Pro Euro DILI Registry Study

Version 1 13/10/19

Sample Processing SOP & lab manual

PRO-EURO DILI REGISTRY

University of Nottingham
UK | CHINA | MALAYSIA

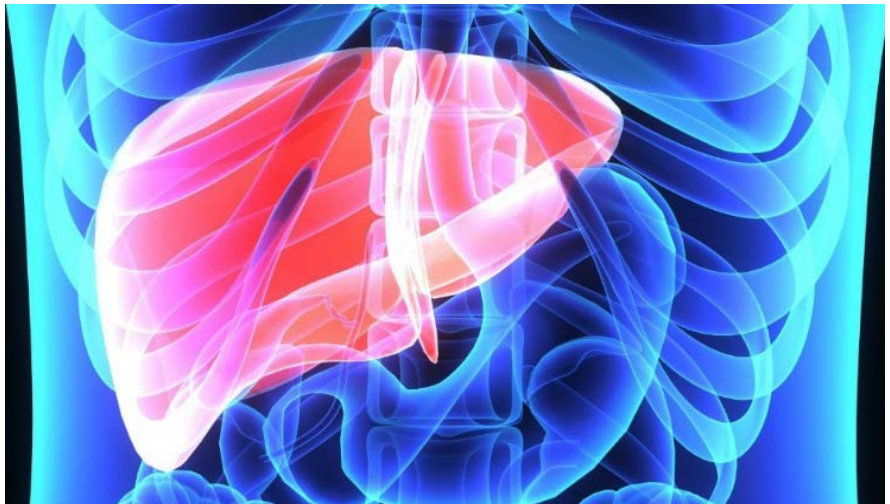
ibima Instituto de Investigación Biomédica de Málaga

Nottingham University Hospitals NHS
NHS Trust

Coordinating Centres:

Guru Aithal
NIHR Nottingham Biomedical Research Centre
Nottingham University Hospitals NHS Trust &
the University of Nottingham, UK.

Raul Andrade
UGC Ap Digestivo, Biomedical Research
Institute of Málaga, Spain



Registry Objective

To collect, store and catalogue biological samples and clinical data, to form a large international patient/control cohort available for subsequent detailed analysis by TransBioLine consortium partners & collaborators which can also be used in current and future epidemiologic and mechanistic studies.

Recruiting: **Suspected DILI** patients and **control** participants

(on medication | untreated | other causes of symptoms)

Pro Euro DILI Registry Study

Design

An international multi-centre, case-control study for DILI patients during onset and until resolution.

Aims

- To collect and store biological samples (blood, urine, stool and liver biopsy) from control groups and patients with idiosyncratic DILI along with clinical and demographic data for collaborative research.

- To identify and analyse candidate disease biomarkers and evaluate utility in monitoring (ensuring drug safety) and diagnosis.

Registry Endpoints

Study now approved until 30/4/24 in UK

1. **Acquisition of biological samples and clinical data**

Long-term stored in Nottingham Biobank

- **'suspected DILI'** cases recruited to give:
  - **300 confirmed DILI** patients (70 in UK)
  - **130 non-DILI cases** (45 in UK)

  (When patients recruited are subsequently found to be non-DILI, their samples will be retained and they will remain in the study)

- **270 healthy control** participants (50 in UK)

  For each DILI case that is enrolled we will recruit one control person who is on the same drug (as the case enrolled), but who has not developed DILI

Includes:

  - 20 cancer patients prior to immunotherapy
  - 20 cancer patients on immunotherapy with no DILI symptoms

- **20 patients diagnosed with auto-immune hepatitis** having DILI-like symptoms (elevated liver enzymes) (Nottm/Bham, UK)

Recruitment of suspected DILI Patients

- **current, suspected acute idiosyncratic Drug-induced liver injury** due to medication or supplement (not paracetamol):
  (*no definite alternate diagnosis at time of recruitment*)

- **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**

  (on day of recruitment
  ie within 24h of visit 1 sampling)

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

ALT: Alanine aminotransferase; ALP: Alkaline Phosphatase; TBL: total bilirubin

Recruitment: Suspected DILI Patient diagnosis pathway

2. **Research Consent**
While LFTs are likely to meet inclusion criteria (usually within 24h of identification but can be up to 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 xULN
or: **ALP** > 2 xULN
or: **ALT** >3 xULN & **TBL** > 2 xULN

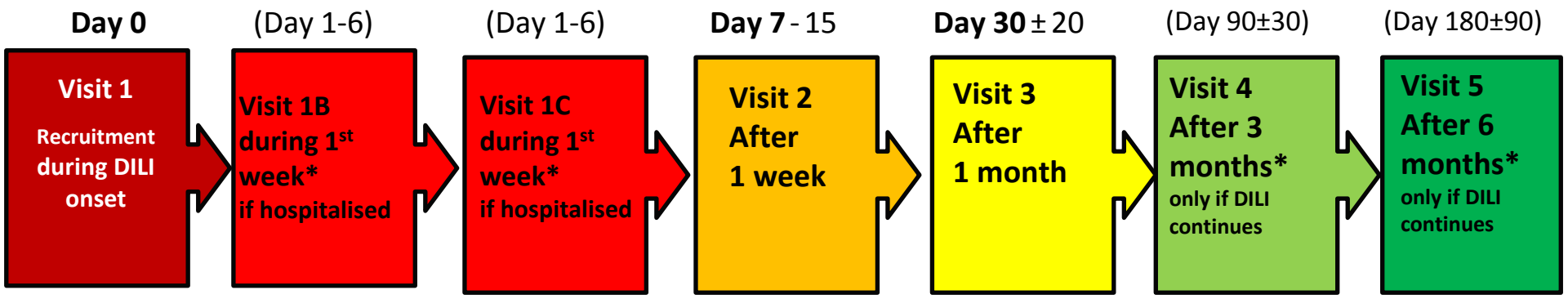
3. **Visit 1**
Research bloods & Clinical bloods at same time: ALT ALP TBL determined

4. **Review case for eligibility:**
Ensure DILI-like symptoms present at V1 (LFTs meet inclusion criteria)

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 (Establish if alternate cause after investigations: E.g. viral infection Biliary obstruction)

TransBioLine Pro-Euro DILI Sampling Schedule



**Optional visits*

Usually up to 35ml research blood per visit plus stool, urine & tissue if available.
Additional 30ml for immunophenotyping where appropriate (at any one visit) is optional.
No more than 80ml to be taken at visit including clinical samples
If liver biopsy is performed as part of patient care, we will request any surplus tissue.

- 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

Consent:

TransBioLine

- **Since it is crucial to recruit patients at time of acute DILI which may be diagnosed at unscheduled/emergency appointment, it may not be possible to provide the patient information sheet 24h beforehand. However a reasonable amount of time should be given for consideration of the study –e.g. 1 hour undisturbed and a full explanation of the project given with adequate opportunity to ask questions. See GCP guidelines.**

https://www.ema.europa.eu/en/documents/scientific-guideline/ich-e-6-r1-guideline-good-clinical-practice-step-5_en.pdf

- **If encephalopathy or dementia/mental health issues are suspected (but not both) then consent via a consultee should be sought. (separate guidance and documents are supplied for this)**

Consent Form should include agreement that:

- 1. Participant Data can be stored and shared in the registry database (anonymised data stored in secure Pro Euro DILI database for 25 years)
- 2. Data can be used in future research
- 3. Samples (anonymised) can be used for biomarker analysis
- 4. Samples can be used for DNA analysis (if applicable)
- 5. Samples can be stored in Pro Euro DILI Biobank (eg Nottingham) during and after the project, to be used in future research (for up to 25 years) by partners/collaborators.

(No point keeping samples without data)

Patient Information on Samples:

We will transfer and store the samples collected to Nottingham Digestive Diseases Centre.

We will send samples to research teams at other institutions for collaborative research, or to commercial service providers for specialist analysis. These may be within or outside the UK. All samples and medical details will be anonymised so you cannot be identified. We will comply with the Human Tissue Act and other International laws.

Various substances and constituents of your blood, urine and stool will be measured.

(e.g. the proteins, RNA & DNA in your blood; the bacterial fragments present in your stool)

- Your blood samples will be analysed to look at DNA & gene variations which may contribute to DILI, if you agree.
- We will not carry out clinical genetic testing of your samples to detect known inherited disorders.

  (we will not be able to give you any results)

Your samples will be labelled with a code not your name or address so you cannot be identified.

Patient Information on Biobanks:

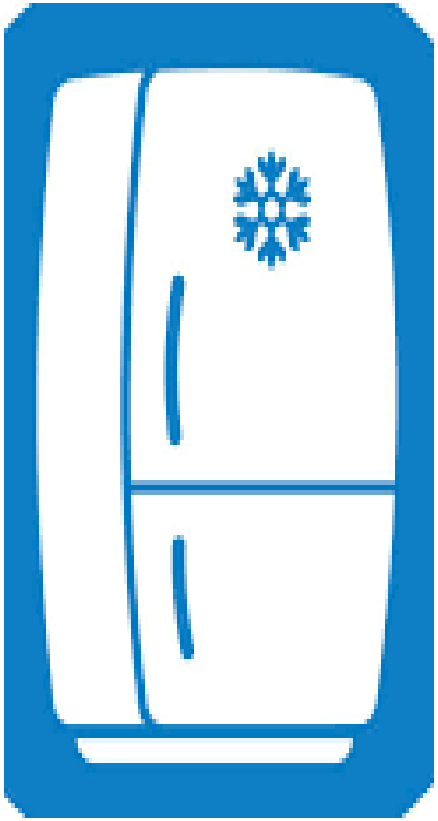
Sample Biobanks

Long-term sample storage facilitating future DILI research

After the study is complete, we would like to store samples left over so they can be made available for future research projects.

Samples from the study will be transferred to custodianship of the University of Nottingham (HTA Licence No. 12265; Designated Individual: Dr William Dunn) and stored in the HRA approved NDDC-BRU research tissue bank at the University of Nottingham for up to 10 years.

If you do not wish your samples to be transferred to a Biobank, indicate it on the consent form or inform your local team.



Patient Information on Data:

We will not share your personal details with anyone outside the research team and regulatory bodies.

When you agree to take part in a research study, the information about your health and care may be provided to researchers running other research studies in this organisation and in other organisations. These organisations may be universities, NHS organisations or companies involved in health and care research in this country or abroad. Your information will only be used by organisations and researchers to conduct research in accordance with the UK Policy Framework for Health and Social Care Research.
This information will not identify you and will not be combined with other information in a way that could identify you. The information will only be used for the purpose of health and care research, and cannot be used to contact you or to affect your care. It will not be used to make decisions about future services available to you, such as insurance.

Data collected during the study may be transferred for the purpose of processing, analysis, etc, to associated researchers within/outside the European Economic Area. All data transferred out of the UK/EU is protected under GDPR.

In line with Good Clinical Practice guidelines, at the end of the study your data will be securely archived for 25 years. Arrangements for confidential destruction will then be made.

Registry Databases: sharing compiled data

The anonymised data compiled in the Pro-Euro DILI databases will be made available to other research partners and collaborators as agreed within the consortium (for 25 years), in line with research funder's policies. Sharing of original data following publication allows open scrutiny of our work. All data is securely stored and is anonymised so you cannot be identified.

You can find out more about how we use your information at **www.nuh.nhs.uk/GDPR** or can request our GDPR policy document from DPO@nuh.nhs.uk

The UK policy framework is described at https://www.hra.nhs.uk/planning-and-improving-research/policies-standards-legislation/uk-policy-framework-health-social-care-research/

Recruitment & study visits:

- **Recruitment (visit 1) should be arranged to coincide with clinical care visit wherever possible so that clinical blood sampling can be done at the same time for patient convenience. This also provides the required ALT, ALP and bilirubin testing on the same day as research samples are taken.** If LFT tests are not performed on day of visit this should be noted in CRF and recruitment log and details of results from previous and subsequent dates noted. (patients will be excluded if this does not confirm they have acute DILI at visit 1; but samples will be retained)

- **No more than a total of 80ml of blood should be taken at the combined visit with up to 35ml for research project.**

- **If more appropriate, with agreement of participant, a separate research visit can be arranged to avoid excessive blood quantity being taken**

Recruitment Log

Recruitment LOG

Site Name	University of Nottingham	Site Code	NOT
Name of PI	Guruprasad P. Aithal	Delegate Investigator	

Site Study Patient ID	Subject Name	Subject Initials	Date of Recruitment DD/MM/YYYY	Date of Birth DD/MM/YYYY	Subject ID on Database	Included/ Excluded	Reason For Exclusion
D001					NOT00003		
D002							
D003							

Inclusion criteria for follow-up visits

TransBioLine

- **Confirmation of eligibility for further visits:**

Visit 1 : ALT > 5xULN *or* ALP > 2xULN *or* ALT > 3xULN + TBL > 2xULN.

Visit 1a and 1b : only if hospitalized and continued clinical testing for LFTs.

Visit 4: only if LFTs are abnormal at visit 3.

Visit 5: only if LFTs are abnormal at visit 4.

Patients should complete a minimum of visits 1, 2 and 3 to complete the study but only 1 visit is acceptable

Adjudication:

Each site PI will present detailed clinical investigation of cases to determine if participant should be included in DILI or non-DILI patient group for collective decision about whether case is DILI or non-DILI or inconclusive at regular meetings.

- **This will be recorded in Pro-Euro DILI database and coordinated by Malaga team (cstephens@uma.es)**

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

Following recruitment of suspected DILI cases, these criteria can be used to identify alternate causes to determine which recruits are DILI and which are non-DILI cases.

- 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

Recruitment of control group patients

- this will be at Nottingham and Birmingham UK sites only.
- **These participants attend just a single 30 min visit for sampling as suspected DILI patients visit 1.**

1. symptomatic patients (raised LFTs) diagnosed with auto-immune hepatitis.

2. Cancer patients (with no DILI symptoms) prior to immunotherapy treatment (ie disease-matched, 'untreated controls') and after 10 week treatment program (i.e. drug-matched, 'medicated controls').

3. Other people taking the same drugs as recruited DILI patients but who have no DILI symptoms i.e. additional drug-matched, 'medicated controls'). Recruited at Nottingham only in UK initially.

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

Dataset shared

paper CRF
eCRF/online data registry
& sample log

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

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

Adjudication
Committee

Phenotyped patient
cohorts for
research projects

Research by
partners/
collaborator
Lab
Biomarker
Analyses

Samples

Nottingham
Sample Hub
(long-term
store)

Future/additional collaborative
projects with partners/non-partners

Blood Collection for Pro Euro DILI:

For Standard Visit (35ml max) *v1-5*

2x 6ml red uncoagulated (12ml)

blood tubes *(foil wrap)* – min 6ml

**these must be protected from light*

(can use gold SST tubes)

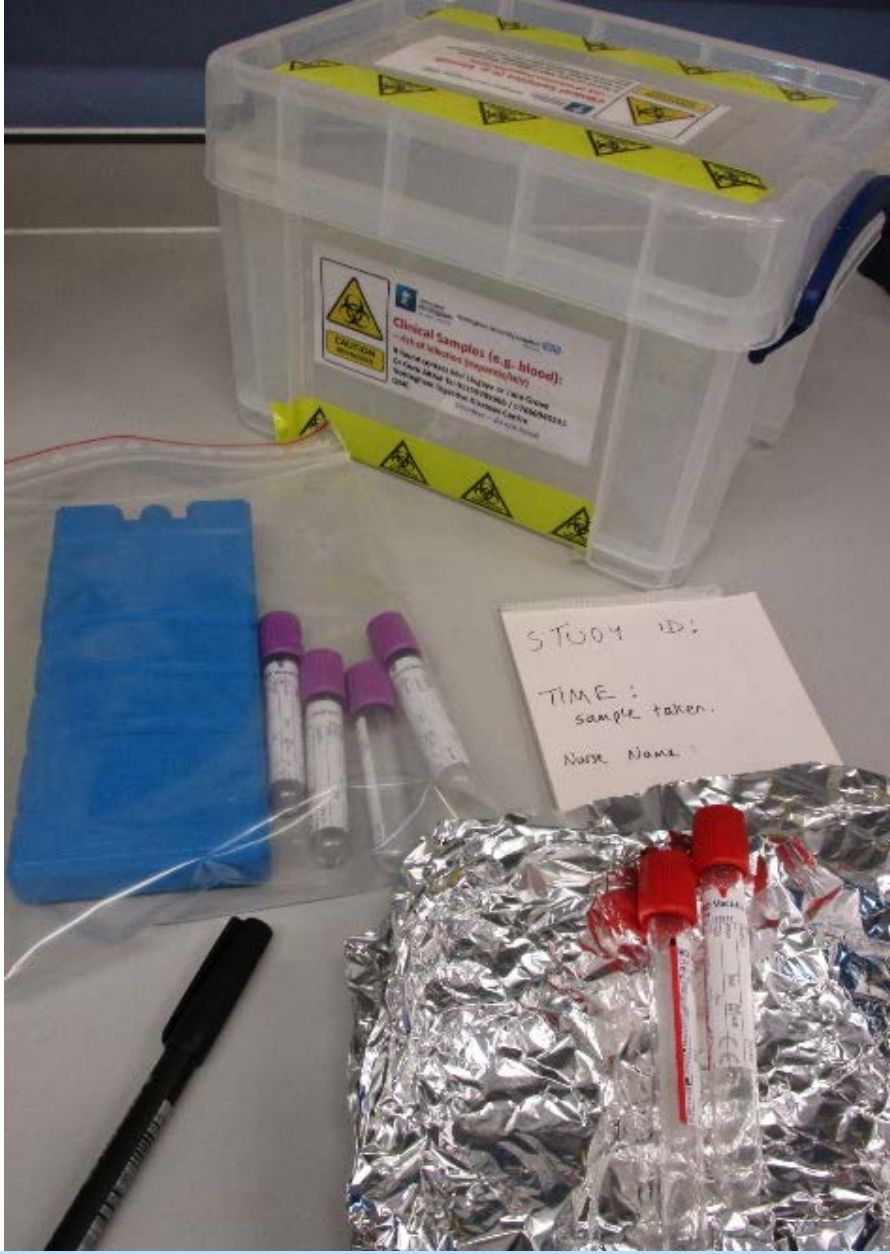
3x 4ml purple EDTA (12ml)

blood tubes - minimum 10ml

* *these must be chilled*

Draw red then purple
Label with permanent marker pen
with patient study ID (not name)
Visit number and time taken and date

Transport to lab within 2 hours



Transport samples to lab in sealed, labelled, double containment UN3373 regulation Biological Substance Category B

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)
PFP = platelet free EDTA plasma PE (PE2)

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)

[D] Visit number: 01 or V1 onwards (v1 *onset visit must correspond to DILI episode*)

Date

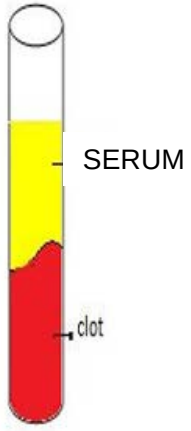
If you have less than minimum amount or not chilled or processed in 2h then continue with processing but *Please indicate this on the CRF & sample log*

Sample Processing SOP page 1

1

6-12ml clotted Blood for Serum

(red tube or yellow serum separator collection tube)



a. Allow to **coagulate for 30-45 min at room temp:**
PROTECT FROM LIGHT (put in foil or bag)

b. Centrifuge 2000g for 10 min at room temp

c. Remove top yellow layer carefully using a pipette or pastette
-avoid disturbing the interface

d. Aliquot 0.5ml into cryovials (6-12 screw cap tubes):

e. Freeze immediately & store at -80ºC
(should be within 2.5 hours of blood taking)

Always store all the serum you obtain

Label:
Study ID: D005
Visit number
Date 04.05.19
Sample type SE

Sample Processing SOP page 2

2

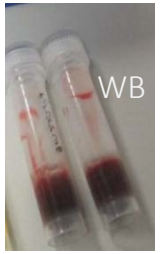
12ml EDTA Blood (purple collection tube)

Pre-chill vacutainer in bag of frozen beads with ice block in cool bag. Pre-chill centrifuge.

a. Collect & Mix blood by gently inverting x10
Keep blood chilled (4ºC or on ice) until processed. Centrifuge within 2 hour.

b. If patient has consented for DNA:
remove 0.5ml whole blood into cryovial x 2.
(this does not need to be done at every visit – just once)

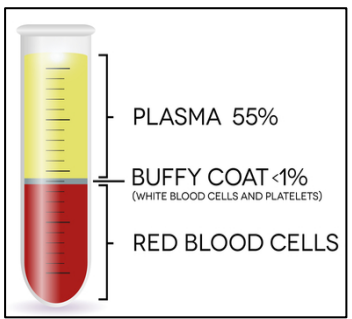
Whole blood for DNA



c. Centrifuge blood tubes **at 2000g for 10 min at 4ºC**

(i) For PFP: remove 1.2ml of top yellow layer to an eppendorf. (not at v3-5)
then centrifuge this at 10,000g in a chilled microfuge for 10 min.
pipette 0.5ml of top layer into **x2** cryovials
(This can be omitted if centrifuge unavailable)

platelet free plasma PFP



(ii) For plasma (PE) pipette 0.5ml top yellow plasma layer after spin to **cryovials (approx. 5-**10)

d. Freeze immediately & **store at -80ºC**
(should be within 2.5 hours of blood taking)

EDTA Plasma

PE

Sample Processing SOP page 3

3 Liver Biopsy Tissue (Biopsy only when clinical care indicates)

Snap freeze surplus at time of biopsy or request FFPE tissue from pathology

4 Urine (UR)

Collect approx. 30ml of midstream urine (not first urine of the day) in 30ml Universal (or equivalent)

Transfer 5 x 1ml into cryovials and
upto 5 x 5ml into bijoux containers

Store at -80ºC

5 Stool (ST)

Patient to collect stool using appropriate standard methods e.g. use cardboard tray (Patient guide available) *Avoid contact with urine.*

Transfer into bijoux container if possible.

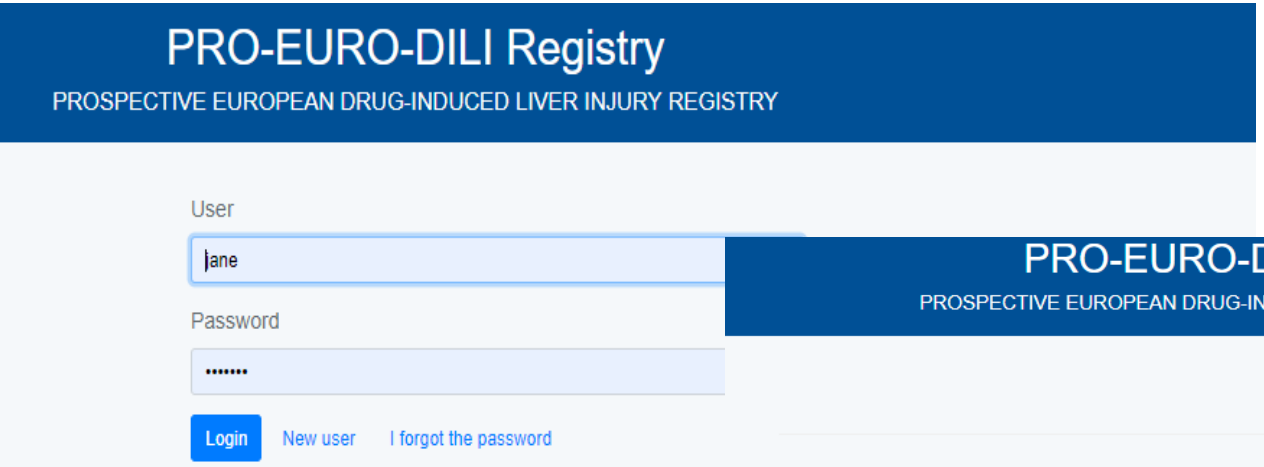
WB is only required for one visit (v1 usually)
PFP is optional and only needed at visits 1-2.
Send all to Nottingham. Record samples in Pro Euro DILI database.

Pro Euro DILI Sample processing and shipping log - XXXX SITE

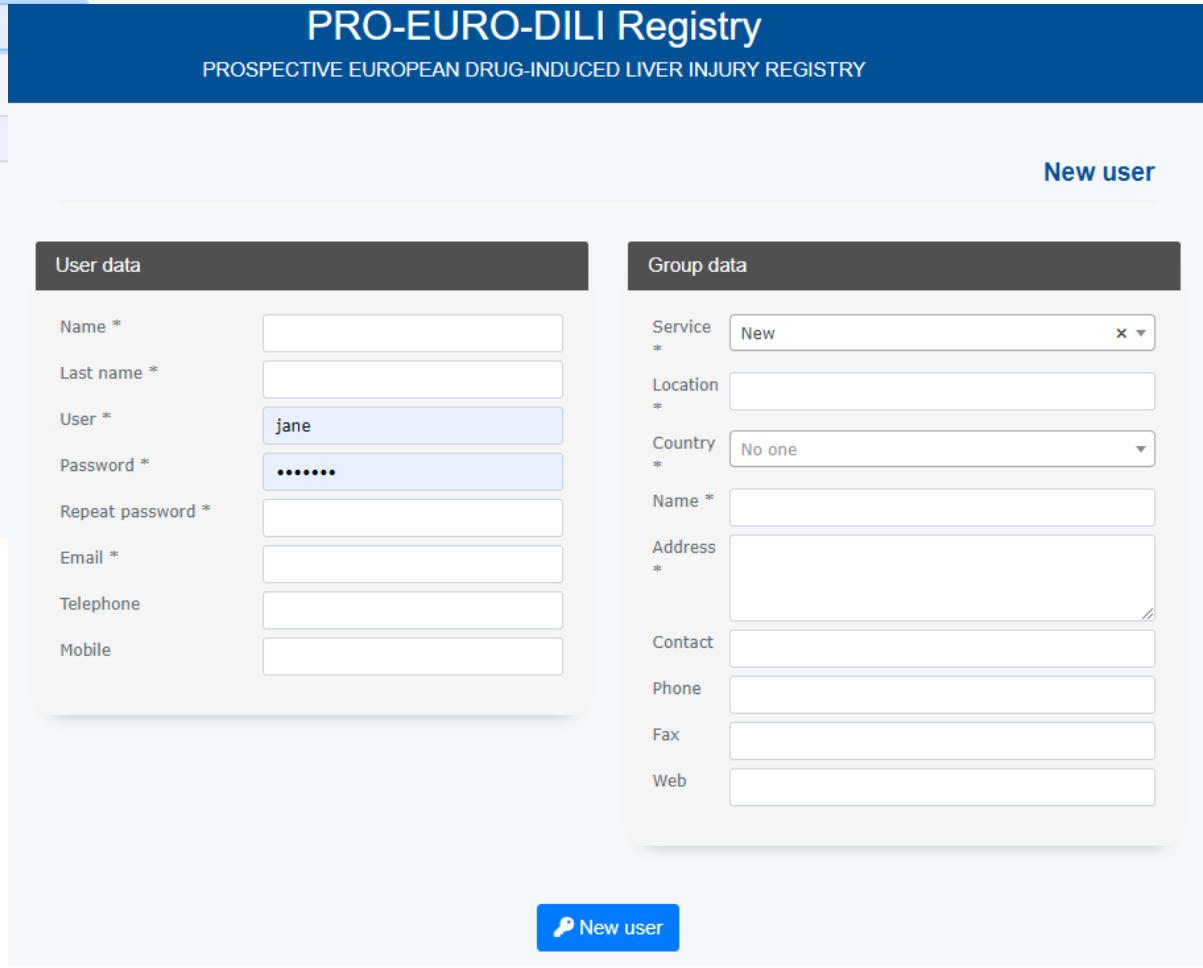
			D001	Site Patient ID (record on samples) 'Internal code'
				Recruited Date
			NOT00001	Database Patient Number
				Visit No.
				visit Date
				TIME SAMPLES RECIEVED IN LAB
				SERUM No. aliquots **(SE)**
				Platelet free **EDTA PLASMA aliquots (PFP)**
				PLASMA EDTA No. aliquots **(PE)**
				EDTA Whole blood No. aliquots **(WB)**
				Urine No. 1ml aliquots **(UR)**
				Urine No. 5ml aliquots **(UR)**
				Liver Biopsy available?
				Stool (ST) Y/N
				WITHDRAWN Sample Disposed of (date/initials)
				Processed by:
				NOTES – frozen within 2.5h of blood collection

Collation of Patient Data on web-based database

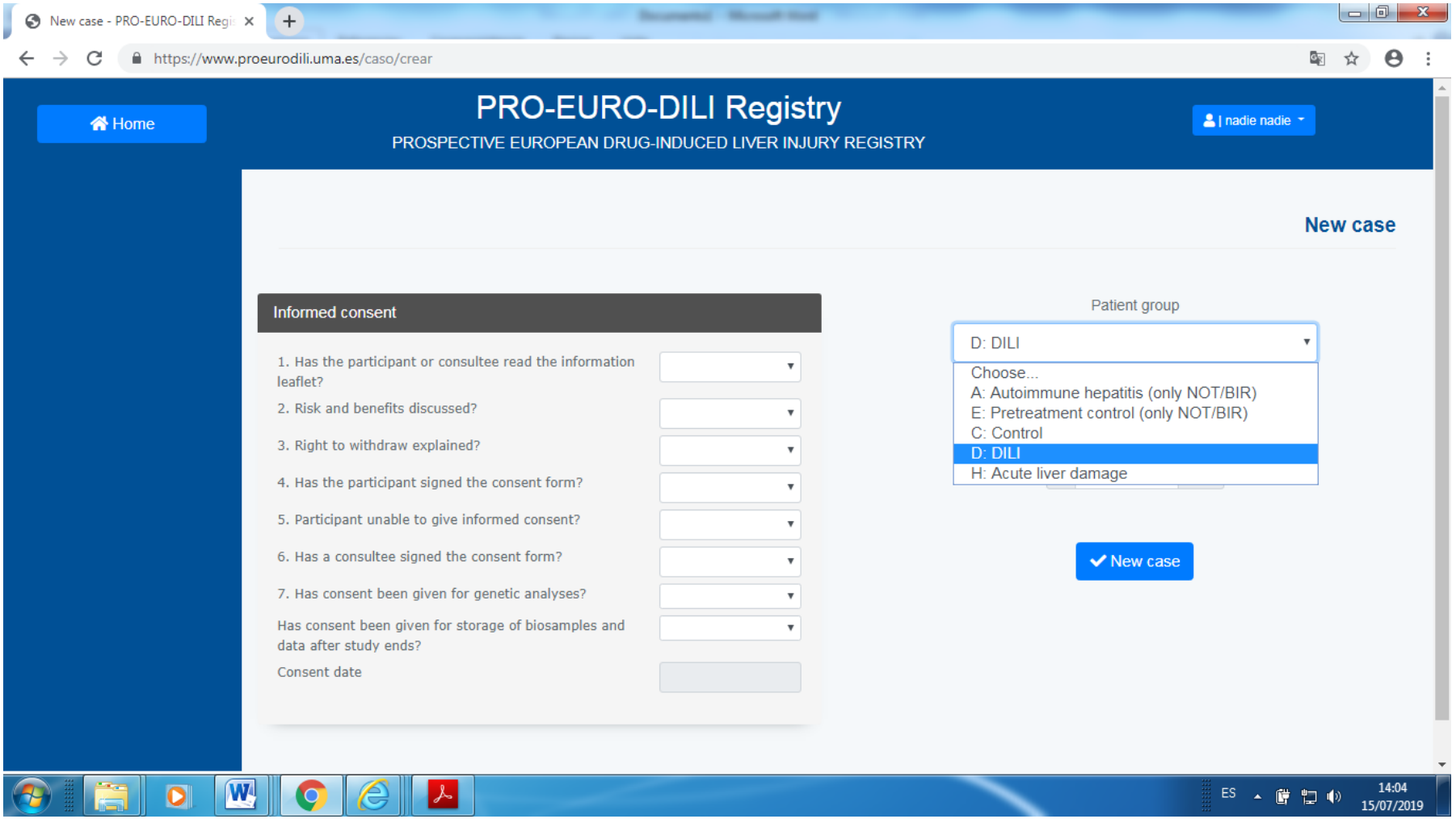
Website: https://www.proeurodili.uma.es/



Request access:
New user



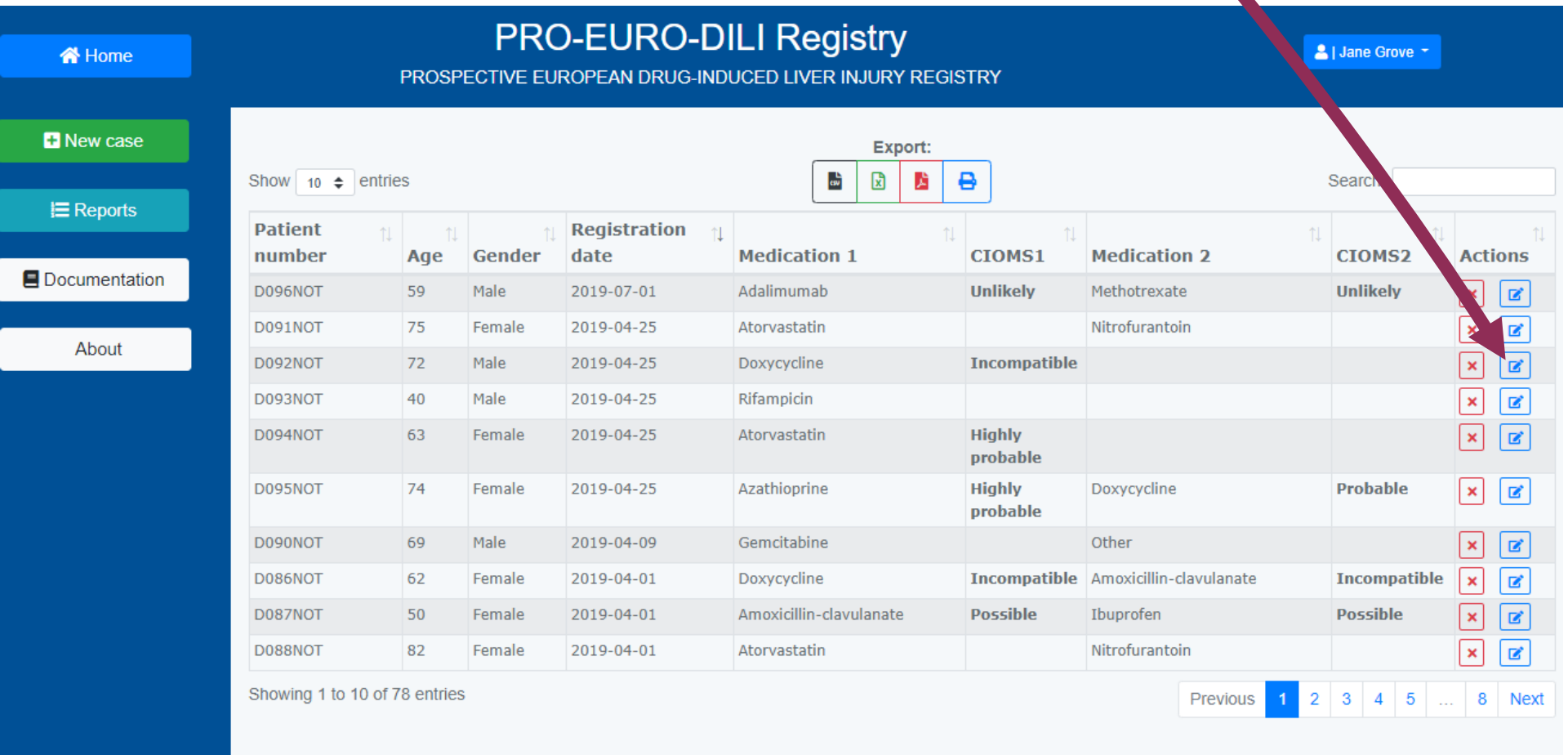
For advice contact
cstephens@uma.es


New case - PRO-EURO-DILI Regi
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

Website: proeurodili.eu

Home: shows patients from your site

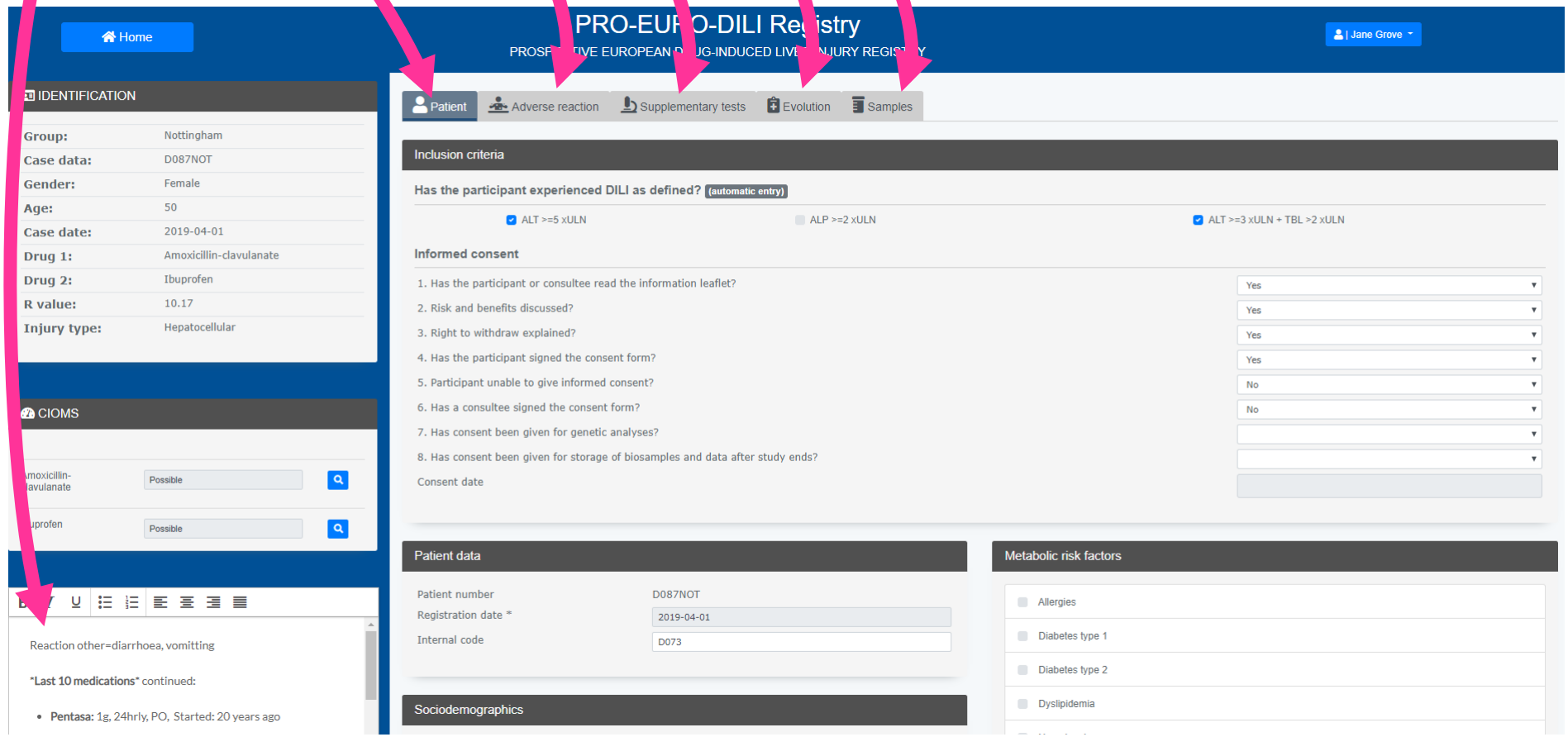
To edit case



Patient info collected ‘Patient Tab’

Add info / notes

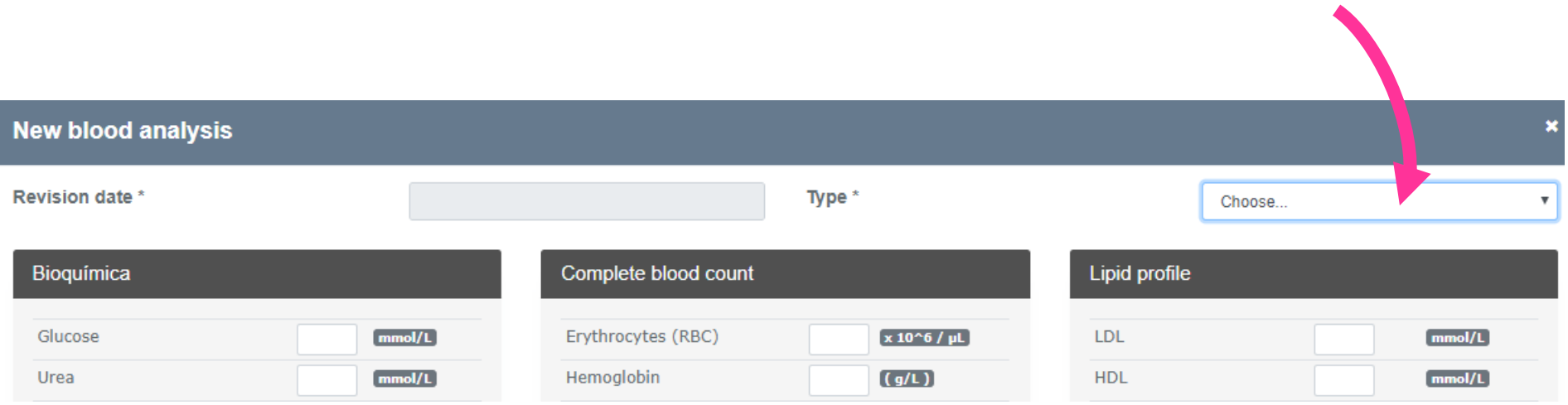
Complete each tab



‘Supplementary Tests’ Tab – for clinical test results

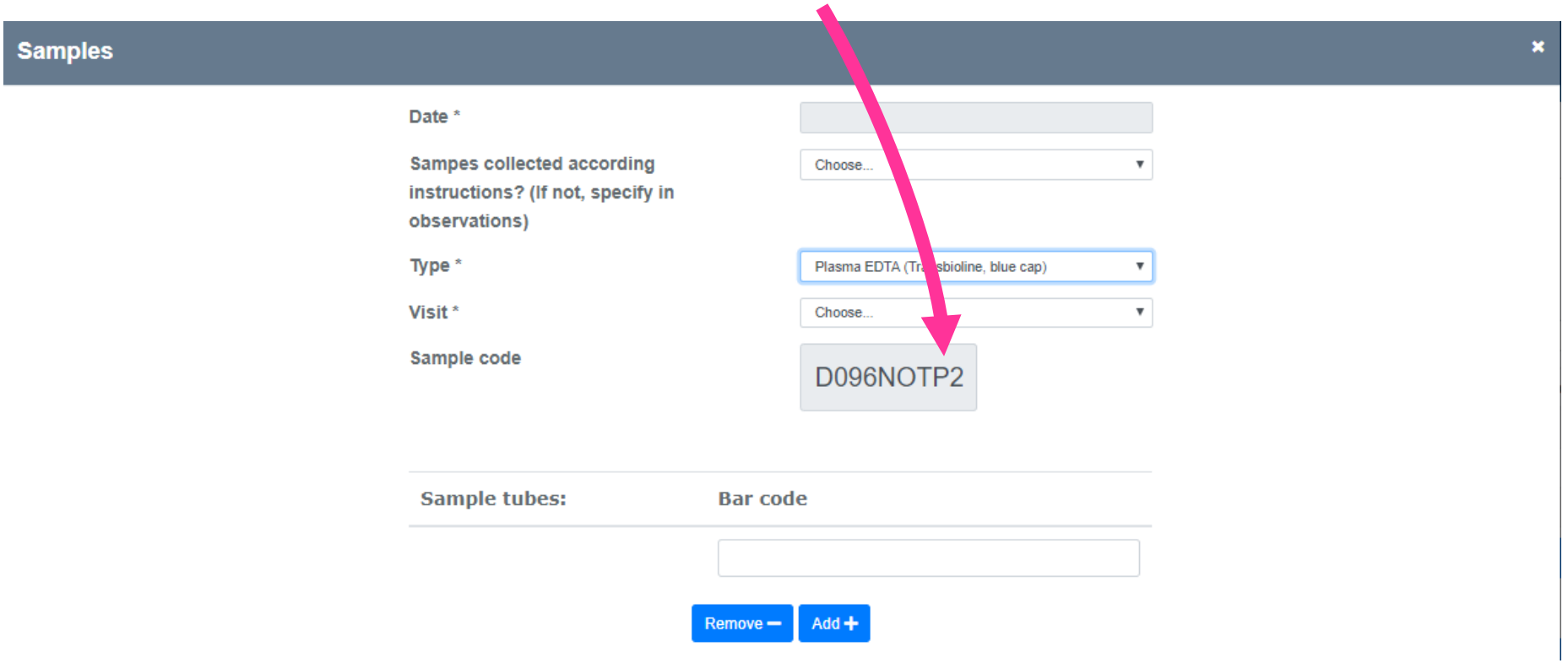
Can add new blood analysis etc

Note when selecting visit date for blood tests choose ‘first that fulfil DILI criteria’ for the first sample time if this is also actually visit 1 (which is likely as this is when meet recruitment criteria LFTs).
If sampling for research not done on date that meet criteria then choose as ‘visit 1’ (but LFTs should still meet recruitment criteria). You must have an entry for ‘first that fulfil’ as needed for CIOMS.



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

On Pro Dili database ‘P2’ is platelet free plasma
‘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.



Nottingham University Hospitals NHS Trust

University of Nottingham UK | CHINA | MALAYSIA

NIHR Nottingham Biomedical Research Centre

PRO-EURO DILI REGISTRY

Beth Robinson
Research Manager

Bethany Robinson@nottingham.ac.uk

Jo Thomas
Lead Nurse

Jo.Thomas@nuh.nhs.uk

Shellie Radford
Senior Research Nurse

Shellie.Radford@nuh.nhs.uk

Melanie Lingaya
Senior Technician

Melanie.Lingaya@nottingham.ac.uk

Guru Aithal

Principal Investigator

Guru.Aithal@nottingham.ac.uk

Jane Grove

Research Scientist Lead

Jane.Grove@nottingham.ac.uk

Stuart Astbury

Immune phenotyping Research

Stuart.Astbury@nottingham.ac.uk

Data Support:

David Simmonds: study coordinator
Kiran Hussain: data collation
Govind Jumbo: IT

Additional Study Materials: posters/leaflets

Stool Collection Advice for Patients

1.Place or hold a cardboard tray to collect stool as passed – avoid passing any urine.

2. Remove the screw cap and spatula ‘spoon’ from the stool container and collect a small piece of stool (about the size of a cherry)

3. Replace the screw cap and close the container tightly.

4.Place container in a plastic bag.

5. Flush any leftover stool down the toilet.

6. Dispose of cardboard into household waste/ normal dustbin.

7. Bring the sample to your healthcare appointment. Thank you.

Advertisement For local clinical teams

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

Open for recruitment:

NDDC Nottingham Digestive Diseases Centre

University of Nottingham UK | CHINA | MALAYSIA

Nottingham University Hospitals NHS Trust

NIHR Nottingham Biomedical Research Centre

Drug-Induced Liver Injury Research Study

Be part of research to develop new ways to predict and prevent drug-induced liver injury (DILI)

Recruitment: adults aged over 18

1. **who are suspected to be having an adverse reaction affecting liver functioning following taking a medication or supplement (absence of other known causes of liver injury)**

with: ALT > 5 xULN

or: ALP > 2 xULN

or: ALT >3 xULN **& TBL** > 2 xULN

2. **or who have autoimmune hepatitis**
3. **or who have had no problematic response after taking specific medications or supplements, or are eligible for immunotherapy**

Schedule:

Contact Jane.Grove@nottingham.ac.uk

Visit 1	during 1st week*	Visit 2	Visit 3	After 3 months*	After 6 months*
Recruitment during DILI onset (symptomatic)	1 or 2 additional visits if hospitalised	After 1 week	After 1 month	only if liver enzymes elevated at previous visit	only if liver enzymes elevated at previous visit

- Up to 80ml blood for serum, plasma, DNA, RNA, immunophenotyping
- urine sample (optional)
- stool sample (optional)
- Medical history & clinical data (eg underlying disease, symptoms)

Work up:

Pharmacological data:
dose, concomitant drugs

Biochemical data:
LFT, serology (IgM anti-HAV, HBsAg, Anti-HCV, CMV, VEB)

Imaging test:
to rule out biliary obstruction;

History/Demographic data

Advertisement For local clinical teams

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

Open for recruitment:

NDDC Nottingham Digestive Diseases Centre

University of Nottingham UK | CHINA | MALAYSIA

Nottingham University Hospitals NHS Trust

NIHR Nottingham Biomedical Research Centre

Drug-Induced Liver Injury research study

TransbioLine Pro-Euro DILI Biorepository

Investigator:
Prof Guru Aithal

Purpose: collect samples from patients with in-depth phenotyping for biomarker research

Inclusion criteria:

- **current, suspected 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

We need suspected DILI patients at time of DILI and until recovered

Plus control groups:

- other causes of DILI-like symptoms
- unaffected people taking same drugs
- cancer patients before immunotherapy

DILI NUH clinical poster V2 11.4.19

Contact: Shellie Radford senior nurse
Shellie.Radford@nuh.nhs.uk
Tel. 0115 9709966

What's involved?

Collection of **blood, urine and stool sample** over 3-5 visits, in line with standard care (Day 1, 7, 30)

Advertisement

For patients: Also patient leaflet available

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Nottingham University Hospitals NHS NHS Trust

NIHR Nottingham Biomedical Research Centre

Drug-Induced Liver Injury Research Study

Be part of research to develop new ways to predict and prevent drug-induced liver injury (DILI)

We need:

Men & women aged over 18
1. who are suspected to be having an adverse reaction affecting liver functioning following taking a medication or supplement;
2. or who have had no problematic response after taking specific medications or supplements.

Participation involves:

- One or more appointments with our research nurse to provide:
  - a blood sample,
  - a urine sample (optional)
  - a stool sample (optional)
  - Medical history

If you are suspected of having DILI, we will arrange to see you as soon as possible. We expect to see you 2-3 times over 30 days then after 3 & 6 months if your symptoms remain.

DILI recruitment poster V2 11.4.19

This will generate a Biobank of samples & detailed information about people who have DILI and unaffected people enabling diagnostic tests to be developed.

- DILI is an unexpected injury to the liver that can be caused by normal dose of prescribed medications, over-the-counter medications, recreational drugs and supplements (not paracetamol overdose).

Contact us for info: Tel. 0115 9709966 e-mail: NDDCBRU@nottingham.ac.uk

See our web site: https://nddcbru.org.uk/pro-euro-dili @NottmBRCLiverGI