Plan Overview

A Data Management Plan created using DMPonline

Title: REpurposing SirolimUS in compensated advanced chronic liver disease. The RESUS proof of concept study (RESUS Study)

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Project abstract:

Research Question:
RESUS is a proof of concept, phase II randomised controlled trial that will determine whether there is preliminary evidence of efficacy for the use of sirolimus as an anti-fibrotic in patients with advanced chronic liver disease. We hypothesise that sirolimus would deactivate previously activated hepatic stellate cells, and thereby slow the progression of fibrosis.

Background:
Chronic liver disease (CLD) of any aetiology is defined by a dysregulated fibrotic response to liver injury, eventually leading to cirrhosis and its associated complications: ascites, variceal bleeds, hepatocellular carcinoma, hepatorenal syndrome and death. Hepatic stellate cells (HSCs) are the liver's resident myofibroblasts which are activated in injury to lay down extra-cellular matrix. The mTOR cellular pathway plays a pivotal role in activating HSCs, and in the upstream production of chemokines which activate HSCs. Sirolimus, a potent mTOR inhibitor is in daily clinical use as a post-organ-transplant immunosuppressant. It has shown a profound liver anti-fibrotic effect in vitro, in mouse models, and serendipitously when used as an immunosuppressant.
Despite CLD being the third biggest cause of premature death in the UK, there are currently no licensed anti-fibrotic agents. The lack of validated, non-invasive tools to quantify fibrosis further inhibits drug development.

Aims:
This study aims to repurpose Sirolimus, a medication routinely used within the NHS for immunosuppression with a well-known side effect profile, as an anti-fibrotic drug. It also aims to validate MRI as a non-invasive fibrosis assessment tool.

Objectives:

1. To determine proportion of HSC deactivation with Sirolimus, when compared to placebo, over 6 months.
2. To compare the change in histological fibrosis stage with changes in multiparametric MRI measures.

Methods:
45 patients with CLD secondary to alcohol or non-alcoholic fatty liver disease will be recruited

from Hepatology clinics at Nottingham University Hospitals Trust. 30 will be randomised to receive Sirolimus, 15 the placebo, for 6 months. At the start and end of the study, participants will undergo a liver biopsy and, if willing, an MRI scan. They will be monitored regularly both clinically and biochemically throughout the study.
HSC activity will be reflected by measuring alpha-SMA expression – a known marker of HSC activation. A 50% alpha-SMA reduction will be considered significant. Fibrosis stage at baseline and 6 months will also be assessed histologically. Novel MRI techniques previously trialled by this research group, and serological markers of fibrosis will quantify potential changes in fibrosis stage.

Timeline:
Recruitment is anticipated to take 15 – 18 months, therefore, the last participant is expected to complete the trial 2 years after study commencement. Analysis of biopsies and stored blood samples will take a further 3 months.

Anticipated impact:
If sirolimus proves to be efficacious, this work should lead to a larger, multicentre trial. As a known entity, sirolimus will have a shorter path to licensing than a novel agent. This study will build on existing evidence for using MRI as a non-invasive fibrosis assessment tool, which would be beneficial for patients, community fibrosis screening, and future clinical trials. The results of this study will be published and disseminated across the scientific community.

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REpurposing SirolimUS in compensated advanced chronic liver disease. The RESUS proof of concept study (RESUS Study)

Data description

What data will you create?

Types of data:

1. CRF

A case report form (CRF) is a form on which individual patient data required by the trial protocol are recorded. Each participant will be assigned a unique trial ID number, allocated on entry into the trial for use on CRFs

CRFs will be treated as confidential documents and held securely in accordance with regulations. The Chief Investigator will make a separate confidential record of the participant's name, date of birth, hospital number or NHS number and trial ID number, to permit identification of all participants enrolled in the study, in accordance with regulatory requirements and for follow-up as required.

CRF forms will contain: past medical history, consent forms recorded details of clinical encounters, recorded details of physical examinations, blood results of all bloods taken in this study, details of phone calls made to participants, details of study drug dose adjustment, concerns participants express throughout the study, adverse events, a signed declaration from the study chief investigator confirming accuracy of data

2. Liver biopsy data

Liver biopsies will be taken at baseline and at 6 months +/- 2 weeks. Routine histological staining (haematoxylin and eosin, reticulin, picrosirius red and Orcein) examination will be undertaken at the Nottingham University Hospitals NHS Trust (NUH) histopathology laboratory. The findings will be published on the NUH clinical results database (Notis and Medway) as per protocol. The first biopsy is part of a participants standard clinical care, therefore does not require special confidentiality arrangements. (Special immunohistochemical staining and analysis will be undertaken at Nottingham NIHR Biomedical Research Centre. Further analysis will take place in Dr Tim Kendall's laboratory at University of Edinburgh. An appropriate material transfer agreement will be in place for the transfer of specimens to University of Edinburgh.

3. MRI data

Storage and analysis of MRI scans done at baseline and after the end of treatment clinic (month 6) will be undertaken at the Sir Peter Mansfield Imaging Centre (SPMIC), University of Nottingham.

Volume of data

1. CRF

Each participant will have 22 clinical encounters, sometimes more than one one the same day. This will generate 22 CRF forms, which will take a member of the study team, on average, 3 minutes to complete during a clinical encounter. 45 participants will be recruited into this study in total. The CRFs will be created on the online platform 'REDCap', which is able to create and store forms.

Only study clinicians will have access granted to view and edit these forms.

Once the study is complete, all data will be exported into a password protected excel spreadsheet.

2. Liver biopsy

Liver biopsy specimens will be collected in formalin in a screw-top microcentrifuge tube (approximately 20 mg) for snap freezing in liquid nitrogen. They will be stored in double locked storage freezers under the jurisdiction of NUH until the last participant has completed the study, then securely transported to Edinburgh once an appropriate data transfer agreement is in place. There will be 90 biopsies in total.

3. MRI

MRI images will be stored securely on the SPMIC servers. There will be 90 MRI events in total.

Data collection / generation

What are your methodologies for data collection / generation? How will you ensure data quality? What data standards will you use?

1. CRF

All CRF data will be inputted by one of 6 members of the research team who will have had training in using REDCap and quality controlled the forms at the Site Initiation Visit (SIV) before study commencement.

10% of CRF data will be quality controlled by the study sponsor and CI

As many CRF questions as possible will be Yes/No or tick box format to ensure uniformity.

2. Blood samples

Blood samples will be collected by experienced research nurses into pre-printed request forms, and processed as per protocol in NUH laboratories.

3. Liver biopsy

Biopsies will be done by Hepatology consultants, giving as high a possible chance of high quality sampling.

4. MRI

MRIs will be carried out and stored by a specialist radiographer who will have attended the study SIV and has much experience in SPMIC data handling.

Data storage and security

Where and how will data will be stored, backed-up, transferred, and secured during the active phase (short to medium term) of research?

I will use UoN-provided storage for my working data. UoN licenses Microsoft OneDrive, allowing for secure and controlled storage and sharing of data. Microsoft OneDrive encrypts data both in transit and at rest and is approved against the University's Handling Restricted Data Policy. The service provides several layers of automatic back up and, in a disaster scenario, files can be recovered. Access to data stored in OneDrive is via secure log-in with multi-factor authentication.

Each participant will have a folder named by their study ID number. All content created in relation to that participant will be stored in that folder. Each clinical visit in the CRF has a number e.g., 'visit_1' 'visit_2', so the title of each form will be study number followed by visit number e.g. '23456_visit_2'

Data management, documentation, and curation

What are your principles, systems, and major standards for data management and creation? What metadata and documentation will you keep?

Metadata

We shall record and provide documentation via a README file that will describe:

- our research aims, objectives and hypotheses;
- our data collection methods, including the hardware and software used and any calibration carried out;
- a description of our data validation and quality assurance procedures undertaken;
- a description of the dataset structure and what each file relationships between files or versions of the dataset.

In addition, we shall provide templates of our interview sheets and consent forms."

"On deposit of our data and associated documentation we shall provide catalogue metadata that will facilitate the discovery of our data. This shall conform with the DataCite metadata schema.

Ethics & Privacy

Are there any ethical or privacy related issues associated with your data?

Participant confidentiality will be always respected, and the principles of the UK Data Protection Act 2018 will be followed. The investigator will ensure that identifiable data is kept securely and protected from unauthorised parties.

Participant data will only be stored if they sign a consent form and give informed consent for personal data to be collected and stored. All participants will agree to data collection and to long-term retention, archiving, and sharing of their anonymised data. The consent process will be reviewed by a a research and ethics committee when obtaining ethical approval for this study. Participants will be informed that they can withdraw their participation at any stage during or after the observations. As we will be working with personal data we will ensure that we comply with the Data Protection Act 2018, including GDPR requirements. This will include providing research participants with the relevant privacy information and ensuring appropriate safeguards for the storage and handling of data are in place.

The investigator or delegate will maintain comprehensive and accurate source documents to record all relevant study information regarding each participant.

Participants will only be identified on the study database by their unique study ID number.

The CRF will only collect the minimum required information for the purposes of the trial. CRFs will be held securely in locked

cupboard or cabinet in a locked room.
Computer held data including the study database will be held securely and password protected.

Data preservation

How will you ensure the long term storage and preservation of data?

All anonymised research data created by the project will be deposited in the UoN research data archive (https://rdmc.nottingham.ac.uk). UoN will retain and preserve research data in line with UoN and [insert your funder's name] requirements for a minimum of 7 years, but data will be retained for longer periods of time where it is of continual value to users. There is no cost for this service.

Data sharing and access

How will the data generated be shared and published?

All data for which consent to share has been obtained will be shared via the University of Nottingham data archive under a CC-BY license. Any data which is deemed to be personally or commercially sensitive will assessed on a case-by-case basis to determine whether it can be shared. There will be no need to update the data past the project period. All published outputs will contain a Data Availability Statement including the datacite DOI that directs to the relevant data set. Data will be released at the same time as any published outputs underpinned by the data or by one year from the end of the project.

Roles & responsibilities

Who will be responsible for managing data, data security, data quality, and data security both during the award and post-award?

The study Chief Investigator will be overall in charge of ensuring data security and quality during the study.
The study team will consist of 6 people, made up of clinicians, research nurses and a pharmacist. Each person's access to each aspect of study data recorded on REDCap will be pre-dertermined by the NUH Research Information System's Officer who created the study REDCap platform and made it live.
The study has the full support of Nottingham BRC, who will provide the services of data handler. She will be able to export data from REDCap into excel, and ensure data is securely stored.

Relevant policies

What are the relevant institutional, departmental or study policies on data sharing and data security?

We will ensure that our research aligns with the requirements of the University's Research Data Management Policy, Information Security Policy, Code of Research Conduct and Research Ethics. As we are working with personal data, we will abide by the University’s Handling Restricted Data Policy and Data Protection Policy. All third party commercial data or new data that may be suitable for commercial exploitation will be protected by the University's Intellectual Property policy.

IPR

Who will own the copyright and IPR of any data that you will collect or create? Will you create a licence(s) for its use and reuse? If you are planning to use existing data as part of your research, do any copyright or other restrictions determine its use?

Copyright & IPR for all project research data is owned by University of Nottingham.

Budgeting

What are the costs or funding required for capturing, processing, storing, and archiving your data?

This study has the full support of Nottingham Biomedical Research Centre for infrastructure and nursing support.
This will include the support of skilled individuals who will guide on data storage, computation and archiving.
There is no cost associated with storage of data on UoN platforms.

Further Help

Would you like your plan to be reviewed by specialists in Libraries?

Saving this plan after checking the "Yes" box will immediately notify Libraries DMP review service, please only do this when you are ready for review.

- No

Would you like a reminder and further guidance on depositing your data? If so, indicate when would be most useful.

Guidance is sent out twice a year, but you can contact library-researchsupport@nottingham.ac.uk at any time for further support.

- No further support