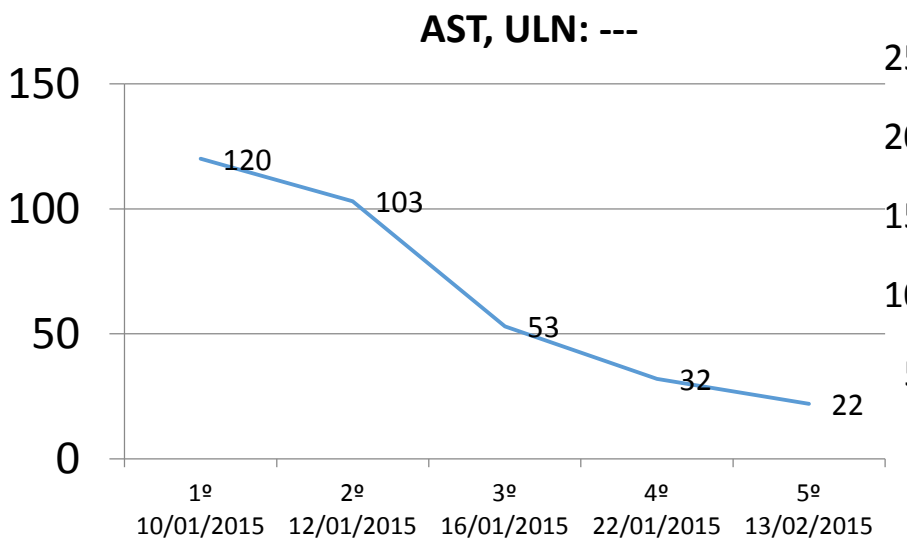
Negative???

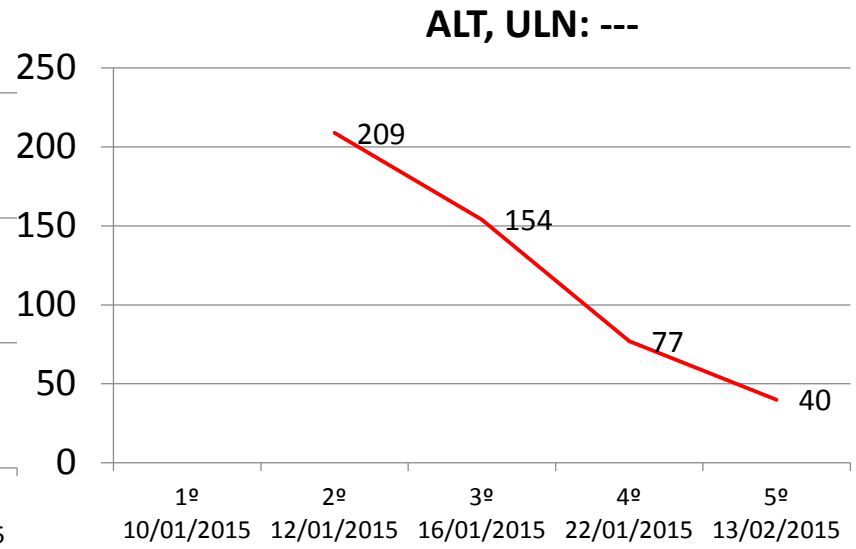
Ultrasound date and observations?

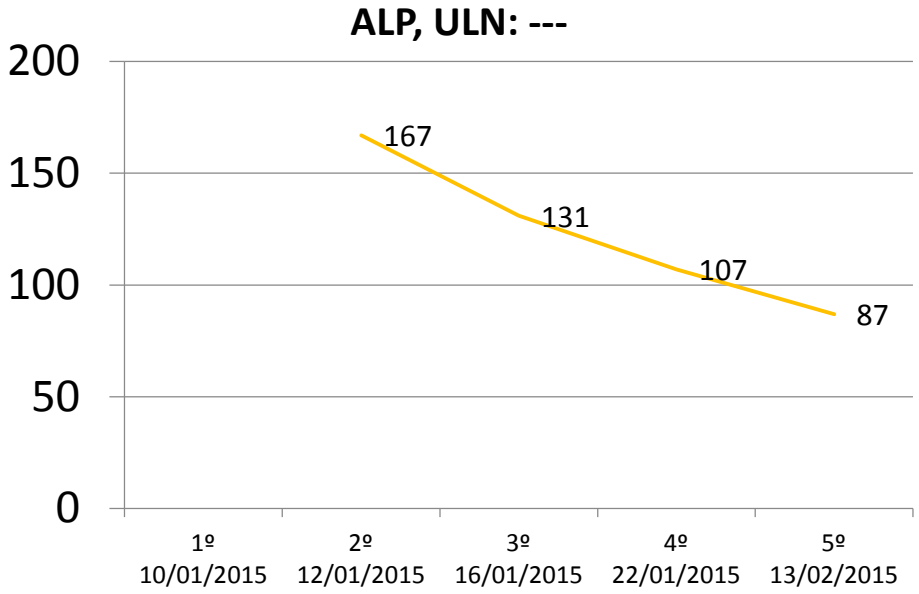
Autoantibodies??

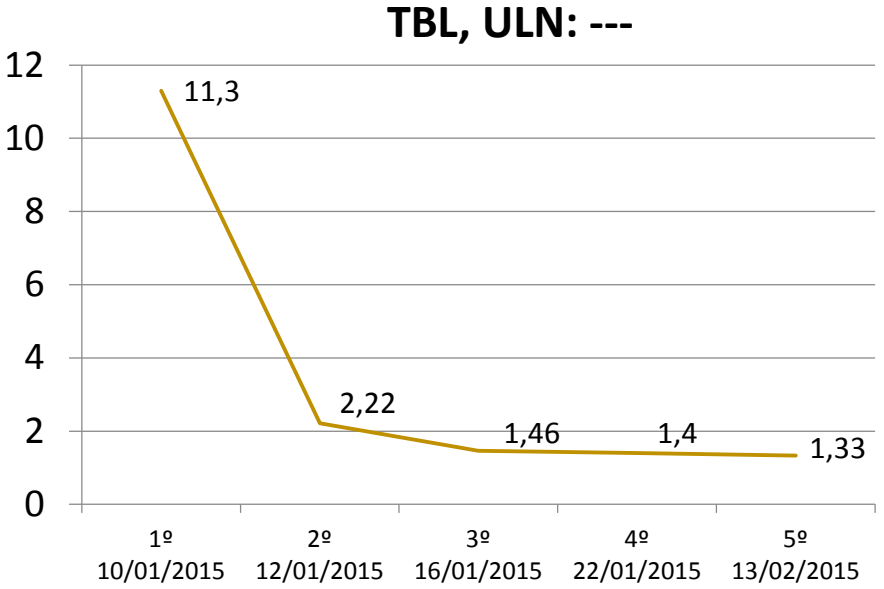
Biopsy??

LFTs evolution over time









Outcome

- Outcome?
- Time to recovery?
- Total days of follow-up?

Summary of events

- Provide an overview time line including date of drug treatments, symptom initiation, see example slide ahead.

RUCAM Scoring

TC Case	
ALT/ULN	
AP/ULN	
R	
DILI Type	
Exposure (first or reexposure)	
Time from drug intake until reaction	
Risk factors:_Alcohol	
Risk factors:_Age>55 y	
Course of reaction	
Concomitant therapy	
Exclusion of non-drug	
Previous information on hepatotoxicity	
Response to re-administration	
Total score	
DILI	

Final Outcome:

Adjudication Finding:

TransBioLine

March 2019 | IMI 28M Euro | 17 European partners

The consortium will generate exploratory and confirmatory data enabling regulatory qualification of new safety biomarkers for application in drug development; establish robust datasets on the **drug-induced Liver, Kidney, Pancreas, Vascular, CNS injury**, mechanism specific diagnostic tool/biomarkers - accepted as qualified drug development tools by EMA, FDA, and PMDA.

Prof Guru Aithal- UoN– Deputy Co-ordinator & DILI WP lead
Gastroenterologist special interest in drug-induced hepatotoxicity

University of Nottingham
UK | CHINA | MALAYSIA

https://nddcbru.org.uk/pro-euro-dili

Includes:

- **established European DILI biorepository hosted by UoN (2016-)**
  - CRN adopted, multi-centre study *led by Nottingham* Jane.grove@nottingham.ac.uk
  - samples **during and after DILI**
  - *blood, urine, stool, liver biopsy tissue*,
  - dedicated secure database for phenotyping & adjudication panel
  - recruitment via consultee if appropriate (eg encephalopathy)
- Aim: **300 cases by 2022**; plus 130 non-DILI controls (alternative causes of symptoms)
  - Plus matched medication taking no-disease group & chronic disease groups
- Biomarkers: miRNA (NGS), bile acids, lipids, CK18, SPP1, HMGB1, MCSF1 , DNA,
  - Immunophenotyping by CyTOF at Bham Uni (starts 2019) Dr Ye Oo

Pro-Euro DILI study DILI/non-DILI patient samples & data

paper CRF
eCRF/online data registry
& sample log

Pro-Euro DILI sites
Already recruiting @ 17 sites
-up to 7 visits
Serum
Plasma
Whole blood
Stool
Urine
Tissue
Optional immune studies

Dataset shared

TransBioLine Database

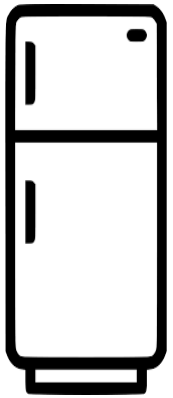
Malaga Pro-Euro DILI Database Limited access Export/Import capability

Adjudication Committee

Samples

Nottingham Sample Hub (long-term store)

Transbioline diagnosed DILI/non 2 visits selected plasma serum (HV/CON 1 visit)



Serum
Plasma

Charite ZeBanc

TransBioLine Lab Analyses

Future/additional collaborative projects with partners/non-partners

CyTOF

Metaheps

Pro-Euro DILI Recruitment

- **current, suspected acute idiosyncratic Drug-induced liver injury**
  due to medication or supplement (not paracetamol):

- Exposure to drugs including any prescription drug, over-the-counter drug, recreational drug, herbal remedies or dietary supplements prior to the DILI onset.

- **age >18**

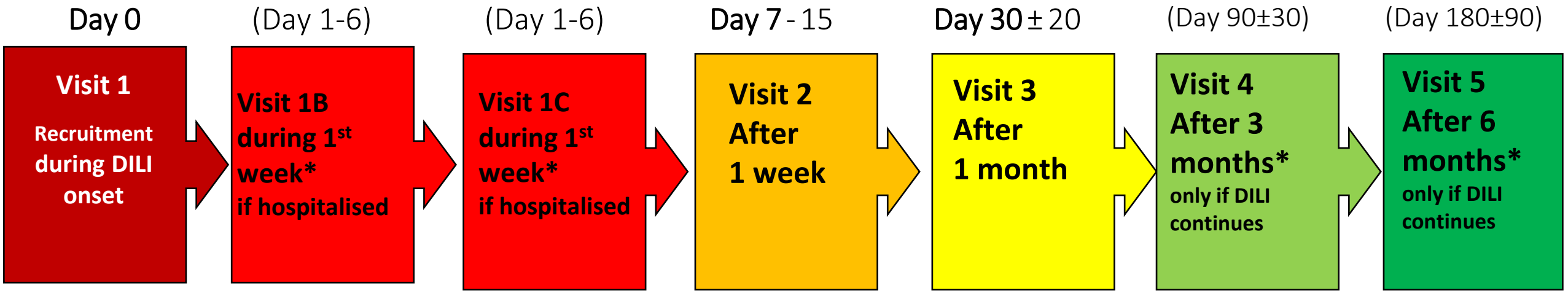
- ALT > 5xULN

or ALP > 2xULN

or ALT > 3xULN + TBL > 2xULN

- Informed consent or by consultee if required for those lacking capacity

Pro-Euro DILI Sampling Schedule



* Optional

Usually up to 35ml research blood per visit plus stool, urine & tissue if available.

- current, suspected acute idiosyncratic Drug-induced liver injury

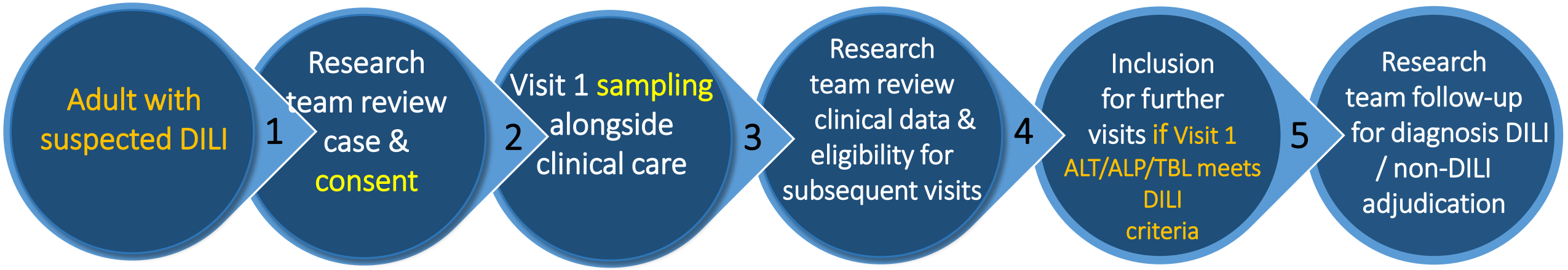
  due to medication or supplement (not paracetamol):

  - age >18
  - ALT > 5xULN

    or ALP > 2xULN

    or ALT > 3xULN + TBL > 2xULN
  - written consent or by consultee if required for those lacking capacity

Recruitment: Patient diagnosis pathway



2. Research Consent
ASAP: Within 8 weeks

1. Identification
Clinical care team identify adult who is suspected to be having an adverse reaction affecting liver functioning following taking a medication or supplement *(likely absence of other known causes of liver injury)*
with: ALT > 5 x ULN
or: ALP > 2 x ULN
or: ALT >3 x ULN **& TBL** > 2 x ULN

3. Visit 1
Research bloods & Clinical bloods at same time: ALT ALP TBL determined

4. Review case for eligibility:
Ensure DILI-like symptoms at V1 (enzymes as 1)

5. Include as eligible DILI/ non-DILI control case for further visits alongside clinical care until ALT, ALP, TBL return to normal levels.

6. Follow-up visits, diagnosis & outcome
by research team for adjudication as DILI case or control by expert panel
No alternate cause identified after investigation:
E.g. viral infection
Biliary obstruction

DILI/Non-DILI criteria – excluding other causes of symptoms

- Acute viral hepatitis due to hepatitis A, B or reactivation of B, C, E, CMV, EBV, HIV
- Acute presentation of auto-immune hepatitis unrelated to the drug.
- Confirmed acute liver injury that explains the clinical manifestation eg: ischemic hepatitis, acute ascending cholangitis.
- Acute exacerbation/ decompensation of known chronic liver disease that explains the acute event.
- Biliary obstruction explaining cholestasis.
- Clinical judgment supporting alternative explanation to the acute event.
- Other factors of exclusion: Leishmaniasis, malaria, yellow fever, Dengue hemorrhagic fever, schistosomiasis, Q fever. Only if there is clinical suspicion (history, travel, symptoms) that require these conditions to be excluded.

These patients may be enrolled and sampled but not included in planned TransBioLine partner Analysis

Distinction of DILI from Non-DILI Adjudication based on review of clinical case

Sample Collection/ Processing Summary

Collect: Bloods for clinical tests for standard care.
Plus:
2x red 6ml (or 3 x 4ml)= 12ml protect from light
for **SERUM** (SE) coagulated for 30-90min, spin 2000g 10 min; store 0.5ml x10.

2x purple lilac 6ml EDTA (or 3 x 4ml) = 12ml stored in thermal bag with ice block.
store whole blood for **DNA** - 0.5ml x 2 at any one visit (if consent for DNA analysis)
for **PLASMA** Spin 4C 2500g 10 min; store 0.5ml x8-12 plasma (PE).

at v1 and v2 for **PFP** remove 1.2ml plasma & re-spin at 10000g 10min

store 0.5ml x2 of double-spin **platelet free plasma** (PFP).

Bloods should be processed within 2h, frozen within 2.5h.
(If you are in TransBioLine consortium can include TransBioLine Sampling at v1 and v2)

Liver tissue surplus from biopsy if available– either snap frozen in liquid nitrogen or FFPE
Stool – if possible -store in bijoux
Urine if possible – store in 1x bijoux 5x 1ml cryovials
Store all at -80C and note if processing deviated from SOP

Participant ID & Sample Labelling: following Pro Euro DILI method

[A] Participants to be sequentially given number by recruiting centre:

Patients: D001 onwards;

[B] 3 digit site code (assigned by database): MAL = Malaga

[C] Sample type:

SE = serum
PH = plasma heparin
PE = plasma EDTA (PE1 or EP)
WB = whole blood (EDTA)
UR = urine
ST = stool
LB = liver biopsy
BC = Buffy coat (EDTA)
PF = platelet free EDTA plasma PE (PE2)

[D] Visit number: 01 or V1 onwards

Date

In Pro Euro DILI database you can assign a patient ID e.g. D0076NOT
To match your local site ID.
Site Patient Study ID:
D001 **= 'local internal code' for suspected DILI**
(A001 is autoimmune cases)