Title: **Reflex testing for metabolic associated fatty liver disease (MAFLD) in patients living with type 2 diabetes compared to usual care - a randomised controlled trial**

Short title: **REFLEX testing for MAFLD in patients with type 2 diabetes**

Sponsor: **University of Southampton**

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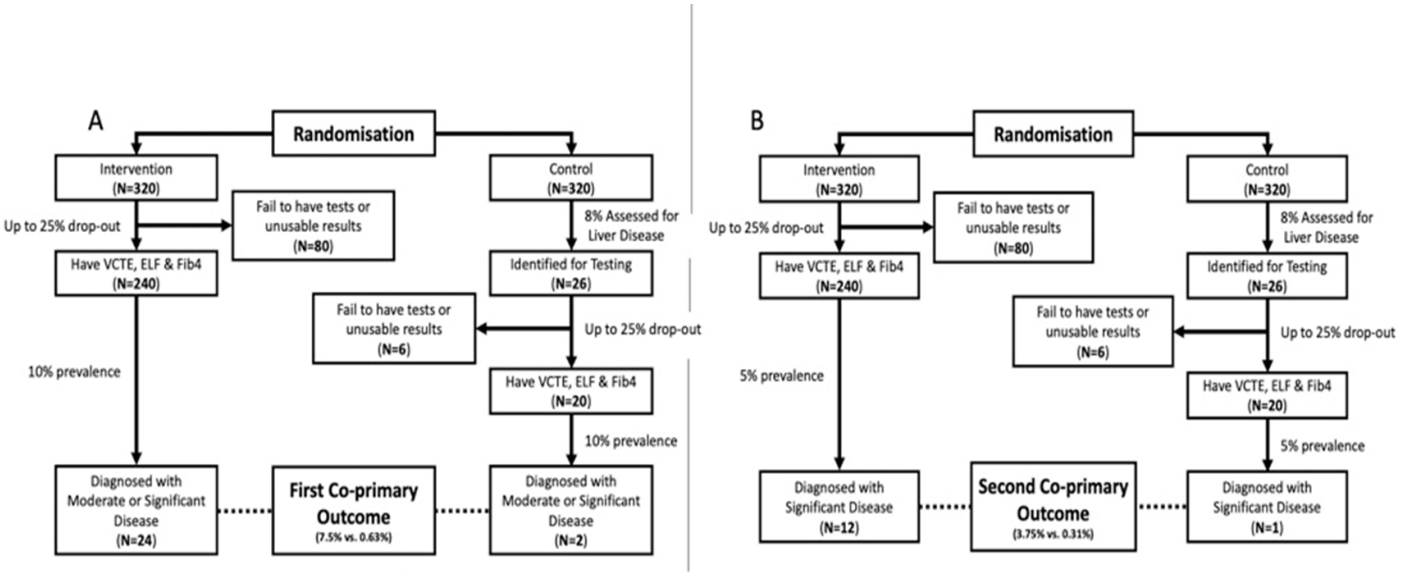
Study Summary

Study Title:	Reflex testing for MAFLD in patients with type 2 diabetes Reflex testing for metabolic associated fatty liver disease (MAFLD) in patients living with type 2 diabetes compared to usual care - a randomised controlled trial
Study design:	Unblinded Randomised controlled trial with a nested cost-effectiveness evaluation comparing reflex testing (i.e. testing all people living with T2DM) for liver disease against standard care.
Study participants:	Patients living with type 2 diabetes.
Planned sample size:	640
Follow up duration:	This is a 10 year study. Once participants have had their liver assessment, they will be followed up remotely over the next 10 years.

End date	The end date is defined as 12 months after the 10 year follow-up data for the last patient has been collected via NHS digital.
Research aim:	To test a new way of identifying liver disease in people living with type 2 diabetes (T2DM). To compare testing everyone with T2DM for liver disease against the existing care pathway – where only those with another risk factor, e.g. harmful alcohol consumption, get tested for liver disease.
Primary outcomes:	1. The number of patients diagnosed with moderate or significant liver disease within a year of randomisation (defined as ≥8.2kPa on VCTE). 2. The number of patients with significant liver disease (defined as ≥12.1kpa* on VCTE) and referred for HCC surveillance.[1] *12.1kpa is the current threshold for referral for HCC surveillance in the Southampton Liver Pathway (SLP) and is consistent with significant liver fibrosis and cirrhosis.[2]
Secondary outcomes:	1. To calculate the 'costs per case' of significant liver disease and severe-advanced liver disease identified via reflex testing for liver disease and usual care. 2. The test or combination of tests for liver fibrosis with the lowest cost per case. 3. The incremental cost effectiveness ratio (ICER) of reflex testing and HCC surveillance for liver disease in people living with T2DM.

Figure 1: Study flow chart



Flow diagrams supporting our sample size calculation for the co-primary outcomes
A – participants diagnosed with moderate and significant liver disease and B – significant liver disease only. The expected flow of patients through the study is based on our own experience with the existing community care pathway for liver disease in Southampton (UK) and published literature describing the prevalence of liver disease in people liver with diabetes.

We will aim to recruit 320 patients into each arm of this study – 640 patients in total. A sample of this size will enable us to address both co-primary outcomes, with a minimum power of 80% after allowing for a conservative 25% drop out. We know that the current attrition rate between GP referral to the community liver service and the patient attending their appointment is ~18%. However, we anticipate that between consent and randomisation in our study, a more realistic drop out rate would be 5%. Thus with a 5% drop out rate the minimum power to test both co-primary outcomes will be at least 91%. (See sample size section in the Research Proposal).

From the existing evidence, we expect that ~10% of tested participants will have ≥F2 fibrosis (moderate disease) and ~5% of participants will have significant liver disease (≥12.1kpa). Currently ~4% of people living with diabetes in the geographical study area are assessed for liver disease per year.

1. Background

Cancer is the leading cause of mortality in people living with type 2 diabetes mellitus (T2DM)[3] and T2DM is strongly associated with site-specific cancers including hepatocellular carcinoma (HCC).[4] The incidence of HCC is increasing, it is the fastest growing indication for liver transplantation[5] and is expected to become the 3rd most common cause of cancer death world-wide by 2030.[6] HCC has a very poor prognosis, and the 5-year survival is just ~20%.[7] However, if cases are identified at an early-stage curative treatments are available which include surgical resection, liver transplant or tumour ablation.[7]

A major drive for increasing deaths from HCC is the increasing global prevalence of type 2 diabetes (T2DM).[6] T2DM causes liver steatosis, inflammation, fibrosis and liver cirrhosis and patients with significant liver fibrosis (≥F2) or cirrhosis are at high risk of HCC.[8 9] There is a high prevalence of all stages of liver disease in people living with T2DM.[10-14] A recent study of 561 patients from the US showing a high prevalence of liver fibrosis and cirrhosis in people living with T2DM and advocated the need for screening for liver fibrosis in people living with T2DM.[12] This study showed that in people living with T2DM the prevalence of liver steatosis was 70% and fibrosis was 21%.[12] Moderate fibrosis (F2) was present in 6% and severe fibrosis (F3) or cirrhosis (F4) in 9%.[12]

In addition to the HCC risk associated with significant liver fibrosis and cirrhosis, evidence also shows that moderate fibrosis (F2) has important consequences for patients. It can progress to more serious liver disease and it increases the risks of extra-hepatic complications including cardiovascular disease.[15 16] There have been calls for the screening for moderate fibrosis in people living with T2DM[12] because, if identified it can facilitate beneficial intervention. Firstly, patients diagnosed with moderate liver fibrosis could access antifibrotic therapeutic drugs as they become available (currently in phase 3 trials) (e.g. [17]). Secondly, patients could be directed towards existing lifestyle intervention pathways[18] and thirdly, patients with moderate fibrosis should be considered for treatments for T2DM that may also attenuate progression of liver disease.[16 19-24]

International guidance recommends biannual surveillance for HCC in patients with liver cirrhosis however, less than one third of incident cases of HCC in people living with T2DM are identified via surveillance.[25] This is important as cancers that are identified via surveillance have better outcomes.[26] Accordingly, the NHS England Cancer alliance have recently incorporated the early detection of HCC into its success metrics as it strives to achieve the objectives of the NHS long-term plan.[27]

To engage people living with T2DM into HCC surveillance it is necessary to firstly identify patients with advanced fibrosis or cirrhosis. Liver disease used to be hard to identify before it reached a very advanced stage because it progresses without signs or symptoms. However, several approaches have now been validated in people living with T2DM to identify asymptomatic disease. These include panels of blood tests – including FIB-4, BARD[28] and the Enhanced Liver Fibrosis (ELF™) test[29] as well as a simple scan of the liver which uses vibration controlled transient elastography (VCTE) to assess the liver stiffness[28 30 31] – a marker of fibrosis.

Liver disease used to be hard to identify before it reached a very advanced stage because it progresses without signs or symptoms. However, several approaches have now been validated in people living with T2DM to identify asymptomatic disease. These include panels of blood tests – including FIB-4, BARD[28] and the Enhanced Liver Fibrosis (ELF™) test[29] as well as a simple scan of the liver which uses vibration controlled transient elastography (VCTE) to assess the liver stiffness[28 30 31] – a marker of fibrosis.

The targeted assessment of liver disease in people living with T2DM is currently not recommended. This is despite the high background prevalence of liver disease in people living with T2DM,[10-13] the availability of validated diagnostic tests and recent calls for screening for liver fibrosis in people living with T2DM.[12]

In 2021 NICE highlighted a lack of evidence in this area and called for further research. Existing National Institute of Care and Excellence (NICE) guidance[32] recommends that targeted testing for liver disease should be restricted to people living with T2DM and a fatty liver on ultrasound or harmful alcohol consumption or abnormal liver function tests.[32] However, routine liver function tests are not recommended in the NICE guidelines for people living with diabetes, which means people with diabetes will not, as a matter of routine care, access diagnostic pathways for liver disease from their annual checks.

Community pathways exist to identify liver disease in people living with T2DM (for example[33]), however, these pathways reflect the NICE guidance by only testing patients with abnormal liver function tests or abnormal ultrasound imaging.[32] The Southampton liver pathway (SLP) is a good example of the NICE guideline operating in NHS practice.[34] Our NHS service provides VCTE assessment for patients in two large geographical areas in the South of England (population ~300,000). In the SLP, if a person living with T2DM has abnormal liver function tests or a fatty liver on ultrasound examination, they are offered a simple ELF™ blood test. If this test result is above a pre-defined threshold the patient is referred for VCTE scanning that operates in the community. If that simple, quick scan (that is very similar to an ultrasound scan) shows that a patient has a high liver stiffness score, they are then referred to Hepatology services operating within University Hospital Southampton (UHS); and those patients with a liver stiffness score of ≥12.1kpa) are offered biannual HCC surveillance.

In keeping with our recent work[35] and that of others,[12] 1 in 10 patients in the SLP is diagnosed with a moderate liver fibrosis or liver cirrhosis (defined as ≥8.2kpa on VCTE). However, we estimate that only ~4% of people living with T2DM in the geographical area covered by the SLP are tested for liver disease per year.

Our proposed study is a response to the recent call by NICE to establish the most effective and cost-effective way to identify liver disease in people living with T2DM. By filling this gap in evidence, the study will identify people living with T2DM who are at risk of primary liver cancer and additional risks associated with moderate and severe liver fibrosis and cirrhosis. The data we generate will support the NHS England Cancer Alliance achieve its objectives to engage more patients with HCC surveillance

Research shows that liver scarring can be identified when blood tests with a simple liver scan are undertaken but currently this happens infrequently in the NHS. We need to know if testing everyone with type 2 diabetes for liver scarring is better than the current model of care for people living with type 2 diabetes.

2. Aims

We are testing whether adding (reflex) testing for liver disease into routine diabetes care is a good way to identify liver disease and if it is good value for money.

Risk factors' for liver disease (described in the current NICE NAFLD guidelines[32]) do not effectively risk stratify for the presence of liver disease in people living with T2DM. Accordingly, we hypothesise 'reflex testing' (i.e. testing all people living with T2DM as part of their routine diabetes care) for liver disease, would lead to increased identification of liver disease.

3. Objectives

To test whether reflex testing (i.e. testing all people living with diabetes) for liver disease leads to a significantly increased number of cases when compared to usual care. To compare the relative cost-effectiveness (measures as an incremental cost-effectiveness ratio) of reflex testing and usual care.

4. Design

The study design will be an unblinded randomised (2-arm) controlled trial with a nested cost-effectiveness evaluation comparing reflex testing (i.e. testing all people living with T2DM) for liver disease against standard care. We will proceed straight to an effectiveness evaluation.

5. Setting

This study is based in primary care. GP practices will be recruited with the assistance from the Wessex Clinical Research Network (CRN). We hope to involve a range of practices in terms of socio-demographics of the community served, including those from urban, suburban and rural setting. Interested practices will express interest to the research team through completion of a google shared document.

6. Potential participant identification

The research team will have no involvement in identifying potential participants. Potential participant identification will be performed by the GP practice staff only.

In collaboration with our Research Team GP co-applicant Dr Karen Malone, we have devised our potential participant identification strategy. These methods are acceptable to GP practices, [36 37] and have successfully been implemented with other research studies conducted in primary care.

The research team will not have any involvement in points 1 to 3 below. These tasks will be performed by practice staff at participating GP surgeries. We will phase in participating GP surgeries throughout the planned recruitment phase of the study (24 months).

6.1 Method A – Potential participant self-referral

Awareness of the study will be generated at some of the participating GP practices using posters (e-poster and notice board); practice waiting room TV feed (short PowerPoint presentation); hard copies of the summary patient information sheet; and via the practice website. The study awareness material will direct potential participants to where they can access further information and who to contact if they would like self-refer their interest in the study.

6.2 Method B - Potential participant identification and invitation to self-refer

Some participating GP practices will identify potential participants from their patient records. The research team will provide these GP practices with a search query, developed with the help of the Wessex CRN, to run on the surgery patient management system. Patients will be screened for eligibility by practice staff. The patients on the list of eligible potential participants will be sent a text/email/postal letter advising them about study, where they can access further information and who to contact if they would like to self-refer their interest in participating.

6.3 Method C - Potential participant identification at surgery appointment

Potentially eligible participants attending a surgery appointment will be asked if they would like information about the study. Patients who express an interest in the study will be given the summary patient information sheet with details of who to contact if they would like to self-refer their interest.

Directly following their surgery appointment, some participating practices will be able to signpost potential participants to the research team to discuss the study face-to-face.

7. Eligibility criteria

7.1 Inclusion criteria

Any adult (≥18 years) patient with a diagnosis of T2DM in Wessex Clinical Research Network (CRN) region able to provide informed consent will potentially be eligible to participate.

7.2 Exclusion criteria

<18 years of age; unable to provide informed consent; a known prior diagnosis of cirrhosis or assessed for liver fibrosis/cirrhosis in the previous 24 months.

8. Consent

Before participants are randomised, verbal consent will be obtained over the telephone by the research team. A signed copy of the consent form will then be obtained from all participants. Participants will be sent their consent form in the post to sign and return to the research team (a stamped addressed envelope will be included with the consent form). There will also be the option of eConsent, where the written consent form will be converted into electronic format on Microsoft Forms and the participant will be able to sign electronically. See **Appendix A** for summary of the three methods of obtaining informed consent form potential participants.

After telephone consent has been obtained, the participant will immediately be randomised and advised which group they have been assigned to: intervention or control arm.

9. Randomisation

To ensure equal numbers of patients within each arm of the study we will use block randomisation with block size of 4. Blocks will be used to ensure a balance between the participants in each arm of the study - strata will be sex, age group and alcohol consumption. This will be managed by the Southampton NIHR BRC (where joint lead applicants Christopher Byrne and Ryan Buchanan are Principal Investigators) using randomisation software.[38]

9.1 Intervention arm – reflex testing

At the point of being randomised to the intervention, participants will be booked for their liver assessment (blood collection and VCTE assessment). The liver assessment will take place in a pre-booked treatment room in a community setting, e.g. at a GP surgery. The appointment will take approximately 20-30 minutes.

VCTE is non-invasive, takes approximately 10 minutes, and provides the user with direct information about the patient's liver health. At the time of their VCTE assessment, patients will be advised of their liver health. Blood samples will be sent to UHS for analysis.

The results of blood tests for liver fibrosis (Fib4 & ELF) and the result of VCTE assessment will be sent the participants GP. According to local pathways – where appropriate participants with abnormal results will be referred directly to hospital services.

9.2 Control arm – standard care

Participants randomised to the control arm will be managed in accordance with the standard care offered at their GP practice. Standard care for identifying and managing liver disease varies across the UK, it is important that we allow patients to continue to be managed as normal, so that we have real life data to use in our analysis. However, after discussion with our PPI groups, participants randomised to this arm will be undergo VCTE (as for the intervention arm, detailed above), approximately 12 months following randomisation. Participants randomised to this arm will be advised by the research team that the research team will contact them in approximately 12 months time to book their liver assessment appointment. The results of the VCTE and the results of blood test for liver fibrosis will then be sent to the participants GP and communicated to the participant.

9.3 Data collection – both study arms

Following consent and randomisation data will be collected over the telephone from all participants. This will include participant information and self reported information including height, weight, sex, ethnicity, current prescription medications, alcohol consumption using AUDIT-C[39]. This baseline data will be supplemented with data from each participants' GP record. All participants will then have a blood sample taken at a convenient community location. For those in the reflex testing group this will coincide with VCTE assessments.

9.3.1 Data collection – Usual care arm only

At 12 months following randomisation we will access the GP records of participants in the usual care arm to assess engagement with liver health services. For those who have not been tested for liver fibrosis/cirrhosis in the 12-month follow up period will have a VCTE assessment with the study team. The result of this test will be recorded.

10. Measurable outcomes

10.1 Primary

1. The number of patients diagnosed with moderate or significant liver disease within a year of randomisation (defined as ≥8.2kpa on VCTE).[1]
2. The number of patients with severe liver disease (defined as ≥12.1 kPa on VCTE)[1] and referred to secondary care.

10.2 Secondary

1. Calculate the 'costs per case' of moderate and significant liver disease identified via reflex testing for liver disease and usual care.
2. The test or combination of tests for liver fibrosis with the lowest cost per case.
3. The incremental cost effectiveness ratio (ICER) of reflex testing and HCC surveillance for liver disease in people living with T2DM.

11. Sample size calculation

We will aim to recruit 320 patients into each arm of this study – 640 patients in total. A sample of this size will enable us to address both co-primary outcomes, with a minimum power of 80% after allowing for a conservative 25% drop out. We know that the current attrition rate between GP referral to the community liver service and the patient attending their appointment is ~18%. However, we anticipate that between randomisation and liver assessment in our study, a more realistic drop rate would be 5%. Thus with a 5% drop out rate the minimum power to test both co-primary outcomes will be 91%. (See appendix 12 for diagrams of the sample size calculation for the co-primary outcomes).

From the existing evidence, we expect that ~10% of tested participants will have ≥F2 fibrosis and ~5% of participants will have significant liver disease (≥12.1 kPa). Currently ~4% of people living with diabetes in the geographical study area are assessed for liver disease per year. Due to the lower rates for significant liver disease (≥12.1 kPa) this is the co-primary outcome that will determine the sample size. To achieve 12 participants with significant liver disease in the reflex arm requires 240 patients assuming at a 5% prevalence. Allowing for a conservative 25% of participants to either not undergo or have invalid VCTE readings, this number increases to 320 per group. With 320 in the usual care arm and allowing for potential contamination to double the expected number being tested to 8%, we would expect 26 to be considered for testing.

Assuming a similar attrition rate and prevalence to the reflex arm you would expect to find 1 participant with significant liver disease in the usual care arm. With these expected percentages: 12/320 (3.75%) in the reflex arm and 1/320 (0.31%) in the usual care arm, a power of 80% with a 5% significance level and allowing for an exact calculation (due to the small expected counts) would require at least 319 participants in each group.

12. Analysis

12.1 Co-primary outcome analysis

We will conduct an 'intention to diagnose' analysis for the primary outcomes. All participants undergoing randomisation will be analysed within the group to which they were assigned regardless of whether they engaged with the diagnostic process within their study arm.

Logistic regression will be used to compare the co-primary binary outcomes between the standard care and intervention arms, adjusting for all of the stratifying variables included in the randomisation. Exact or penalised likelihood estimation methods will be used to avoid the small-sample bias that otherwise would be present with such small expected outcome numbers. All estimates will be presented with 95% confidence intervals and p values <0.05 will be considered statistically significant.

12.2 Cost-effectiveness evaluation

Data from the study including the micro-costs of testing (see above), drop-out rates from the diagnostic pathways (usual care and reflex testing), the relative proportions of different stages of liver disease and the demographic characteristics of the cohorts will be used in a cost-effectiveness evaluation led by Dr Keith Cooper (KC), Senior Research Fellow in Health Economics at the University of Southampton.

We will use a Markov state transition model (developed in Microsoft Excel® for Mac 2017) and estimate the disease associated QALYs and costs associated with liver disease and HCC. The model structure will be similar to previous models for HCC surveillance.(e.g.(2)). The model will consist of health states for T2DM, T2DM+stages of liver disease and HCC. In the model, patients will move between health states in cycles, according to the transition probabilities. Transition probabilities will be taken from the published literature. The modelling will be constructed according to best practice guidelines.(3,4)

For the analysis, two cohorts of 1000 persons living with T2DM with a spectrum of liver disease matching the study cohorts will entered the model at year 0. At the end of the time horizon disease costs and quality-adjusted life years (QALYs) will be calculated and compared for a cohort of 1000 people living with T2DM who have undergone reflex testing for significant liver disease – and hence widespread HCC surveillance and a second cohort of patients with mostly undiagnosed significant liver disease and consequentially low rates of HCC surveillance. The difference in costs and QALYs between these populations was then used to calculate an incremental cost- effectiveness ratio (ICER) in accordance with the following equation:

ICER=Cost of intervention including HCC surveillance and reflex testing-Cost of control QALY of intervention-QALY of control

We anticipate increased QALYs to be associated with the cohort of people living with T2DM who undergo reflex testing for significant liver disease and associated greater HCC surveillance. However, these will be offset by the greater costs associated with reflex testing and increased surveillance.

The cost effectiveness analysis is based on simulated data (the two cohorts of 1000 people).

13. Ethical and regulatory considerations

Some Participants may find they have significant and previously unsuspected liver disease - this is the purpose of the study. Participants will be under the care of an NHS specialist liver unit who have expertise in dealing with these issues.

The project may be participant to inspection and audit by the University of Southampton, under their remit as sponsor, and other regulatory bodies to ensure adherence to ICH GCP, Research Governance Framework for Health and Social Care, applicable contracts/agreements and national regulations.

We have a strong experienced team and the support of the Wessex Clinical Research Network.

14. Protocol deviations and serious breaches

Aim: To demonstrate how protocol compliance will be managed.

Definition: Protocol deviations, non-compliances or breaches are departures from the approved protocol.

Accidental protocol deviations can happen at any time. They will be adequately documented the relevant forms and reported to the Chief Investigator and Sponsor immediately.

Deviations from the protocol which are found to frequently recur are not acceptable, they will receive immediate action as they could potentially be classified as a serious breach.

For any deviation where corrective actions are required and/or there is a risk of recurrence and preventative actions are required, we will notify the Sponsor immediately. A corrective action and preventative action form (CAPA) will be completed and sent to the Sponsor via rginfo@soton.ac.uk.

15. Adverse event reporting

A Serious Adverse Event (SAE) is defined as an untoward occurrence that:

(a) results in death;
(b) is life-threatening;
(c) requires hospitalisation or prolongation of existing hospitalisation;
(d) results in persistent or significant disability or incapacity;
(e) consists of a congenital anomaly or birth defect; or
(f) is otherwise considered medically significant by the investigator. An SAE occurring to a research participant will be reported to the REC where in the opinion of the Chief Investigator the event was:
- "Related" – that is, it resulted from administration of any of the research procedures, and
- "Unexpected" – that is, the type of event is not listed in the protocol as an expected occurrence.

SAEs will be reported to Sponsor at rgoinfo@soton.ac.uk within 24 hours of the study team becoming aware. Reports of related and unexpected SAEs will be submitted within 15 days of the Chief Investigator becoming aware of the event, using the SAE report form for non CTIMPs published on the HRA website.

16. Clinical care

We expect some patients with previously undiagnosed liver disease will be discovered in the course of this study. Participants who are found to have liver disease or who need further tests for any reason will be managed exactly as if they were a patient who is looked after in the NHS. The clinical research team at University Hospital Southampton (UHS) will review all patient results and ensure any additional tests or referrals are requested either at UHS or through the close connections the clinical research team have with secondary care across the research site.

17. Data protection and patient confidentiality

All patients will be given a unique patient identification (UPI). No patient identifiable data will be stored with the UPI. Only the research team will have access to the study database. All data files will be encrypted and the data will be entered into a secure password protected database on the Faculty of Medicine server at the University of Southampton.

E-records (e.g. e-consent) and all patient data will be entered into a secure password protected database on the Faculty of Medicine server at the University of Southampton. No personal identifiable data will be stored on computer. Any paper records will be stored in locked cabinets in locked offices with coded access.

The research team will have access to participants personal data during the study, but only once the participant has provided informed consent. The consent form details which information we need to collect and why. Data storage and analysis will be overseen by Professor Christopher Byrne, Associate Professors Ryan Buchanan, and Scott Harris (statistician), Tina Reinson and Josh Bilson. The data and database is the responsibility of the Investigators. Data will be reviewed and checked for omissions. Only authorised personnel will make corrections to the database and all corrections will be documented in an audit trail.

One of the purposes of this study is to establish a long term cohort of patients with early liver disease detected using VCTE technology and blood tests. We wish to follow these patients at a distance having obtained consent to access their medical records. The time course for the progression of liver disease from early fibrosis to cirrhosis liver failure and the development of the hepatocellular carcinoma can be long. We would like to be able to follow up the cohort remotely for at least 10 years.

The University of Southampton (UoS) is committed to protecting the privacy and security of the personal information for all participants in our research. Its privacy notice describes how UoS collects and uses personal information about research participants when you are participating in a research project run by the university, in accordance with the General Data Protection Regulation (GDPR).

18. Dissemination policy

The PPI contributors to the protocol viewed dissemination as a vital activity which they can support. They identified two main audiences: people living with diabetes and health care professionals (including GPs, pharmacists, those working at retinopathy screening centres and those providing health education).

People living with diabetes

Throughout this research, we will engage with people living with T2DM and their communities to feedback regarding progress. We aim to learn the most effective ways of engaging with minority ethnic groups. Such groups have often not been prioritised for dissemination of healthcare research. We will explore methods, including face-to-face meetings, presentations and written articles. Use of the internet, social media and involvement of community venues (e.g., mosques, churches, gurdwaras, community centres) will be checked.

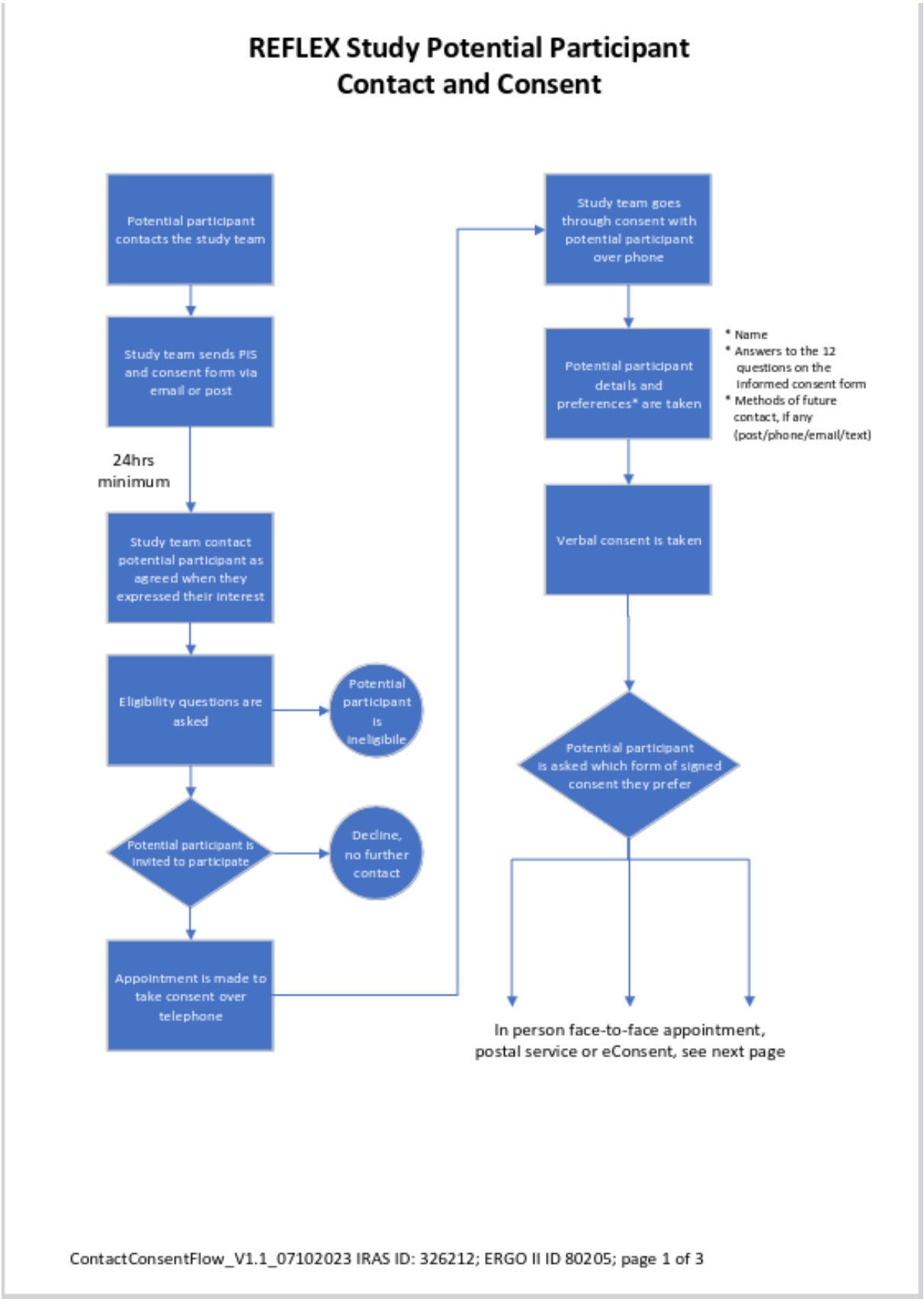
Health care professionals

The research team will publish the research findings in professional and academic journals. All recruiting centres and contacts will be sent written summaries of the study findings. The research team will also report findings at professional and academic conferences, such as the Diabetes UK Professional Conference. We would like to explore possibilities for including PPI contributors presenting together with the research team at conferences. In this way our PPI contributors can share their experiences which can stimulate impactful learning.

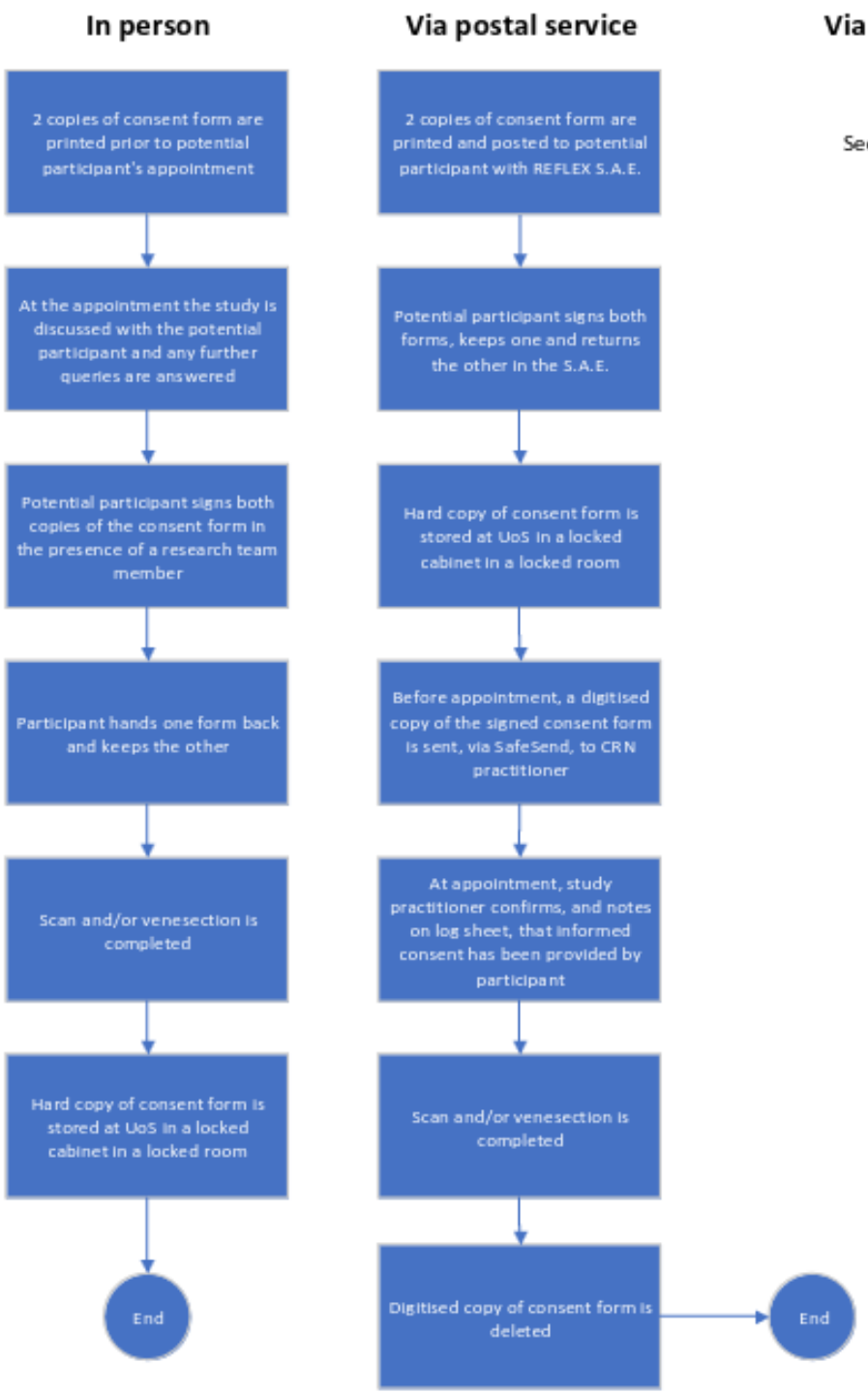
The University of Southampton provides educational programmes for healthcare professions, including doctors, nurses and allied health professionals. This latter group includes occupational therapists, physiotherapists and podiatrists. We will explore possibilities for sharing our patient experiences and study findings with students, to influence future healthcare practice.

Appendices

Appendix A - method of obtaining informed consent from potential participants



Signed consent flow



Signed consent flow (cont.)

Via eConsent

*HMAC: Hash-based message authentication code

ContactConsentFlow_V1.1_07102023 IRAS ID: 326212; ERGO II ID 80205; page 3 of 3

Approved by C.B.

07/10/23

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