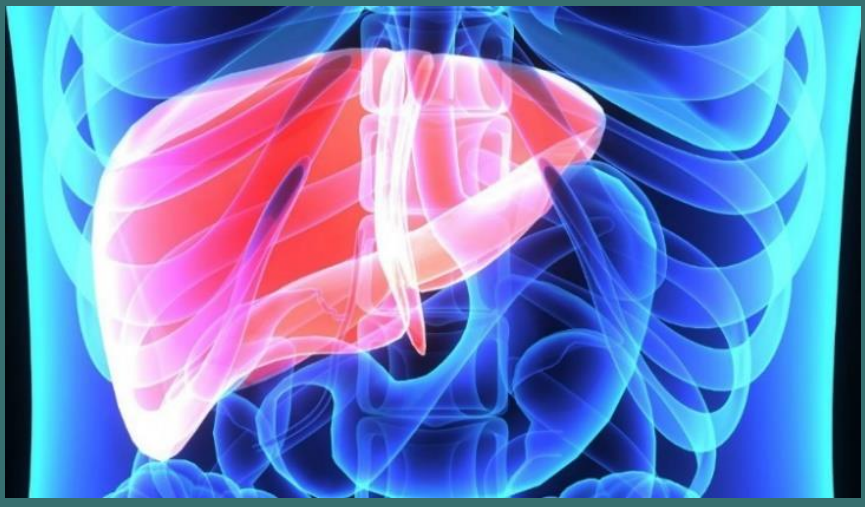
PATIENT INFORMATION

NDDC
Nottingham Digestive Diseases Centre

Drug-induced Liver Injury Study

Version 8.0 | 11.04.2022 | PATIENT GROUP | IRAS ID: 167142 | REC Ref: 15-YH-0294



We invite you to take part in this research study:

- Before you decide whether to take part, it is important for you to understand why the research is being done and what it will involve.

If you decide not to take part, this will not affect the standard of care you receive.

- Please take time to read the following information carefully.
  - Discuss it with friends and relatives and/or your GP if you wish.
- Ask us if there is anything that is not clear or if you would like more information.

Contents:

Study Summary

We need: Men & women aged over 18

1. who appear to have an adverse reaction to a medication or supplement which affected liver functioning;

***Or* 2. who have had no problematic response to taking specific medications or supplements.**

***Or* 3. who are about to begin a course of immunotherapy drugs**

***Or* 4. who have been diagnosed with auto-immune hepatitis**

Participation involves:

- Several visits/appointments with our research nurse (coinciding with your medical care where possible) to provide:
  - a blood sample,
  - a urine sample (optional)
  - a stool sample (optional)
  - Medical history

We will not be testing any drugs, treatments or procedures.

Principal Investigator:

Prof Guru Aithal

Lead Study Doctor; Consultant Hepatologist

Tel 0115 9709966

nddcbru@nottingham.ac.uk

University of Nottingham UK | CHINA | MALAYSIA

NIHR | Nottingham Biomedical Research Centre

Our Research Centre

The Nottingham Digestive Diseases Clinical Research Facility is on E floor in West block of the Queens Medical Centre.

It is part of the NIHR Nottingham Biomedical Research Centre funded by the NHS.

This work is part of the TransBioLine Project

https://transbioline.com

TransBioLine Translational Safety Biomarker Pipeline

Purpose of the Study

'to develop new ways to predict and prevent drug-induced liver injury (DILI) by establishing International collaboration to collect and analyze samples and medical details of patients (with and without DILI) across Europe. '

Key facts about drug-induced liver injury (DILI)

- DILI is an unexpected injury to the liver that can be caused by prescribed medications, over-the-counter medications, recreational drugs and supplements.
- Some drugs such as paracetamol are known to be harmful to the liver in high doses but other drugs, taken at a normal dose can unpredictably damage the liver of certain people.
- DILI is a rare, unpredictable disease and it is not known why certain individuals are more likely to develop drug-induced liver injury than others. This can be life-threatening.
- Specific genetic risk factors can contribute to individual susceptibility but they do not fully explain why people get DILI.
- DILI is difficult to diagnose and often has similar features to auto-immune hepatitis.

Reasons for doing the Research

- Drug-induced liver injury can be a severe adverse reaction which can have serious life-threatening effects.
- There are currently no specific treatments available or reliable methods for definite diagnosis. Usually the affected patient would be advised to stop taking all medications which may be the underlying cause. This means other symptoms they had can reappear as they are no longer controlled if alternative medications are not be available.
- Doctors are currently unable to predict if or when DILI may occur and cannot avoid it.

Since DILI is rare, caused by many different medications and diet supplements and highly variable, it is very difficult to study.

In order to understand the disease a large collection of patients is needed to investigate the disease features. This means an International collaboration is necessary to achieve our goal.

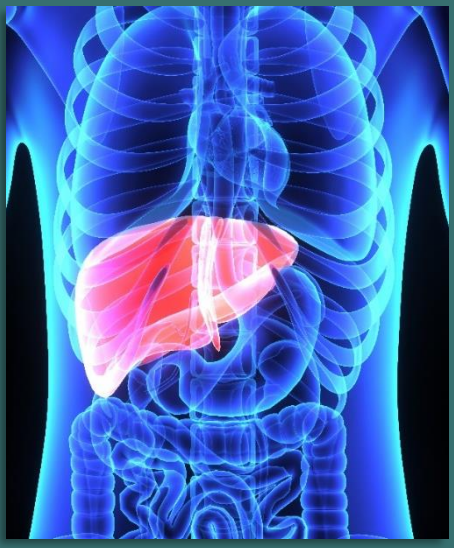
PRO-EURO DILI REGISTRY

TransBioLine
Translational Safety Biomarker Pipeline

TransBioLine International Collaboration

We are organising a unique project with academic and industry partners to investigate drug-associated diseases across Europe and coordinate the formation of a large shared Bio-resource of biological samples with detailed information from people who have had DILI and from people who had symptoms of DILI but were subsequently found not to have DILI.
This project will collect samples from patients at the time of symptoms and over the period of recovery so that the disease process can be followed.

We also plan to collect samples from people who have taken the same medications but have not experienced any adverse effects so we can compare their characteristics and identify differences in samples collected.
To achieve this we will create a shared database of cases which holds details such as drug dose, duration, other medications, individual characteristics (such as age and weight) and other conditions, as well as clinical features and blood test results over the course of the DILI until recovery.



This will enable researchers to better understand DILI and its causes, develop new diagnostic tests and identify risk factors that increase susceptibility to DILI.

Study Aims:

'to create a unique International Bio-resource and determine disease characteristics in detail to enable better understanding of the causes of drug-induced liver injury (DILI) so that new, non-invasive diagnostic tests can be developed through collaboration.'

This research will:

- Improve our understanding of how medications cause DILI
- Identify risk factors for DILI development
- Develop and evaluate new non-invasive tests to specifically diagnose DILI.

Our Goal:

To predict and prevent drug-induced liver injury (DILI) so patients can be safely treated with medications they need.

Important things to know

1. Who can I contact to ask about the study?

If you have questions or concerns about any aspect of the study, please contact the research team members or the lead investigator, Prof Aithal. nddcbru@nottingham.ac.uk Tel 0115 9709966.

Who is organising the study?

The research is being led by Guru Aithal, a Professor of Hepatology at Nottingham University Hospitals NHS Trust (NUH) and Nottingham Digestive Diseases Centre.

The study is funded by the IMI TransBioLine award, the NIHR Nottingham Biomedical Research Centre and the European Association for the Study of the Liver.

Translational Safety Biomarker Pipeline (TransBioLine):

Enabling development and implementation of novel safety biomarkers in clinical trials and diagnosis of disease.

International Consortium of leading European research institutions, SMEs and EFPIA companies coordinated by the University of Zurich.

2. Who can take part?

Men & women aged over 18 can participate – we would like:

- Patients suspected to currently have drug-induced liver injury or auto-immune hepatitis causing severe liver malfunctioning, diagnosed by their doctor (this may be later found to have another cause, but you can continue in the study).
- People who are taking specific medications without any adverse effects or are about to begin a drug treatment.

You have been chosen to participate because your liver function test results and medical history indicate that you probably have drug-induced liver injury or auto-immune hepatitis.

3. What will I be asked to do?

A nurse from the research team will visit you on the ward or arrange an appointment for you at your treatment centre/hospital (if possible at the same time as your medical appointment).

You will be given a reasonable amount of time to read this patient information booklet and adequate opportunity to consider enrolment before being approached for consent by the research team.

If needed appropriate steps will be taken to ensure that you are able to discuss participation in the study with someone who is not involved in the research.

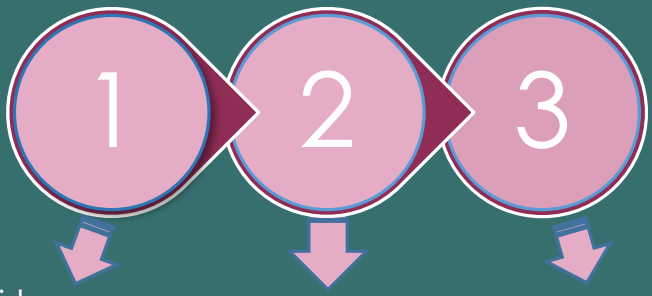
If you decide to take part, you will be asked to sign a consent form to confirm you understand what is involved. This may be done face-to-face or over the telephone.

Your participation is voluntary and you are free to withdraw at any time, without giving any reason, and without your medical care or legal rights being affected. If you wish to withdraw from the study, please let your local study team know or contact the Chief Investigator.

If you withdraw then some information collected so far cannot be erased and this information may still be used in the project analysis. Based on your study code assigned by your research team, we will contact the database and sample managers or biobanks to remove any associated data and samples that remain if you wish. However it may not be possible to destroy samples already sent for analysis.

We will not inform your GP about your participation in this study since it has no effect on your care and provides no information about your health.

What is involved?



We will provide information about the study for you to consider and offer an appointment with our nurse

Our nurse will meet with you to discuss your health, the study & collect samples

Each patient will have a clinical follow up until the liver recovers or 12 weeks after the first event, whichever occurs later.

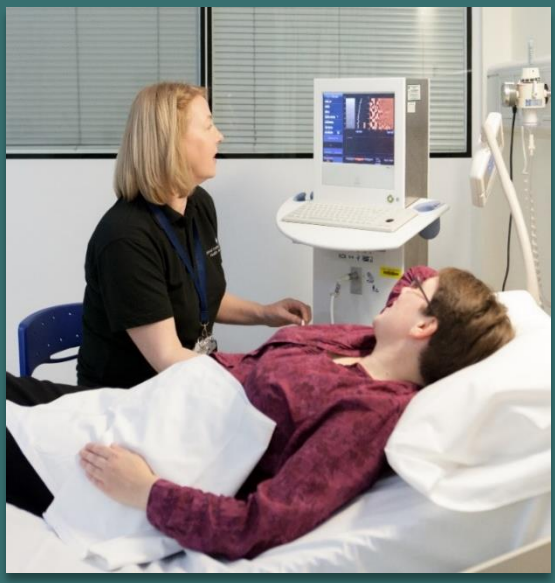
The research nurse will:

- **try to answer any questions you have,**
- **discuss your health & medical history (including medications),**
- **collect up to 80mls of blood (4½ tablespoons).**
- **confirm you consent to DNA genetic analysis**
  (this is optional- you can indicate this on the consent form)
- **ask if you can provide a urine and/or stool ('poo') sample.**
  (this is optional - you can indicate this on the consent form)
- **ask if you are willing to donate any surplus samples left over from your diagnostic tests (such as biopsy tissue), for research**
  (this is optional- you can indicate this on the consent form)
- **confirm you consent to anonymised data and samples being shared with collaborators worldwide.**
- **ask if you consent to us accessing your digital medical records to follow your recovery.**
- **ask if you are willing to donate any samples left over from this study to a research tissue bank for future projects**
  (this is optional- you can indicate this on the consent form)
- **ask if we can keep your details in our secure database to contact you about our future research where relevant.**
  (this is optional- you can indicate this on the consent form)

We will not be testing any drugs, treatments or procedures

Study Visits

If you are suspected of having DILI, we will arrange an appointment 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.



Each visit is expected to last about 30 minutes.

- We would like to take samples from all patients at recruitment and after 1 week and 1 month.
- If you are an in-patient, we will collect additional data and samples on 1-2 additional days during your period of hospitalization.
- If your liver functioning has not returned to normal, you will be asked to return after 3 months and after 6 months.
- Visits will be adapted to fit in with (coincide or replace) your routine hospital care and clinic visits whenever possible.
- Samples for research will be collected alongside your clinical care blood tests.
- If you have a liver biopsy as part of your clinical care, we will also ask you if we can use any surplus sample material leftover afterwards for future research.

Following recruitment, if your symptoms are later found to be due to other causes after further detailed investigations, (and not to be due to medications) you are still eligible to continue to take part in the study. Your samples are valuable to compare to those from DILI patients so that we can distinguish DILI specifically from similar causes of liver injury.

Your samples:

We will store the samples collected at Nottingham Biomedical Research Centre (BRC) and send a proportion to Central Biomaterial Bank of the Charité (ZeBanC) in Berlin (https://biobank.charite.de/en/) who will coordinate sample distribution for the TransBioLine project.

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.

Blood samples:

During each visit no more than 80 ml in total will be taken for any clinical tests you need and research.

Generally we expect to take 35ml for research but at one or two of these visits we may request an additional 30mls of blood. Where possible we can take this extra blood at a separate appointment/time to suit you or at the same time as your clinic bloods.

Additional blood will enable us to carry out specialised antibody tests on particular white blood cells (immune cells) which could help us to distinguish DILI from other forms of liver injury where the immune system attacks the liver cells.

The amount of blood taken will be more than what is normally taken at a routine clinical visit. Your blood samples will be taken by a trained nurse who can explain the process to you and answer any queries or concerns you have about the volume of blood being taken.

It will be documented your medical records that you are participating in this study.

4. What will be done with my samples?

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)

Advanced Immunological Analyses:

At some visits you may be asked to provide a blood sample for specialised detailed immunological characterisation. This blood will be sent to our research collaborators:

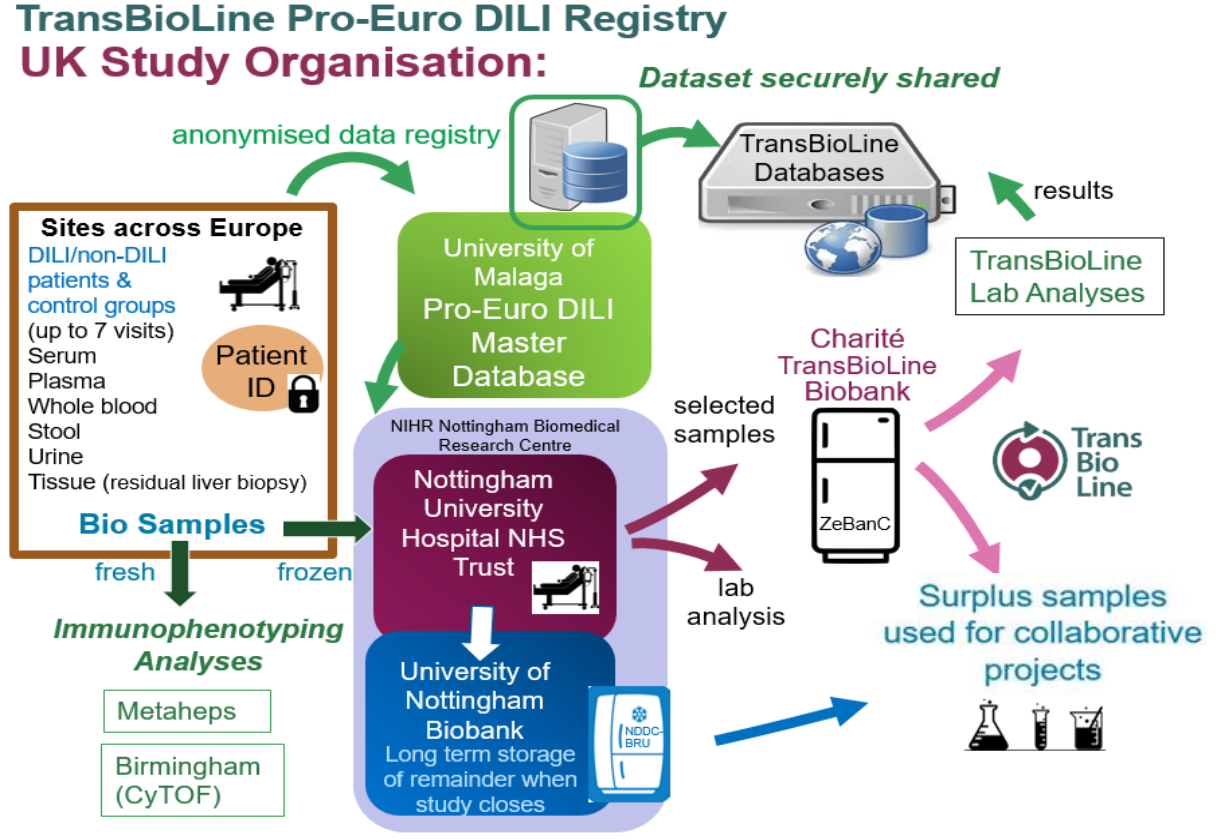
Metaheps® (Germany)

Certain types of white blood cells will be isolated from your blood and maintained in the lab in order to act as a model to investigate how drugs could affect liver cells.

Dr Ye Htun Oo (University of Birmingham, UK)

Deep immunophenotyping

Immune cell types in your blood will be identified using Cy-TOF technology to determine how the immune system specifically responds to drug-induced liver injury.



Sample Biobanks

Long-term sample storage facilitating future DILI research

After the study is complete, we would like to store some un-used samples left over from TransBioLine Lab analysis at ZeBanC so they can be made available for future ethically approved research projects following approval by the TransBioLine Review Board.

The ZeBanC is an official Core Facility of the Charité – University Hospital Berlin, established for long-term biobanking activities and is able to host biomaterials for up to 25 years (https://biobank.charite.de/en/) .

Any remaining samples left over in Nottingham 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 at least 10 years. Samples and data will only be used for ethically approved research studies.

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

5. Is this kept confidential?

Yes, your involvement in the study and all personal information and related health records obtained will remain strictly confidential and will be stored securely at Nottingham University Hospitals NHS Trust.

- We will follow ethical and legal guidelines for our research and comply with UK data protection laws (GDPR).
- Nottingham University Hospitals NHS Trust (NUH) is the sponsor for this study based in the United Kingdom.

- **Your samples will be labelled with a code not your name or address so you cannot be identified.**
- **We will not share your personal details with anyone outside the research team, regulatory bodies and the Study Monitor.**

We will be using information from you and your medical records in order to undertake this study and will act as the data controller for this study. This means that we are responsible for looking after your information and using it properly. NUH will keep identifiable information about you until 6-12 months after the study has finished. Arrangements for confidential destruction will then be made.

Your rights to access, change or move your information are limited, as we need to manage your information in specific ways in order for the research to be reliable and accurate. If you withdraw from the study, we will keep the information about you that we have already obtained. To safeguard your rights, we will use the minimum personally-identifiable information possible.

The information collected about you may also be shown to authorised people from the UK Regulatory Authority; this is to ensure that the study is carried out to the highest possible scientific standards. All will have a duty of confidentiality to you as a research participant. Your personal data may also be shared with the Study Monitor who will conduct source data verification for audit purposes.

Protection of your Personal Data

Your treatment centre/hospital will collect information from you and your medical records for this research study in accordance with our instructions. Your treatment centre/hospital will use your name, NHS/hospital number and contact details to contact you about the research study, and make sure that relevant information about the study is recorded for your care, and to oversee the quality of the study.

Individuals from NUH, regulatory organisations and the Study Monitor may look at your medical and research records to check the accuracy of the research study. The department that recruits you to the research study at your treatment centre/hospital will pass these details to NIHR Nottingham Digestive Diseases Clinical Research Facility and/or Research and Innovation Department (both of which are part of Nottingham University Hospitals NHS Trust, the sponsor), along with the information collected from you and your medical records. The only people in NUH who will have access to information that identifies you will be people who need to contact you to about the study or audit the data collection process. The people who analyse the information will not be able to identify you and will not be able to find out your name, NHS/hospital number or contact details. NUH will keep identifiable information about you from this study for 6-12 months after the study has finished.

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.

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/

6. What are the benefits and risks of taking part?

There is no direct benefit to you from taking part in the study.

However, the information we get from this study will help us understand the causes of DILI, improve diagnosis and may help other patients suffering from this potentially serious problem.

Having blood taken may cause temporary discomfort and sometimes bruising to your arm. Blood sample collection will be performed by trained personnel only, so we do not expect any complications.
We do not offer any payment to you for participating but will try to minimize any inconvenience by arranging an appointment which follows your usual medical/clinic visit.

Ethical Review

All research in the NHS is looked at by an independent group of people called a Research Ethics Committee, to protect your safety, rights, well-being and dignity.

The research study has been independently reviewed and approved by the Research Ethics Committee (Yorkshire and the Humber – Leeds East).
The study is approved and supported by Nottingham University Hospitals NHS Trust (NUH).

7. Will the Research Findings be made Public?

- We will publish our findings in research journals and explain them at scientific meetings.
- We will provide a summary of our findings on our website: **https://nddcbru.org.uk/pro-euro-dili**
- Our achievements are described on our website **https://nddcbru.org.uk/** (see profile for Guru Aithal).
- A written summary of the research will also be available.

Registry Databases: sharing compiled data

The anonymised data compiled in the TransBioLine and Pro-Euro DILI databases will be made available to other research partners and collaborators as agreed within the consortium, 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.

8. Who can I contact if I have concerns or complaints about the study?

If you wish to complain about any aspect of the study, please contact the lead investigator,

Prof Guru Aithal

Tel 0115 7465124;

Guru.Aithal@nottingham.ac.uk

Formal complaints can be made via the National Health Service complaints procedure or NHS Patient Advice & Liaison Service (PALS): NUH NHS Trust, c/o PALS, Freepost, NEA 14614, Nottingham NG7 1BR

Tel 0800 183 0204, Email: pals@nuh.nhs.uk

In the event that something does go wrong and you are harmed during the research study there are no special compensation arrangements. If you are harmed and this is due to someone's negligence then you may have grounds for a legal action for compensation but you may have to pay your legal costs. The normal National Health Service complaints mechanisms will still be available to you.

For Information about Liver Disease:

NHS choices

www.nhs.uk/conditions/liver-disease/

BRITISH LIVER TRUST

www.britishlivertrust.org.uk

https://nddcbru.org.uk/

New Information

Sometimes during the course of a study, new information becomes available. If this happens, we will tell you about it and discuss with you whether you want to or should continue in the study. If you decide to withdraw, we will make arrangements for your care to continue. If you decide to continue in the study you will be asked to sign an updated consent form.

On receiving new information, we might consider it to be in your best interests to withdraw you from the study. If so, we will explain the reasons and arrange for your care to continue.

If the study is stopped for any other reason, you will be told why and your continuing care will be arranged.

We also need volunteers to be members of our Patient & Public Advisory Group

To:

- Comment on our research ideas;
- Comment on how research studies should be done;
- Assist us in recruiting people to our clinical trials
- Provide us with you thoughts on how we can better communicate our work.

➢ ask or contact us for more information :

Tel. 0115 9709966

Email: NDDCBRU@nottingham.ac.uk

Thank You
for taking the time to read this information

Together we can create a unique biobank resource to enable research into the causes and characteristics of drug-induced liver injury (DILI), so that new, non-invasive diagnostic tests can be developed.

NDDC
Nottingham Digestive Diseases Centre

@NottmBRCLiverGI

TransBioLine
Translational Safety Biomarker Pipeline

If you would like to take part or find out more, please contact us at the address below:

Your local research team is:

Research/Specialist Nurses:
Sophie Cusick/ Elise Fawcett
Tel: 0115 9249924 Ext 80732 Mobile: 07812277082

Doctor/Principal Investigator:
Prof Guru Aithal Tel. 0115 8231149

Study Coordinators:
Dr Jane Grove

Nottingham Digestive Diseases Centre / Clinical Research Facility:
Queens Medical Centre, Nottingham NG7 2UH. U.K.
Tel. 0115 9709966 | nddcbru@nottingham.ac.uk | http://nddcbru.org.uk