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Screening to identify people with type 2 diabetes at risk of liver cancer in primary care - a randomised controlled trial PROTOCOL

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Screening to identify people with type 2 diabetes at risk of liver cancer in primary care - a randomised controlled trial PROTOCOL

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Abstract

Introduction

Hepatocellular carcinoma (HCC) is expected to become the 3rd most common cause of cancer death world-wide by 2030. The increase in HCC is in large part due to the rising prevalence of risk factors such as type 2 diabetes (T2DM). Up to 1 in 20 people living with T2DM have liver cirrhosis and they have a 1-2% incidence of HCC per year.

Patients with cirrhosis enter surveillance for HCC to identify early-stage, curable tumours. A diagnosis of T2DM does not mandate testing to identify patients with cirrhosis with testing restricted to those with additional risks. There has never been a trial and nested cost-effectiveness evaluation comparing screening all patients with T2DM for cirrhosis against usual care.

Aim

Determine the effectiveness and cost-effectiveness of screening all adults with T2DM to identify those at high risk of HCC.

Methods and analysis

A multi-site, unblinded individual randomised controlled trial comparing screening for liver cirrhosis in people with T2DM against usual care. Our recruitment strategy has been supported by patient and public involvement (PPI). Participants will be identified via an automated search of primary care records and invited to participate via text.

320 participants will be randomised to screening. Screening will include measurement of bio-markers (ELF™ and Fib-4) and vibration controlled transient elastography. Another 320 participants will be randomised to usual care.

Primary outcome is the proportion of participants in each arm who are referred into HCC surveillance over 12months by specialist services. The results will be used to calculate the incremental cost-effectiveness ratio of screening via a Markov model.

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Ethics and dissemination

The results of this study will be presented directly to NHS England. Additional dissemination via conference proceedings and publication will be supported by our PPI team. The study has full ethical approval – IRAS N° 326212, REC reference 23/WS/0102.

Trial registration: ISRCTN17017677

Article summary

Strengths and limitations of this study

- First comparison via an RCT between risk factor-based testing for liver disease in people with T2DM (usual care in the United Kingdom) and screening offered to all adults with T2DM.
- Provides definitive cost-effectiveness of both approaches and impact on liver cancer diagnosis and survival in a real-world setting.
- Will delineate relative cost-effectiveness of different non-invasive tests to identify significant liver disease in people with T2DM.
- Trial limited to United Kingdom so usual care may not be internationally representative.
- Short study time-horizon therefore observation of clinical outcomes subject of modelling rather than real-world observation.

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Introduction

Cancer is the leading cause of mortality in patients with type 2 diabetes mellitus (T2DM)(1) and T2DM is strongly associated with site-specific cancers including hepatocellular carcinoma (HCC).(2) 830,200 people died from HCC in 2020 and the incidence of HCC is expected to increase by 55% in the next 20 years.(3) HCC is now the fastest growing indication for liver transplantation(4) and it is expected to become the 3rd most common cause of cancer death worldwide by 2030.(5) HCC has a very poor prognosis with a 5-year survival of ~20%.(6) However, if cases are identified at an early stage curative treatments are available which include surgical resection, liver transplant or tumour ablation.(6)

A major risk factor for increasing deaths from HCC is the increasing global prevalence of T2DM.(3,5,7) T2DM causes liver steatosis, inflammation, fibrosis and liver cirrhosis and patients with significant liver fibrosis or cirrhosis are at risk of HCC.(8,9) There is a high prevalence of all stages of liver disease in people living with T2DM.(10–14).

International guidance recommends biannual surveillance for HCC in patients with liver cirrhosis via ultrasound imaging however, less than one third of incident cases of HCC in patients with T2DM are identified via surveillance.(15) Identification of HCC via surveillance is important as cancers that are identified in patients who are undergoing regular surveillance have better outcomes.(16) To engage patients with T2DM with HCC surveillance it is necessary to first identify patients with cirrhosis. In the past liver disease was hard to identify because it progresses without signs or symptoms. However, several approaches have now been validated in patients with T2DM to identify asymptomatic disease. These include utilization of blood tests such as the Fibrosis-4 test (FIB-4) (17) and the Enhanced Liver Fibrosis (ELF™) test (18), as well as a simple scan of the liver which uses vibration controlled transient elastography (VCTE) to assess the liver stiffness(17,19–21) as a validated marker of fibrosis.

In addition to HCC surveillance early-diagnosis of liver disease can facilitate positive interventions aimed at improving patient outcomes. These include optimisation of blood glucose control in people with T2DM, dietary modification and treatments to facilitate weight loss, moderation, or complete abstinence from alcohol (a co-factor in liver disease progression for these patients(22)) and potentially pharmacotherapy that reduces fibrogenesis. With respect to the latter, on 14th March 2024, Resmetirom(23) was given conditional approval by the US Food and Drug Administration (FDA) for the

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treatment of adults with noncirrhotic non-alcoholic steatohepatitis (NASH) with moderate to advanced liver scarring (fibrosis) alongside diet and exercise. Furthermore, selected patients could be prescribed beta blocker therapy to reduce mortality from bleeding oesophageal varices and to reduce risk of liver decompensation.(24)

In addition to being recommended in the USA(25,26), screening for liver disease in patients with T2DM and obesity has recently been adopted as a national pilot in England that has been funded by the National Health Service England (NHSE) cancer service.(27) The national pilot uses a primary care based search algorithm for T2DM as well as other risk factors for liver disease (such as hazardous alcohol consumption) and then invites patients into a cascade of non-invasive tests for fibrosis.

Whilst patients with T2DM are known to have an increased risk of fibrosis and cirrhosis(28) there is a lack of empirical evidence supporting implementation of this NHSE programme. Just three studies have tested a diagnostic pathway for liver disease against a contemporaneous control(29–31) and just one specifically focussed on liver disease in patients with T2DM(30).

The NHSE pilot is different from the current national (NICE) guidelines in the UK which recommends testing for liver disease is restricted to patients with risk factors for liver cirrhosis including a fatty liver on ultrasound imaging, abnormal liver enzyme levels and potentially harmful levels of alcohol consumption.(32) T2DM alone is not a risk factor that currently mandates assessment. The reason for these narrow criteria is a lack of cost-effectiveness data supporting wider eligibility for testing.(33)

The NICE NAFLD guideline (ng49) was published in 2016(32) and since its publication researchers have modelled the cost-effectiveness of testing for liver disease in patients with T2DM(34–36). Published models have compared testing strategies that include novel biomarkers and VCTE against standard care where standard care includes history, physical examination, liver 'function' tests (LFTs) and an ultrasound scan. The sensitivity and specificity of each approach is pre-defined and parameterises models that calculate the health gain for patients correctly categorised with liver disease and offsets this against the cost of the different testing approaches by calculating an incremental cost-effectiveness ratio (ICER).(34,36) Most recently, Forlano et al. modelled the ICER for screening in patients with T2DM. The model was parameterised using cross-sectional data from a cohort of patients with T2DM living in London (UK) that were all tested for liver cirrhosis using with FIB-4, ELF™, VCTE and in 19/249 cases,

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liver biopsy. The costs and outcomes associated with testing this cohort were compared to a usual care (primary care diagnosis) that was less accurate. In the base case analysis the ICER was well below NICE cost-effectiveness thresholds with the additional costs of testing being offset by the gain from an accurate early diagnosis.

However, there are challenges with extrapolating prior models to a real-world intervention such as the NHSE pilot that aims to test a broader range of adults with T2DM for liver disease as part of routine care. Firstly, we don't know which patients respond to an invitation from primary care for liver assessment. For example, it is likely that patient age and comorbidities will influence their probability of having liver disease and their personal gain from an early diagnosis. Secondly, we don't know what proportion of this cohort meet clinical criteria for interventions that convey the advantage of early diagnosis, e.g. what proportion enter an HCC surveillance pathway and what proportion have CSPH and are started on beta blockers. Thirdly, we don't know the real-world performance of standard care in the UK. Most patients with T2DM do not get tested for liver disease, despite their heightened risk because they are not assessed for the additional risk factors that are needed to qualify for testing. For example, LFTs are not part of an annual diabetes check up in the UK and may or may not be measured when patients are considered for statin treatment; liver ultrasound is not a routine test, and alcohol consumption is not accurately or consistently assessed in primary care. Finally, previous economic evaluations are outdated as they use primary care-based assessments (e.g. history and examination) that do not incorporate tests for fibrosis (e.g. Fib-4 and VCTE). Since the NICE NAFLD Guideline in 2016, tests for liver fibrosis are widely integrated into community diagnostic pathways for liver disease and therefore in future studies models of 'usual care' need to reflect this.

This study protocol describes a randomised controlled trial with a nested cost-effectiveness evaluation. The study aims to accurately record the performance of standard care and compare this with a real-world pathway where patients with T2DM are universally offered screening for liver disease with serum fibrosis biomarkers and VCTE.

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Method and analysis

The trial is described in accordance with the SPIRIT checklist.(37) The design will be an unblinded randomised controlled trial with a nested cost-effectiveness evaluation comparing the offer of screening (i.e. offering testing to all patients with T2DM) for liver disease against standard care. We will proceed straight to an effectiveness evaluation rather than conducting a formal feasibility/pilot study because the components of the intervention (i.e. testing for liver disease in a primary care setting) are widely implemented and data such as the attrition rate from the diagnostic pathway is already known (see sample size section).(38) Undertaking a randomised controlled trial in this setting is very important as this provides the opportunity to have a contemporaneous usual care arm.

Primary outcome

i) The number of participants referred to secondary care with suspected liver disease within 12 months of randomisation who are subsequently referred for HCC surveillance.

As an unblinded trial it is important our primary outcome is as objective as possible and independent of the research team. In both study arms patients with high liver stiffness measurements will be referred to nearby hepatology services (with thresholds defined by local practice). Via usual care the responsible local clinician will then assess the severity of liver disease. In real-world practice this may include history, examination, no further tests or repeat VCTE, additional tests for fibrosis and in some case liver biopsy. Regardless of the clinical approach taken the primary outcome will be whether the clinician felt the disease was severe enough to warrant referral for HCC surveillance. Since the trial sites cover a variety of different regions across the south of England, this pragmatic approach is likely to closely reflect current UK practice.

Secondary outcomes

1. The test or combination of tests for liver cirrhosis with the lowest cost per case diagnosed*
2. The sub-group with the lowest cost per case diagnosed*
3. The incremental cost effectiveness ratio (ICER) of screening for liver cirrhosis in people with T2DM
4. The number of cancer deaths avoided by screening (as per Markov modelling)

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5. The number of patients diagnosed on VCTE with ≥F2 disease (defined as a liver stiffness of ≥8.2kpa)(21)

*see i) for definition of a 'case'

Participants

Inclusion criteria

Any adult (≥18 years) patient with a known diagnosis of T2DM according to the primary care record in the Hampshire, Wiltshire, Dorset, and the Isle of Wight (all UK) areas will potentially be eligible to participate. Non-English speaking patients will be eligible for inclusion.

Exclusion criteria

- <18 years of age
- Evaluated for liver disease with either an ELF™ test or VCTE in the 2 years prior to the date of consent.
- A known prior clinical diagnosis of significant liver disease* due to any cause
- A known diagnosis of autoimmune hepatitis, primary biliary cholangitis, primary sclerosing cholangitis or viral hepatitis (irrespective of whether this has progressed to fibrosis or cirrhosis)

*Significant fibrosis or cirrhosis and in active hospital follow up

Setting

The study will be conducted in 16-20 Primary care practices and diabetes community care hubs in Wessex (including Hampshire, Wiltshire, the Isle of Wight and Dorset (UK)). The setting of the study is important as it includes a range of existing community liver pathways which means the intervention is compared to a diverse representation of standard care – which are representative of diverse interpretations of the current NICE guidelines.(32)

Community hubs will be used for research data collection including VCTE and blood sampling. Primary care centres will be identified via the local Primary Care Network and the Primary Care NIHR clinical

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research network (CRN). The number of practices we are using is justified in the later dedicated sections of the form.

Participant identification

Practices will identify potential participants from their patient records. The research team will provide these practices with a search query to run on their patient management systems (SystmOne or EMIS) (see supplementary material and trial website (reflexstudy.org)) Flagged patients will be screened for eligibility by practice staff. The patients on the list of potential participants will be sent a text 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 (see supplementary material).

Consent & Randomisation

If a participant contacts the research team they are sent an information sheet and given time to consider participation before providing written consent with the research team (see supplementary material). After giving consent each participant will be randomised. 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 Biomedical research centre (BRC) team using randomisation software.(39)

Arm 1 – Screening

Participants in this arm will be referred by the research team directly for liver fibrosis assessment at a community hub. This assessment will include VCTE and venepuncture for an ELF™ test and a FIB-4 index. The result of the VCTE and any abnormalities identified in the blood tests will be managed in accordance with the local liver disease care pathway (as per the usual care arm described below). VCTE will be performed by an experienced single operator after a minimum of a 3 hour fast and previously published criteria for a valid reading will be applied to each participant.(40)

Arm 2 – Standard care – NICE guidelines based – T2DM + additional risk factor testing

Participants in the standard care arm will not be contacted for VCTE. Usual care varies across the study area but is based on 2016 NICE guidance (**Figure 1**). In the 2016 NICE NAFLD guideline, the presence of T2DM does not trigger an assessment for liver disease in the absence of other specific risk factors.(32)

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'Risk factors' to enter standard care vary in the study areas but broadly include: harmful alcohol consumption, an elevated ALT and a fatty liver on ultrasound examination. If risk factor thresholds are met then the usual care pathway varies further but in all areas involves VCTE with or without a biomarker for liver fibrosis (e.g. FIB-4 or ELF™) **(Figure 1)**. The variation in standard care is very important as it increases the external validity of our study by being representative of the heterogeneity across the UK.

After discussion with our PPI groups, participants included in the standard care arm will be given the opportunity to undergo VCTE and a biomarker test to assess them for liver fibrosis >12 months following randomisation (arranged at mutual convenience with the research team).

Data collection

Baseline data collection

All participants will give consent for access to their primary care records. These alongside a brief questionnaire will provide participant baseline data including demographics, medication and co-morbidities that cover the Charlson index(41) (giving an overall score for co-morbidity) and other prevalent co-morbidities in the study population (Table 1).(42) Participants are not asked to complete further data collection activities as we want to minimise potential Hawthorne effect in our control group – we are concerned prolonged exposure to the research team may lead usual care participants to change behaviour and either seek or perhaps decline liver assessment.(43)

Primary Outcome data collection

The primary outcome - referral to HCC surveillance following a referral with suspected liver disease from primary care will be assessed by the research team from each participant's health care records. Participants will not need to be recontacted for outcome data. For usual care participants the GP care record will be reviewed for a referral letter to secondary care or a community liver assessment service that was sent within 12months of randomisation. For both trial arms records will be reviewed for evidence (e.g. a letter from hepatology services) that the patient has been enrolled in HCC surveillance. The GP record review will take place up to 36 months from randomisation to ensure enough time has elapsed for the patients to have been assessed by secondary care.

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Cost data collection

We will collect micro-costs(44) on the following components of the pathway:

- Item costs for ELF™ & FIB-4 tests and venepuncture cost
- Nursing time for: venepuncture, VCTE, results delivery and onward referral
- Cost per VCTE assessment including equipment, equipment servicing and training
- Community venue hire for liver assessment

Data management plan

Participant data will be managed according to the study data management plan which is available on the study website (reflexstudy.org). Study data including participant identifiable data will be stored securely in accordance with ethical approvals.

Data analysis

Primary outcome

We will conduct an 'intention to diagnose' analysis for the primary outcome where all participants undergoing randomisation will be analysed within the group to which they were assigned, regardless of whether they engaged with the diagnostic process following referral within their study arm. Logistic regression will be used to compare the binary outcome between the standard care and intervention arms. Exact or penalized likelihood estimation methods will be used to avoid the small-sample bias that otherwise would be present with such small expected outcome numbers.

Cost-effectiveness analysis

For the cost effectiveness evaluation, data from the study will be incorporated into a decision analytical model (developed in Microsoft Excel®). These data include: the micro-costs of testing and follow up, drop-out rates from the diagnostic pathways (usual care and screening), the relative proportions of different stages of liver disease and the demographic characteristics of the cohorts.

The model will consist of a decision tree for the diagnostic process and a Markov state transition model for the long term disease process (**Figure 2).** It will estimate the quality adjusted life years (QALYs) and costs associated with liver disease. The model structure will be similar to previous models for HCC

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surveillance.(e.g. (34,36)) and calculate the difference in costs and QALYs between different testing approaches and no testing. Patients with characteristics based on our study population and study outcomes will enter the model. The model will have one year cycles and a lifetime horizon (i.e until the cohort age is 100 years). Costs will be calculated using an NHS and Personal Social Services perspective. Costs and utilities for the model health states will be taken from a targeted review of the medical literature.

Our base-case analysis will closely match real-world practice. In both cohorts patients identified with liver cirrhosis and referred for HCC surveillance will enter a separate health state – named F4_SURV. Based on recently published data, participants in this health state who develop HCC will have a higher chance of cure (i.e. return to their original F4 SURV health state) and a lower chance of progression to death or transplantation.(16) Similarly, a proportion of those in F4_SURV will have a lower risk of progressing to a decompensated state that reflects the real-world number of participants who commence B blockers in accordance with recent guidelines.(45,46) Participants identified with F2 or F3 disease will enter monitoring states (F2_Mon and F3_Mon) and undergo biannual assessment for progression to F4 disease. Monitoring will stop when participants in the model reach 80 years of age.

As part of our base case analysis, we will calculate the cost-effectiveness (cost per QALY) of four testing strategies that are broadly reflective of current testing strategies in the study region and the NHSE pilot (described in the background). These will be compared against 'no testing' and presented as ICERs that can then be compared between strategies.

1. Usual care
2. Reflex testing with VCTE only (i.e. everyone offered VCTE)
3. FIB-4 then VCTE for patients with FIB-4 >3.25
4. ELF™ then VCTE for patients with an ELF™ >9.5

We will conduct probabilistic sensitivity analyses where model parameters are probabilistically varied across pre-specified distributions and ranges. The results of the probabilistic sensitivity analyses will be presented as a scatter plot and a cost effectiveness acceptability curve.

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Finally, we will conduct a one-way sensitivity analyses varying the input parameters in the model and scenarios around the main model assumptions. Specifically, we will test a scenario where we introduce a hypothetical anti-fibrotic agent that is given to patients in the F2_Mon and F3_Mon health states. As part of this we will conduct a threshold analysis where we will calculate ICERs for the hypothetical drug at different levels of therapeutic effectiveness. Anti-fibrotic therapy is not part of our base-case analysis as it is not currently part of usual care in England. **Figure 3** shows a Study flow chart showing how the study arms and nested cost-effectiveness evaluation are linked. The rationale for study sample size is also conveyed.

Sample Size

We will aim to recruit 320 patients into each arm of this study – 640 patients in total (**Figure 3**). A sample of this size will enable us to address the primary outcome, with a minimum power of 80% after allowing for a very conservative 25% drop out rate from the diagnostic pathway in both arms. A more realistic drop out rate would be 5% which would give a power to test the primary outcome of >90%.

We are concerned that the conduct of our study may increase liver disease diagnosed via usual care due to Hawthorne effect on participants randomised to usual care or on primary care physicians who are more likely to request testing because they are, as a consequence of participation, more aware of liver disease.(43) Our sample size therefore also accounts for a doubling of background liver fibrosis testing in usual care. The background testing activity for liver disease in the study setting has been very important in calculating our samples size. We have estimated the background testing activity from what we know about the number of patients tested for liver fibrosis who have T2DM in a year and the total population of people with T2DM (Figure 3).

All sample size calculations were conducted using nQuery advisor 7.0.

Patient and public involvement

To design the trial we have worked with two PPI representatives (one as PPI lead) and two PPI groups. Our PPI group was struck by the risk of liver cancer in people with diabetes. This was not something they were previously aware of. Both groups of contributors shared the views that cancer and specifically surveillance for liver cancer should be the focus of our research. Our groups are diverse - 8 participants in total; 2 female; two non-white British; one born in eastern Europe. The PPI groups have helped

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develop our study recruitment strategy and our participant facing study materials. Both groups raised some concerns about the use of a control arm. They advised us to ensure liver assessment was offered to all participants at the end of the study and this has been incorporated into our study procedures.

Discussion

The application, effectiveness and cost-effectiveness of screening for liver disease in patients with T2DM has not been well studied. Despite this it is now recommended practice in some countries and subject to national clinical pilots in others. We aim to fill this knowledge gap.

The robust assessment via a RCT of a screening intervention for liver disease in T2DM with an objective primary outcome that is assessed independently of the researchers will have a significant impact. If effective the trial would provide evidence toward justifying widespread screening in an enormous, and growing proportion of the global population with a knock-reduction in liver death. If not effective, it could prevent further roll out of a massive, costly programme of work that will have significant resource implications for health service systems. Looking forward the trial will also quantify the effect size required and suitable pricing for novel anti-fibrotic therapies to meet cost-effectiveness thresholds.

A strength of the study design is the incorporation of a usual care arm that is a diverse representation of standard practice where testing for liver disease is applied to a few, selected patients with T2DM. The design therefore allows for real-world comparisons between the status quo and (via the intervention arm) a close representation of what a screening programme for liver disease in patients with T2DM might look like.

Ethical approval and dissemination plans

The University of Southampton is the study sponsor, ERGO II submission ID 80205. Ethical approval was granted by the West of Scotland Research Ethics Service (WoSRES) on 2nd August 2023, REC reference 23/WS/0102. Any amendments to the study protocol will require authorisation from the ethical approvers. We expect that participants will be identified with liver disease as part of this study. We will work closely with clinicians in the study areas to ensure they are referred and reviewed in line with local practice. We also have academic clinicians within the study team (RB and CB) who can support participants if the need arises.

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Our PPI group will explore the use of the internet, social media and involvement of community venues (e.g., mosques, churches, gurdwaras, community centres) to reach marginalised populations and convey the study findings. Our PPI lead will aim to publish articles in local newspapers and newsletters and explore possibilities for translation. We aim to submit our findings in abstract form to the European Liver conference in January 2026 and submit to a high impact liver medicine journal later that year.

Author contributions

RB drafted the manuscript and the trial design alongside TR and CB. JB, SH planned the statistical analysis plan and KC planned the cost-effectiveness analysis. KM and HW designed the participant identification strategy and GP recruitment procedures. All authors edited the manuscript.

Funding statement

This work was supported by Echosens LTD and University Hospital Southampton NHS Foundation Trust, Southampton Hospitals Charity and the Southampton National Institute for Health and care research (NIHR) Biomedical Research Centre (NIHR203319). Funders had no role in developing the study protocol and will have no role in data collection, data analysis or manuscript preparation.

Competing interest statement

TR received a one-off consultancy fee from Echosens LTD in 2023. Other authors have no other conflicts of interest to declare.

Data statement

Search codes of primary care data that are being used to identify participants are included as an appendix. As a protocol, this article does not present collected data and therefore a data repository is not included or needed. The final study dataset will held by the chief investigator and accessible to the co-investigators the study funders will not have access to the data.

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Table 1 - **Baseline participant characteristics that will collected and where the data will be collected**

Baseline demographic characteristic	Collected at recruitment	Can be collected via EMIS/SystmOne*
Age, years	✓	
Sex, male (%)	✓	
Ethnicity (white European or minority ethnic group)	✓	
Alcohol consumption (AUDIT-C score)	✓	
Measured Height (cm)		
Measured weight (kg)	✓	
Smoking status (current, ex, never)		✓
Index of multiple deprivation (IMD) (from postcode)	✓	
Duration of diabetes, (years)		✓
Medical treatment for diabetes – tablets or insulin (currently, previously, never)	✓	
Currently prescribed medications		
Antiglycaemic treatment (any)	✓	
Sulphonylurea (e.g. gliclazide)	✓	
Metformin	✓	
Insulin	✓	
GLP-1 agonist (e.g. semaglutide)	✓	
Pioglitazone	✓	
SGL2 inhibitor (e.g …flozins)	✓	
Anticoagulants (DOAC or warfarin	✓	
Antihypertensives (any)	✓	
ACE (e.g. ramipril)	✓	
ARBs (e.g. candesartan)	✓	
B-blockers (e.g. bisoprolol)	✓	
Thiazides (e.g. BTZ)	✓	
Calcium channel blockers (e.g. amlodipine)	✓	
Antidepressants	✓	
Fibrates	✓	
Statins	✓	
Co-morbidities (to calculate Charlson co-morbidity index)		
Definitive or probable previous myocardial infarction	✓	✓
Congestive heart failure (dyspnoea with response to CHF medication)	✓	✓
Peripheral vascular disease (intermittent claudication, previous by-pass grafting)	✓	✓
Any end organ damage due to T2DM	✓	✓
Moderate to severe chronic kidney disease	✓	✓
Solid tumour (non, localized, metastatic)	✓	✓
Lymphoma (either cured, in remission or active)	✓	✓
Hemiplegia	✓	✓
AIDs	✓	✓
Peptic ulcer disease	✓	✓
Connective tissue disease (e.g. SLE, rheumatoid arthritis, not osteoarthritis)	✓	✓
Additional prevalent comorbidities in patients with T2DM	✓	✓
Hypertension	✓	✓
Asthma	✓	✓
Hypothyroidism	✓	✓

*EMIS and Systm1 are primary care software programmes used throughout England

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Figure legends

Figure 1
An overview of usual care for liver disease assessment and management within primary and secondary care liver services in study areas – highlighting the complexities and subtle variations in practice.

Figure 2
Markov model structure used to calculate incremental cost-effectiveness of different testing strategies. The findings from the trial will parameterise this model. Numbers 1-4 correspond to the benefits of early detection that will be incorporated into the modelling.

Figure 3
Study flow chart showing how the study arms and nested cost-effectiveness evaluation. Rationale for study sample size is also conveyed.

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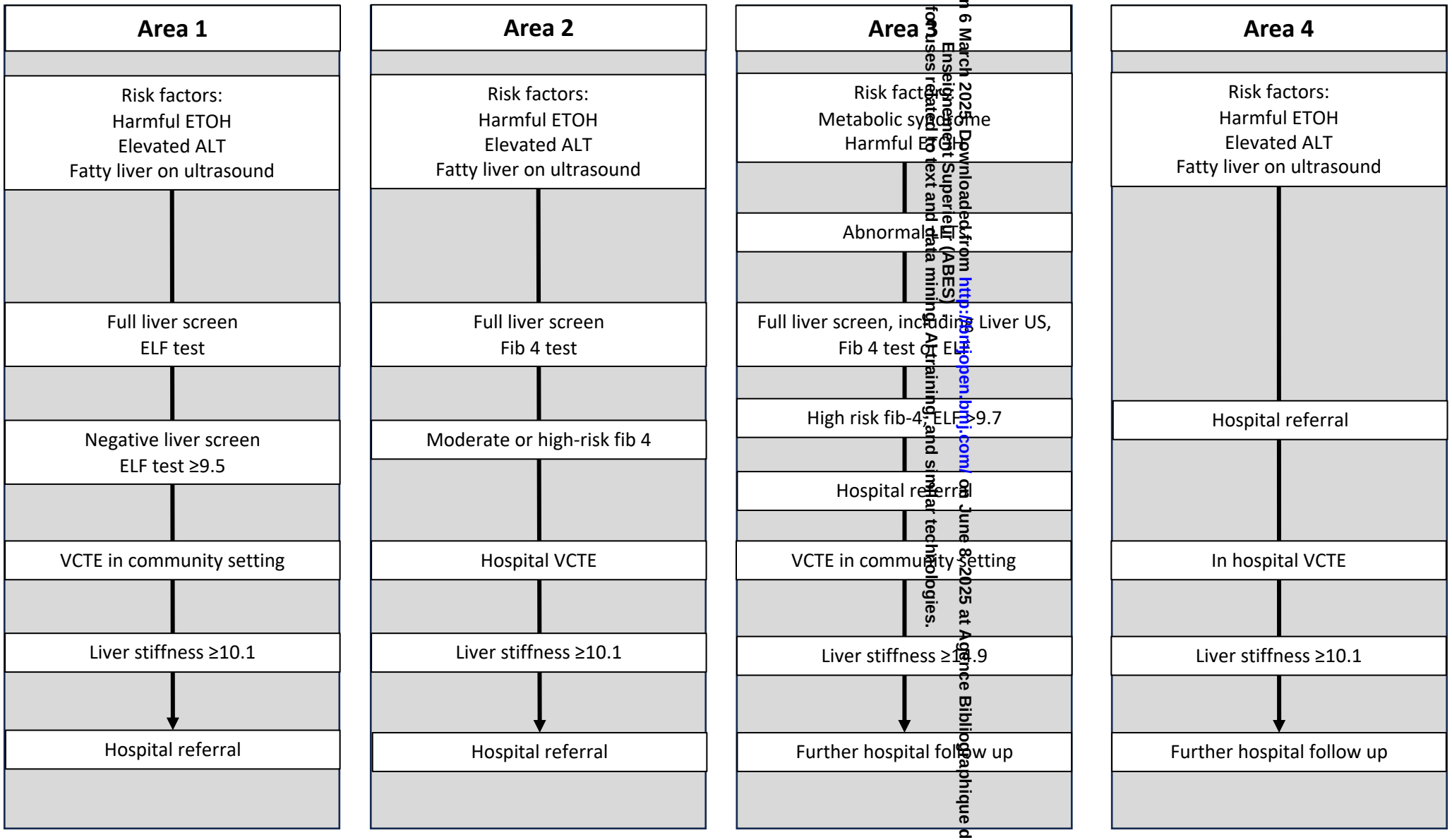

Figure 1

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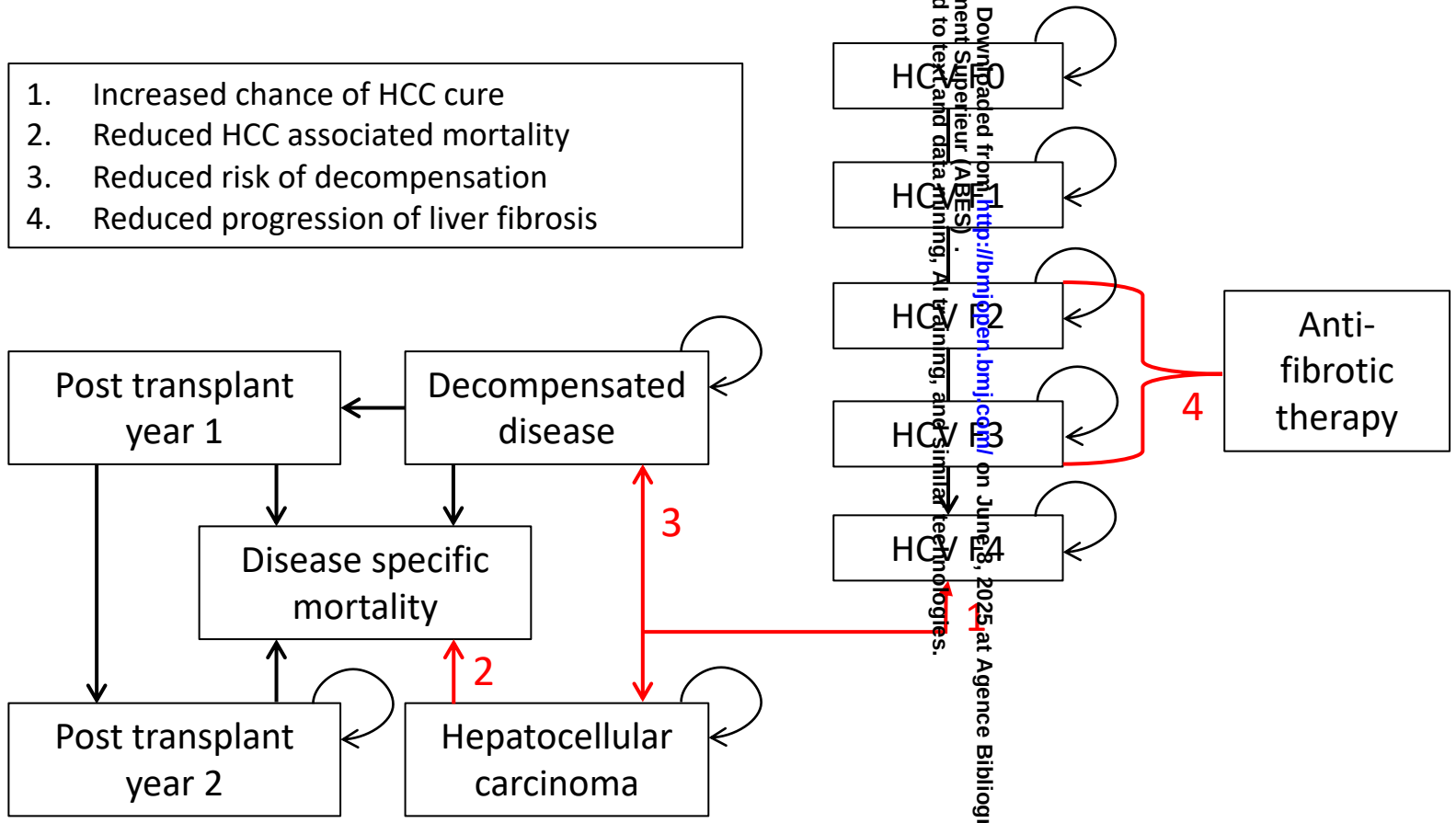

Figure 2

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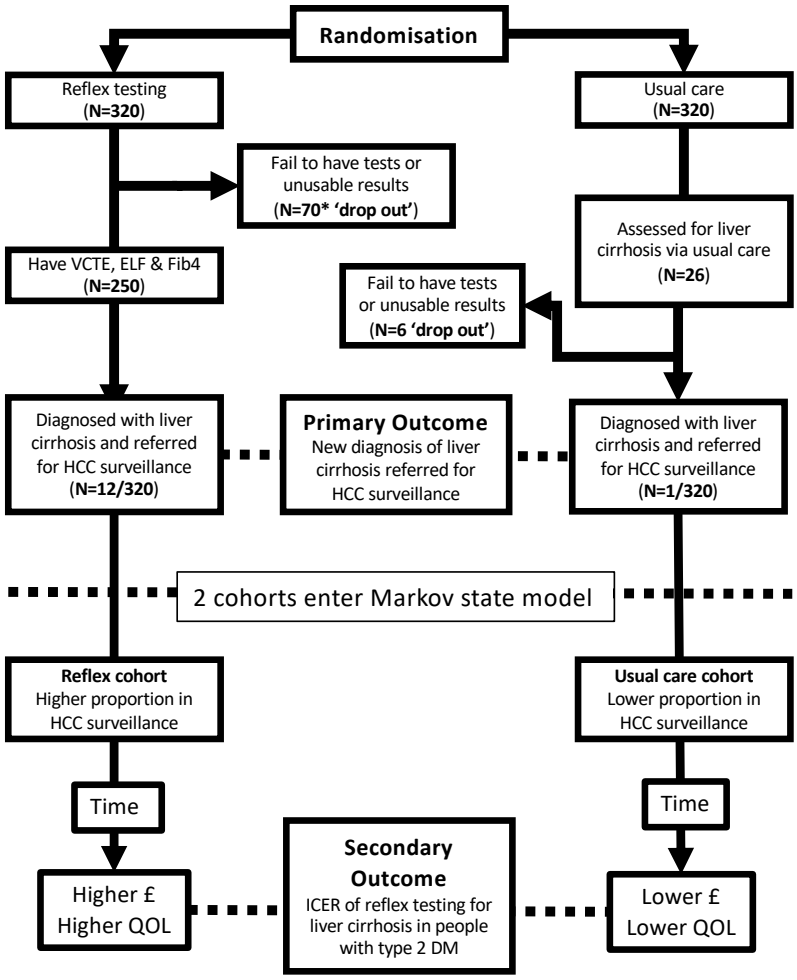

HCC – hepatocellular carcinoma, DM – diabetes mellitus, Qol – Quality of life, ICER – incremental cost effectiveness ratio, Kpa – kilopascals
*very conservative more likely to be ~34 people

Figure 3

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REFLEX Supplementary Information

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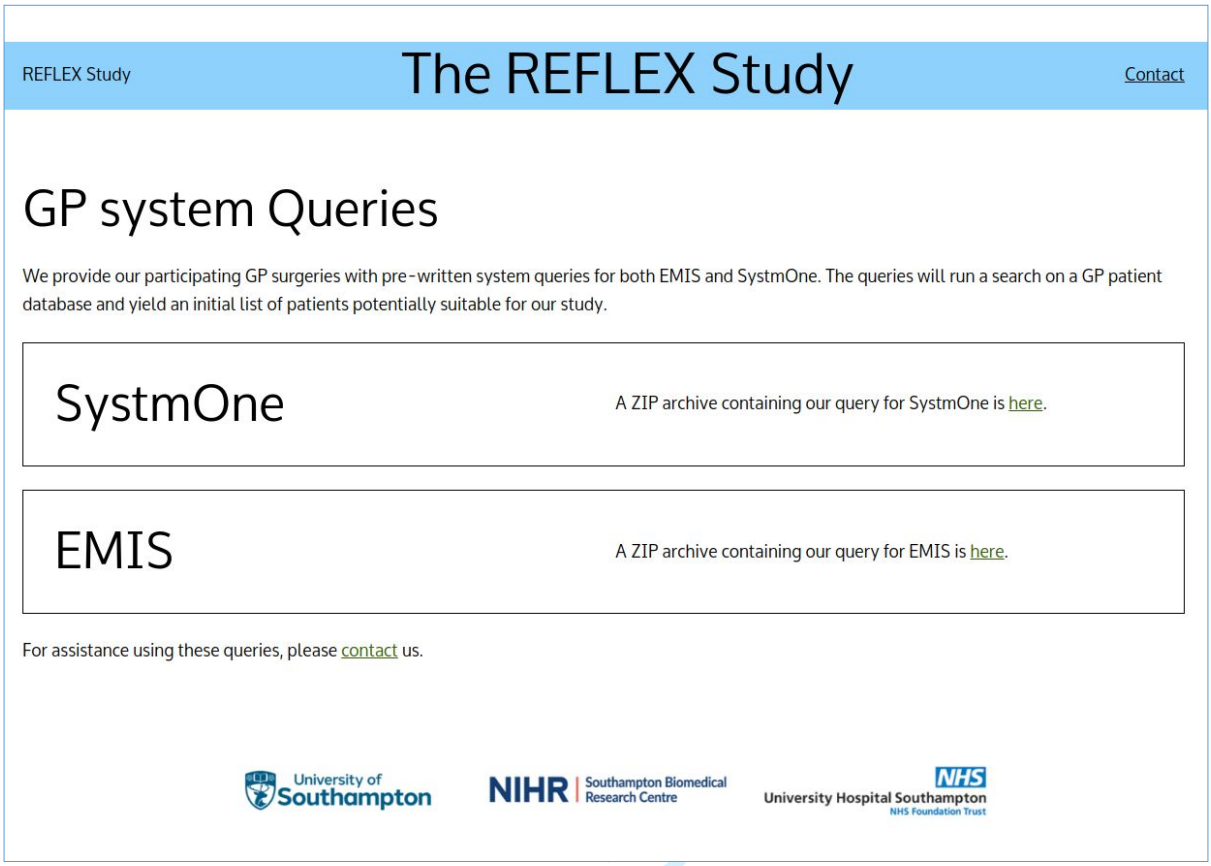
Supplementary 1 – Search Queries

https://www.reflexstudy.org/gp-system-queries/



REFLEX Study

The REFLEX Study

Contact

GP system Queries

We provide our participating GP surgeries with pre-written system queries for both EMIS and SystmOne. The queries will run a search on a GP patient database and yield an initial list of patients potentially suitable for our study.

SystmOne

A ZIP archive containing our query for SystmOne is here.

EMIS

A ZIP archive containing our query for EMIS is here.

For assistance using these queries, please contact us.

University of Southampton

NIHR | Southampton Biomedical Research Centre

NHS University Hospital Southampton NHS Foundation Trust

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Supplementary 2 – EOI

https://www.reflexstudy.org/wp-content/uploads/2023/08/eoi.pdf

Appendix 5

Expressions of interest sent by participating GP practices via (a) text or (b)email/postal letters to potential participants:

(a) Text:

Dear *<insert patient name>*

<Insert name of GP surgery> has partnered with the University of Southampton to invite patients living with type 2 diabetes to take part in a study investigating liver health. Details of the study can be found at https://www.reflexstudy.org. Alternatively, you can call the research team directly on 07751 009483 / tina.reinson1@nhs.net for further information.

(b) Postal letter/email:

Dear *<insert patient name>*

<insert name of GP surgery> has partnered with the University of Southampton to invite patients living with type 2 diabetes to take part in a study investigating liver health.

We have *enclosed/attached* details about the study.

If you would like to take part in the study or have any questions, please contact the research team directly on 07751 009483 / tina.reinson1@nhs.net.

Yours sincerely

<insert name of GP surgery>

<Enc/attached>: Patient information sheet; consent form.

14 July 2023
A1_EOI_PotentialParticipants_V2.1
IRAS project ID: 326212
ERGO ID: 80205

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Supplementary 3 – Introductory Letter

https://www.reflexstudy.org/wp-content/uploads/2023/08/intro_letter.pdf

University of Southampton

Professor Christopher Byrne
Professor of Endocrinology and Metabolism
University of Southampton
Human Development and Health Academic Unit
Faculty of Medicine
IDS, MP887
Southampton General Hospital
Tremona Road
Southampton, SO16 6YD

<insert date>

<Insert Patient name>
<Insert address>

Dear *<Insert patient name>*

Thank you for contacting the research team and requesting further information about our study that is investigating the liver health of people living with type 2 diabetes (The REFLEX Study).

Please find enclosed a patient information sheet (PIS_V3.5.1 and a consent form (ConsentForm_V3.2).

If you would like to participate or have any questions, please contact the research team on: 07751 009483 / tina.reinson1@nhs.net who will be happy to help.

Yours sincerely

Christopher Byrne
Professor of Endocrinology and Metabolism
and Chief Investigator of The REFLEX Study

Enc: Patient information Sheet
Patient Consent Form

14 July 2023
A2_EOI_IntroductoryLetter_V2.1
IRAS project ID: 326212
ERGO ID: 80205

pg. 4

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Supplementary 4 – Eligibility Questionnaire

https://www.reflexstudy.org/wp-content/uploads/2023/08/eligibility_qs.pdf

University of Southampton

Eligibility Questionnaire

Study title: Reflex testing for MAFLD in patients with type 2 diabetes

Chief Investigator: Professor Christopher Byrne **Participant Identification Number**: _____

Please ask each potential participant the following questions.

1. Do you have type 2 diabetes

Yes - go to question 2

No – go to statement 1.1

1.1 Thank the potential participant for their time and interest in the study and explain that they cannot take part because this study is looking to identify liver disease in participants living with type 2 diabetes.

2. Have you been diagnosed with liver cirrhosis?

Yes - go to statement 2.1

No – go to end statement

2.1 Thank the potential participant for their time and interest in the study and explain that they cannot take part because this study is looking to identify liver disease in participants who do **not** already have a diagnosis of advanced liver disease.

End statement

Thank you for answering our screening questions. You are eligible to take part in our study.

P0_EligibilityQuestionnaire_V2
26/3/2023

IRAS ID: 326212
ERGO ID 80205

pg. 5

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Supplementary 5 – Consent Form

https://www.reflexstudy.org/wp-content/uploads/2023/08/consent_form.pdf

University of Southampton

CONSENT FORM

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

ERGO ID: 80205 **IRAS ID:** 326212 **Chief Investigator**: Professor Christopher Byrne

Participant Identification Number*:* _____

1	I have read and understood the information sheet *<insert date /version no. of participant information sheet>* and have had the opportunity to ask questions about the study.	
2	I agree to take part in this research project and understand that I will be randomised to one of two groups. Group A or B.	
3	I consent to have a liver assessment using the FibroScan device and provide a blood sample.	
4	If randomised to Group B: (i) I understand that I will be offered my Fibroscan approximately 12 months after today (date of consent). I give permission for the research team to contact me to organise the liver assessment. (ii) I understand that the research team will need access my GP records over the next 12 months.	
5	I consent for my blood sample to be stored at the University of Southampton for the duration of this study	
5a	At the end of the study, I consent/do not consent for my left-over blood to be sent for archive storage at the Southampton Faculty of Medicine Tissue Bank (Human Tissue Authority Licence No: 12009) for use in future ethically approved health related studies.	
6	I understand that that all my details will be kept confidential, my name will not appear on any documents and I will not be directly identified in any reports of the research.	
7	I consent for the research team to access my patient records to obtain health data relevant to this study and for my data to be used for the purpose of this study .	
7a	I consent/do not consent for the research team to access my patients records to obtain health data for the next 10 years where it is relevant for research.	
8	I understand that where it is relevant to my taking part in this research, sections of my medical notes and data collected during the study may be looked at by the research team, regulatory authorities, the research sponsor or the NHS Trust. I give permission for these individuals to have access to my records.	
9	I understand that the results of my liver assessment will be overseen and monitored by clinicians at University Hospital Southampton who may need to contact me or refer me directly to liver health services that are local to me	
10	I consent for you to inform my GP of my liver assessment results.	
11	I understand my participation is voluntary and I may withdraw at any time for any reason without my participation rights, medical care or legal rights being affected.	
12	I would/would not be interested in receiving information about any future relevant liver studies (delete as appropriate). Please contact me via email/text/telephone/post (delete as appropriate) on: _____ _____	

Name of participant (print name): ..... Date: .....

Signature of participant: .....

Name of researcher (print name) ..... Date: .....

Signature of researcher .....

P1_ConsentForm_V3.2
14/07/2023
Copies to: participant; research file

IRAS ID: 326212

ERGO ID: 80205

pg. 6

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Supplementary 6 – Participant Initial Questionnaire

https://www.reflexstudy.org/wp-content/uploads/2023/08/initial_q.pdf

University of Southampton

Participant Initial Questionnaire

Study title: Reflex testing for MAFLD in patients with type 2 diabetes

Chief Investigator: Professor Christopher Byrne **Participant Identification Number**: _____

Date: _____ **Researcher:** _____

Date of Birth (day/month/year)					
Sex					
Ethnicity					
Current prescription medications					
AUDIT-C [1] [1]Bush K, Kivlahan DR, et al (1998). The AUDIT alcohol consumption questions (AUDIT-C): An effective brief screening test for problem drinking. Ambulatory Care Quality Improvement Project (ACQUIP). Arch Intern Med. 158:1789-95)					
How often do you have a drink containing alcohol?	Never	Monthly or less	2-4 times a month	2-3 times a week	4 or more times a week
How many standard drinks containing alcohol do you have on a typical day?	1 or 2	3 to 4	5 to 6	7 to 9	10 or more
How often do you have six or more drinks on one occasion?	Daily or almost daily	Weekly	Monthly	Less than monthly	Never
AUDIT-C score					
Venesection performed?	Yes / No				
Location and number of attempts					
Blood samples obtained?	Yes / No				
Refer patient elsewhere for venesection	Yes / No If yes, remember to provide patient with labels for test tubes				
Liver Assessment					
Has the patient fasted? Y/N	Date:		Probe size: XL / M		

P2_ParticipantInitialQuestionnaire_V1.1
13/7/2023

IRAS ID: 326212
ERGO ID 80205

pg. 7

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University of Southampton

VCTE reading (kPa):	IQR/MED:	CAP (Db/m^2):
Patient advised of VCTE assessment? Y/N		
Additional information		

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Supplementary 7 – PIS

https://www.reflexstudy.org/wp-content/uploads/2023/08/pis.pdf

University of Southampton

Participant Information Sheet

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

Chief Investigator: Professor Christopher Byrne

ERGO ID: 80205 **IRAS ID:** 326212

You are being invited to take part in the above research study. To help you decide whether or not you would like to take part, it is important that you understand why the research is being done and what it will involve. Please read the information below carefully and ask questions if anything is not clear or you would like more information before you make your decision. You may like to discuss it with others but it is up to you to decide whether or not to take part. If you are happy to participate you will be asked to sign a consent form.

What is the research about?

Research, including our work, has shown that 15% of people living with type 2 diabetes are at risk of long-term complications to their health, including liver problems. However, we do not know what is the right way to monitor people living with type 2 diabetes for liver problems.

The aim of our study is to test a new way of identifying liver disease in people living with type 2 diabetes to see if it better than what we are currently doing.

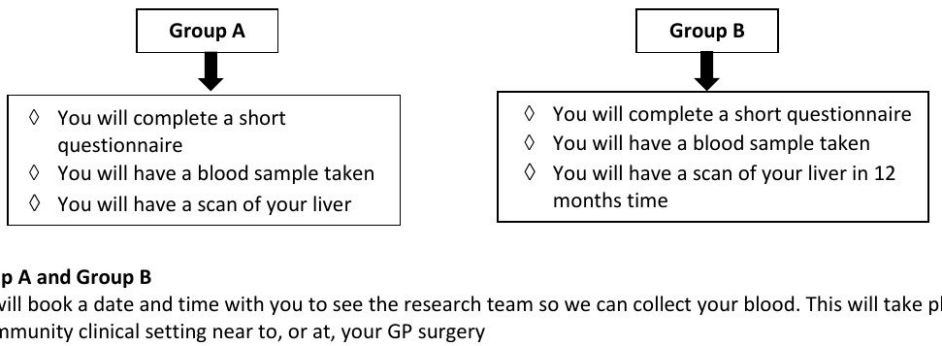
EchoSens, France, is funding this research. The University of Southampton is the study sponsor.

Why have I been asked to participate?

You have been asked to participate because you have type 2 diabetes. We are aiming to recruit 640 patients living with type 2 diabetes to the study.

What will happen to me if I take part?

You will be randomly put into one of two groups. The diagram below shows what will happen depending on which group you are put in.



Group A and Group B

We will book a date and time with you to see the research team so we can collect your blood. This will take place in a community clinical setting near to, or at, your GP surgery

Liver Scan

Group A will have their liver scanned directly following blood collection. Group B will be contacted in 12 months time to book their liver scan. The appointment will last approximately 20-30 minutes.

PIS_V3.5.1
14 July 2023

ERGO ID: 80205
IRAS Project ID: 326212

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Figure 1: Patient receiving a liver assessment using the FibroScan machine

Source: https://apexhealthtech.com/product/fibroscan/?lang=en

The FibroScan uses ultrasound technology to measure the speed at which a sound wave returns from your liver. You will need to lie down on your back and raise your right arm so that the FibroScan probe can be placed in a gap between your ribs (**Figure 1**). This scan doesn't break the skin, is painless and takes about 10 minutes.

Group B

We need to see what happens to you over the next 12 months. To do this we will need to access the results of any standard care tests you have had done within the 12 month period.

Your liver assessment results

The results of your FibroScan assessment and blood test scores will all be reviewed by the clinical team at University Hospital Southampton (UHS). Any additional tests will be organised by the clinical team at UHS who will contact you to discuss these. We will notify you of your liver assessment results and convey this information to your GP.

After your liver assessment there is no further follow up from the research team. However, if you have any questions at any time, please contact the study team on: *< insert contact details>.*

Are there any benefits in my taking part?

During the study all participants will have the opportunity to have their liver health assessed by blood tests and a scan. More broadly the information we get from the study will help us understand how best to monitor people with type 2 diabetes for complications to their health.

We would also like to offer you with a £15 voucher for taking the time to participate in our study.

Are there any risks involved?

The FibroScan assessment is a painless noninvasive procedure. Collecting blood involves using a needle stick which may hurt a bit – like a usual blood test. There is a small risk of bruising, a rare risk of infection, and you may feel lightheaded.

If you have any questions before or after your participation, then please contact the research team. See below for contact information.

What data will be collected?

The personal data we would like to collect includes: name, contact details (including email, home address, phone numbers), sex, ethnicity, NHS number, hospital number, date of birth, height, weight, alcohol consumption, and any current prescription medications you may be taking. We would also like to have access to your medical records.

Your blood sample will be sent to University Hospital Southampton for analysis. We will analyse your blood using two tests that are commonly used to assess liver health: the enhanced liver fibrosis (ELF™) test and Fibrosis-4 (FIB-4) test. We will archive your blood to use at a later date for measurement of cardio metabolic risks (e.g. cholesterol levels) and factors that are known to modify the severity of liver disease. Your blood will not be labelled with any identifiable data. For the duration of this study we will store your blood at the University of Southampton in -80'C freezers on Level A, in the Institute of Developmental Sciences (IDS) building.

On all the materials we collect from you we will put a unique number. This number will be used, instead of your name, to identify any data relating to you. Your data will be entered in to a password protected study database by

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a member of the research team. The study database will be stored on a secure server at the University of Southampton. There will be no identifying information stored with the research data we collect, this will be stored on a separate database and only the study principal investigator, or nominated representative, will have the key to unlocking and identifying patients.

Future research
At the end of the study, your blood will be sent for archive storage at the Southampton Faculty of Medicine Tissue Bank (Human Tissue Authority Licence No: 12009) for use in future ethically approved health related studies. Only non-identifiable samples will be shared with other researchers for future use.

As part of this study we want to better understand the progression of liver disease, so that the time span between liver assessments is optimal. However, liver disease develops slowly over many years, therefore we would like to remotely track any relevant changes to your health and continue to build our database of valuable liver disease information. We will therefore link your unique number onto an anonymised dataset and obtain any relevant information from NHS digital over the next 10 years regarding changes to your health. To do this we will need to share your name, date of birth and NHS number with NHS digital.

If you consent to be contacted for future studies, then we will keep your contact details separate from the study database and store them on the secure server at the University of Southampton.

Will my participation be confidential?
Your participation and the information we collect about you during the course of the research will be kept strictly confidential. Only the research team will have access to the research data. The study will be overseen and monitored by the University of Southampton, where the study Chief Investigator Christopher Byrne is Professor of Endocrinology & Metabolism.

Only members of the research team and responsible members of the University of Southampton may be given access to data about you for monitoring purposes and/or to carry out an audit of the study to ensure that the research is complying with applicable regulations. Individuals from regulatory authorities (people who check that we are carrying out the study correctly) may require access to your data. All of these people have a duty to keep your information, as a research participant, strictly confidential.

Do I have to take part?
No, it is entirely up to you to decide whether or not to take part. If you decide you want to take part, you will need to sign a consent form *<insert date and version number>* to show you have agreed to take part.

What happens if I change my mind?
You have the right to change your mind and withdraw at any time without giving a reason and without your participant rights or routine care being affected.

If you wish to withdraw from the study, please contact the research team *<insert contact details>.*

If you withdraw from the study, we will keep the information about you that we have already obtained for the purposes of achieving the objectives of the study only.

What will happen to the results of the research?
Your personal details will remain strictly confidential. Research findings made available in any reports or publications will not include information that can directly identify you without your specific consent.

The results of this study will be published. All participant details will remain strictly confidential and no patient identifiable information will be used.

Where can I get more information?
You can contact the research team on *<insert research team contact details>.*

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The British Liver Trust and Diabetes UK have plenty of useful information. You can speak directly to a liver nurse on: 0800 652 7330 or go to their website: www.britishlivertrust.org.uk. Contact details for Diabetes UK: 0345 123 2399 / www.diabetes.co.uk

What happens if there is a problem?

If you have a concern about any aspect of this study, you should speak to the researchers who will do their best to answer your questions.

If you remain unhappy or have a complaint about any aspect of this study, please contact the University of Southampton Research Integrity and Governance Manager (023 8059 5058, rgoinfo@soton.ac.uk).

Data Protection Privacy Notice

The University of Southampton conducts research to the highest standards of research integrity. As a publicly-funded organisation, the University has to ensure that it is in the public interest when we use personally-identifiable information about people who have agreed to take part in research. This means that when you agree to take part in a research study, we will use information about you in the ways needed, and for the purposes specified, to conduct and complete the research project. Under data protection law, 'Personal data' means any information that relates to and is capable of identifying a living individual. The University's data protection policy governing the use of personal data by the University can be found on its website (https://www.southampton.ac.uk/legalservices/what-we-do/data-protection-and-foi.page).

This Participant Information Sheet tells you what data will be collected for this project and whether this includes any personal data. Please ask the research team if you have any questions or are unclear what data is being collected about you.

Our privacy notice for research participants provides more information on how the University of Southampton collects and uses your personal data when you take part in one of our research projects and can be found at http://www.southampton.ac.uk/assets/sharepoint/intranet/ls/Public/Research%20and%20Integrity%20Privacy%20Notice/Privacy%20Notice%20for%20Research%20Participants.pdf

Any personal data we collect in this study will be used only for the purposes of carrying out our research and will be handled according to the University's policies in line with data protection law. If any personal data is used from which you can be identified directly, it will not be disclosed to anyone else without your consent unless the University of Southampton is required by law to disclose it.

Data protection law requires us to have a valid legal reason ('lawful basis') to process and use your Personal data. The lawful basis for processing personal information in this research study is for the performance of a task carried out in the public interest. Personal data collected for research will not be used for any other purpose.

For the purposes of data protection law, the University of Southampton is the 'Data Controller' for this study, which means that we are responsible for looking after your information and using it properly. The University of Southampton will keep identifiable information about you for 10 years after the study has finished after which time any link between you and your information will be removed.

To safeguard your rights, we will use the minimum personal data necessary to achieve our research study objectives. Your data protection rights – such as to access, change, or transfer such information - may be limited, however, in order for the research output to be reliable and accurate. The University will not do anything with your personal data that you would not reasonably expect.

If you have any questions about how your personal data is used, or wish to exercise any of your rights, please consult the University's data protection webpage (https://www.southampton.ac.uk/legalservices/what-we-do/data-protection-and-foi.page) where you can make a request using our online form. If you need further assistance, please contact the University's Data Protection Officer (data.protection@soton.ac.uk).

Thank you for taking the time to read this information sheet and considering taking part in the research.

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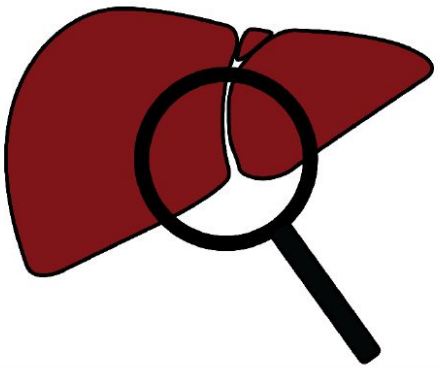
Supplementary 8 – Poster

https://www.reflexstudy.org/wp-content/uploads/2023/08/poster.pdf

Participants needed

REFLEX is a study investigating liver health in people living with type 2 diabetes



Who do we need?

People living with type 2 diabetes, 18 years +

What's involved?

A single 20-30 appointment where we will collect a blood sample and assess the health of your liver with a machine that uses ultrasound based technology.

Contact for more information

CONTACT REFLEX

07751 009483

Tina.reinson1@nhs.net

REFLEX STUDY

ERGO II ID: 80205
IRAS ID: 326212
Poster_V2.2_14/07/2023

University of Southampton

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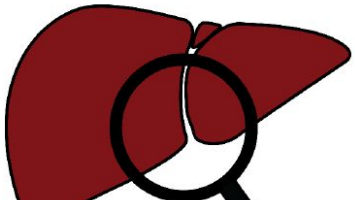
Supplementary 9 – Summary PIS

https://www.reflexstudy.org/wp-content/uploads/2023/08/summary_pis.pdf

Participants needed

REFLEX is a study investigating liver health in people living with type 2 diabetes



Who do we need?

People living with type 2 diabetes, 18 years +

Research, including our work, has shown that 15% of people living with type 2 diabetes are at risk of long-term complication to their health, including liver problems. However, we do not know what is the right way to monitor people living with type 2 diabetes for liver problems.

What will happen to me if I take part?

You will be randomly put into one of two groups. Both groups will complete a short questionnaire and have a blood sample taken. Group A will have a scan of their liver straight away, Group B will have a scan of their liver in 12 months time. The appointments will take place in a community clinical setting near to, or at, your GP surgery. The appointment will between 20 and 30 minutes.

Figure 1: Patient receiving a liver assessment using the FibroScan machine

Source: https://apexhealthtech.com/product/fibroscan/?lang=en

The FibroScan uses ultrasound technology to measure the speed at which a sound wave returns from your liver. You will need to lie down on your back and raise your right arm so that the FibroScan probe can be placed in a gap between your ribs (**Figure 1**). This procedure is non-invasive, painless and takes about 10 minutes.

Are there any benefits in my taking part?

During the study all participants will have the opportunity to have their liver health assessed by blood tests and a scan. More broadly the information we get from the study will help us understand how best to monitor people with type 2 diabetes for complications to their health.

Are there any risks involved?

The FibroScan assessment is a painless noninvasive procedure. Collecting blood involves using a needle stick which may hurt a bit – like a usual blood test. There is a small risk of bruising, a rare risk of infection, and you may feel lightheaded.

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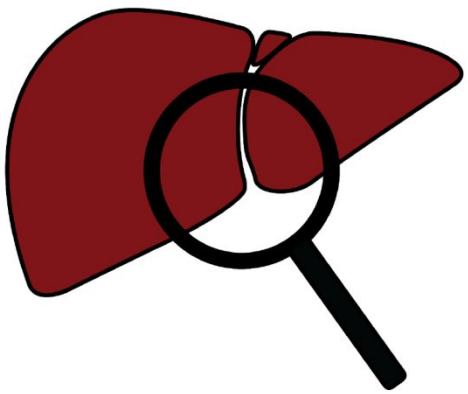
Supplementary 10 – TV Feed

https://www.reflexstudy.org/wp-content/uploads/2023/08/TV_feed.pdf

We have partnered with the University of Southampton on The REFLEX Study that is investigating the liver health of people living with type 2 diabetes

University of Southampton

REFLEX_PowerPointPresentionV2.2
13 July 2023; ERGO ID 80205; IRAS ID 326212



We do not know the most effective way to assess patients for complications of type 2 diabetes

REFLEX_PowerPointPresentionV2.2

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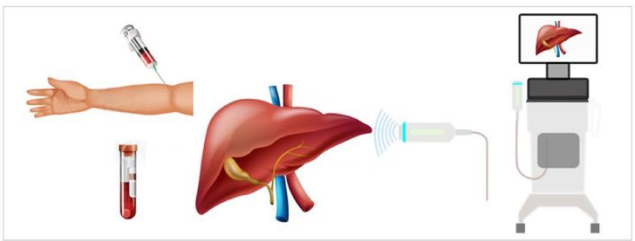
If you are living with type 2 diabetes and over the age of 18 years you may be eligible to take part in our study

University of Southampton

REFLEX_PowerPointPresentionV2.2

Our study involves one single 20-30 minute appointment
In this time we will:

- Collect a blood sample
- Assess the health of your liver with a machine that uses ultrasound technology



Source: https://www.internationaldrugmart.com/blog/liver-function-test/

REFLEX_PowerPointPresentionV2.2

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If you would like further information about The REFLEX Study please contact the research team on:

07751 009483

Tina.reinson1@nhs.net

Or visit the study website:

REFLEXstudy.org

University of Southampton

REFLEX_PowerPointPresentionV2.2

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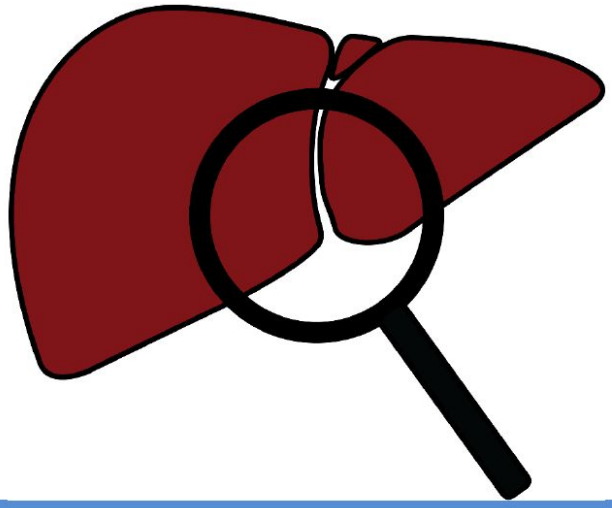
Supplementary 11 – GP Website

https://www.reflexstudy.org/wp-content/uploads/2023/08/gp_website.pdf

We have partnered with the University of Southampton on a study investigating liver disease in people living with type 2 diabetes – The REFLEX study



What's involved?

A single 20-30 minute appointment where we will collect a blood sample and assess the health of your liver with a machine that uses ultrasound based technology.

Contact for more information

REFLEX STUDY

Further information can be found at:

https://www.reflexstudy.org

07751 009483

tina.reinson1@nhs.net

CONTACT REFLEX

REFLEX_PracticeWebsite_V3.2
14/07/2023
ERGO ID: 80205
IRAS Project ID: 326212

University of Southampton

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Supplementary 12 – Flyer

https://www.reflexstudy.org/wp-content/uploads/2023/08/Appendix_3_SummaryPIS_V2.4_double_page.pdf

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Participants needed

REFLEX is a study investigating liver health in people living with type 2 diabetes

Who do we need?

People living with type 2 diabetes, 18 years +

What's involved?

A single 20-30 minute appointment where we will collect a blood sample and assess the health of your liver with a machine that uses ultrasound based technology.

ERGO II ID: 80205
IRAS ID: 326212
Summary_PIS_V2.4, 13/07/2023

University of Southampton

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

What is the research about?
Research, including our work, has shown that 15% of people living with type 2 diabetes are at risk of long-term complication to their health, including liver problems. However, we do not know what is the right way to monitor people living with type 2 diabetes for liver problems.

What will happen to me if I take part?
You will be randomly put into one of two groups. Both groups will complete a short questionnaire and have a blood sample taken. Group A will have a scan of their liver straight away, Group B will have a scan of their liver in 12 months time. The appointments will take place in a community clinical setting near to, or at, your GP surgery. The appointment will between 20 and 30 minutes.

Figure 1: Patient receiving a liver assessment using the FibroScan machine

The FibroScan uses ultrasound technology to measure the speed at which a sound wave returns from your liver. You will need to lie down on your back and raise your right arm so that the FibroScan probe can be placed in a gap between your ribs (**Figure 1**). This procedure is non-invasive, painless and takes about 10 minutes.

Source: https://openhealthtech.com/product/fibroscan/?lang=en

Are there any benefits in my taking part?
During the study all participants will have the opportunity to have their liver health assessed by blood tests and a scan. More broadly the information we get from the study will help us understand how best to monitor people with type 2 diabetes for complications to their health.

Are there any risks involved?
The FibroScan assessment is a painless noninvasive procedure. Collecting blood involves using a needle stick which may hurt a bit – like a usual blood test. There is a small risk of bruising, a rare risk of infection, and you may feel lightheaded.

Further information can be found at: https://www.reflexstudy.org/ or call Tina Reinson on : 07751 009483; email: tina.reinson1@nhs.net.

REFLEX STUDY

Participants needed

REFLEX is a study investigating liver health in people living with type 2 diabetes

Who do we need?

People living with type 2 diabetes, 18 years +

What's involved?

A single 20-30 minute appointment where we will collect a blood sample and assess the health of your liver with a machine that uses ultrasound based technology.

ERGO II ID: 80205
IRAS ID: 326212
Summary_PIS_V2.4, 13/07/2023

University of Southampton

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

What is the research about?
Research, including our work, has shown that 15% of people living with type 2 diabetes are at risk of long-term complication to their health, including liver problems. However, we do not know what is the right way to monitor people living with type 2 diabetes for liver problems.

What will happen to me if I take part?
You will be randomly put into one of two groups. Both groups will complete a short questionnaire and have a blood sample taken. Group A will have a scan of their liver straight away, Group B will have a scan of their liver in 12 months time. The appointments will take place in a community clinical setting near to, or at, your GP surgery. The appointment will between 20 and 30 minutes.

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REFLEX STUDY

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Supplementary 13 – Patient Letter

https://www.reflexstudy.org/wp-content/uploads/2023/08/patient_letter.pdf

<Insert UHS logo>

University of Southampton

<insert name of clinician>
<Address>
Southampton, SO16 6YD
<email>

<insert date>

<Insert GP name>
<Insert GP address>

Dear Dr <insert GP name>

Reference patient: <insert patient name; NHS number and date of birth>

The above patient took part in the REFLEX testing for metabolic associated fatty liver disease (MAFLD) in patients with type 2 diabetes study on <insert date>.

<Insert patient name> agreed that we may inform you of their liver assessment finding:

FibroScan result: <insert liver stiffness and steatosis readings, and IQR/MED>

Table 1: Interpretation of FibroScan results

Liver stiffness reading interpretation[1]			CAP (controlled attenuation parameter) score interpretation[2]		
Fibroscan reading	Fibrosis stage[a]	Interpretation	CAP score	Steatosis stage	Accumulated fat in the liver
<6.0 kPa	F0	No scarring	<250 dB/m²	S0	<11%
≥6.0 kPa to 8.1 kPa	F1	Mild fibrosis	>250 dB/m² and <301 dB/m²	S1	11% and 33%
≥8.2 kPa to 9.6 kPa	F2	Moderate fibrosis	>301 dB/m² and <325 dB/m²	S2	34% and 66%
≥9.7 kPa to 13.5 kPa	F3	Severe fibrosis	>325 dB/m²	S3	>66%
≥13.6 kPa	F4	Advanced fibrosis or cirrhosis			

[a]Liver biopsy validated fibrosis stages; [1]Eddowes PJ, Sasso M, Allison M, et al. Accuracy of FibroScan Controlled Attenuation Parameter and Liver Stiffness Measurement in Assessing Steatosis and Fibrosis in Patients With Nonalcoholic Fatty Liver Disease. Gastroenterology. 2019 May;156(6):1717-1730. doi: 10.1053/j.gastro.2019.01.042; [2]PLoS One. 2014 Jun 5;9(6):e98689. doi: 10.1371/journal.pone.0098689. eCollection 2014.

Diagnosis: <insert diagnosis and interpretation>
Action: Please <insert any relevant clinical notes as advised by study clinicians at the time of assessment>

At the time of the VCTE assessment <insert patient name> was advised of <his/her/their> VCTE result.

Patient follow up has now finished.

If you have any queries, please contact the study team on: <insert telephone number and email address>

With kind regards

<Insert clinician name and position>

Cc: ***<insert patient name>***

26 March 2023
B1_PatientLetter_V2
IRAS project ID: 326212
ERGO ID: 80205

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BMJ Open

Screening to identify people with type 2 diabetes at risk of liver cancer in primary care - a randomised controlled trial PROTOCOL

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Screening to identify people with type 2 diabetes at risk of liver cancer in primary care - a randomised controlled trial PROTOCOL

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Abstract

Introduction

Hepatocellular carcinoma [HCC] is expected to become the 3rd most common cause of cancer death world-wide by 2030. The increase in HCC is in large part due to the rising prevalence of risk factors such as type 2 diabetes [T2DM]. Up to 1 in 20 people living with T2DM have liver cirrhosis and they have a 1-2% incidence of HCC per year.

Patients with cirrhosis enter surveillance for HCC to identify early-stage, curable tumours. A diagnosis of T2DM does not mandate testing to identify patients with cirrhosis with testing restricted to those with additional risks. There has never been a trial and nested cost-effectiveness evaluation comparing screening all patients with T2DM for cirrhosis against usual care.

Aim

Determine the effectiveness and cost-effectiveness of screening all adults with T2DM to identify those at high risk of HCC.

Methods and analysis

A multi-site, unblinded individual randomised controlled trial comparing screening for liver cirrhosis in people with T2DM against usual care - where additional risk factors are needed to qualify for screening. Our recruitment strategy has been supported by patient and public involvement [PPI]. Participants will be identified via an automated search of primary care records and invited to participate via text.

320 participants will be randomised to screening. Screening will include measurement of bio-markers [ELF™ and Fib-4] and vibration controlled transient elastography. Another 320 participants will be randomised to usual care.

Primary outcome is the proportion of participants in each arm who are referred into HCC surveillance over 12months by specialist services. The results will be used to calculate the incremental cost-effectiveness ratio of screening via a Markov model.

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Ethics and dissemination

The results of this study will be presented directly to NHS England. Additional dissemination via conference proceedings and publication will be supported by our PPI team. The study has full ethical approval – IRAS N° 326212, REC reference 23/WS/0102.

Trial registration: ISRCTN17017677

Article summary

Strengths and limitations of this study

- First comparison via an RCT between risk factor-based testing for liver disease in people with T2DM [usual care in the United Kingdom] and screening offered to all adults with T2DM.
- Provides definitive cost-effectiveness of both approaches and impact on liver cancer diagnosis and survival in a real-world setting.
- Will delineate relative cost-effectiveness of different non-invasive tests to identify significant liver disease in people with T2DM.
- Trial limited to United Kingdom so usual care may not be internationally representative.
- Short study time-horizon therefore observation of clinical outcomes subject of modelling rather than real-world observation.

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Introduction

Cancer is the leading cause of mortality in patients with type 2 diabetes mellitus [T2DM][1] and T2DM is strongly associated with site-specific cancers including hepatocellular carcinoma [HCC].[2] 830,200 people died from HCC in 2020 and the incidence of HCC is expected to increase by 55% in the next 20 years.[3] HCC is now the fastest growing indication for liver transplantation[4] and it is expected to become the 3rd most common cause of cancer death worldwide by 2030.[5] HCC has a very poor prognosis with a 5-year survival of ~20%.[6] However, if cases are identified at an early stage curative treatments are available which include surgical resection, liver transplant or tumour ablation.[6]

A major risk factor for increasing deaths from HCC is the increasing global prevalence of T2DM.[3,5,7] T2DM causes liver steatosis, inflammation, fibrosis and liver cirrhosis and patients with significant liver fibrosis or cirrhosis are at risk of HCC.[8,9] There is a high prevalence of all stages of liver disease in people living with T2DM.[10–14].

International guidance recommends biannual surveillance for HCC in patients with liver cirrhosis via ultrasound imaging however, less than one third of incident cases of HCC in patients with T2DM are identified via surveillance.[15] Identification of HCC via surveillance is important as cancers that are identified in patients who are undergoing regular surveillance have better outcomes.[16] To engage patients with T2DM with HCC surveillance it is necessary to first identify patients with cirrhosis. In the past liver disease was hard to identify because it progresses without signs or symptoms. However, several approaches have now been validated in patients with T2DM to identify asymptomatic disease. These include utilization of blood tests such as the Fibrosis-4 test [FIB-4][17] and the Enhanced Liver Fibrosis [ELF™] test [18], as well as a simple scan of the liver which uses vibration controlled transient elastography [VCTE] to assess the liver stiffness[17,19–21] as a validated marker of fibrosis.

In addition to HCC surveillance early-diagnosis of liver disease can facilitate positive interventions aimed at improving patient outcomes. These include optimisation of blood glucose control in people with T2DM, dietary modification and treatments to facilitate weight loss, moderation, or complete abstinence from alcohol [a co-factor in liver disease progression for these patients[22]] and potentially pharmacotherapy that reduces fibrogenesis. With respect to the latter, on 14th March 2024, Resmetirom[23] was given conditional approval by the US Food and Drug Administration [FDA] for the

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treatment of adults with noncirrhotic non-alcoholic steatohepatitis [NASH] with moderate to advanced liver scarring [fibrosis] alongside diet and exercise. Furthermore, selected patients could be prescribed beta blocker therapy to reduce mortality from bleeding oesophageal varices and to reduce risk of liver decompensation.[24]

In addition to being recommended in the USA[25,26], screening for liver disease in patients with T2DM and obesity has recently been adopted as a national pilot in England that has been funded by the National Health Service England [NHSE] cancer service.[27] The national pilot uses a primary care based search algorithm for T2DM as well as other risk factors for liver disease [such as hazardous alcohol consumption] and then invites patients into a cascade of non-invasive tests for fibrosis.

Whilst patients with T2DM are known to have an increased risk of fibrosis and cirrhosis[28] there is a lack of empirical evidence supporting implementation of this NHSE programme. Just three studies have tested a diagnostic pathway for liver disease against a contemporaneous control[29–31] and just one specifically focussed on liver disease in patients with T2DM.[30]

The NHSE pilot is different from the current national [NICE] guidelines in the UK which recommends testing for liver disease is restricted to patients with risk factors for liver cirrhosis including a fatty liver on ultrasound imaging, abnormal liver enzyme levels and potentially harmful levels of alcohol consumption.[32] T2DM alone is not a risk factor that currently mandates assessment. The reason for these narrow criteria is a lack of cost-effectiveness data supporting wider eligibility for testing.[33]

The NICE NAFLD guideline [ng49] was published in 2016[32] and since its publication researchers have modelled the cost-effectiveness of testing for liver disease in patients with T2DM[34–36]. Published models have compared testing strategies that include novel biomarkers and VCTE against standard care where standard care includes history, physical examination, liver 'function' tests [LFTs] and an ultrasound scan. The sensitivity and specificity of each approach is pre-defined and parameterises models that calculate the health gain for patients correctly categorised with liver disease and offsets this against the cost of the different testing approaches by calculating an incremental cost-effectiveness ratio [ICER].[34,36] Most recently, Forlano et al. modelled the ICER for screening in patients with T2DM. The model was parameterised using cross-sectional data from a cohort of patients with T2DM living in London [UK] that were all tested for liver cirrhosis using with FIB-4, ELF™, VCTE and in 19/249 cases,

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liver biopsy. The costs and outcomes associated with testing this cohort were compared to a usual care [primary care diagnosis] that was less accurate. In the base case analysis the ICER was well below NICE cost-effectiveness thresholds with the additional costs of testing being offset by the gain from an accurate early diagnosis.

However, there are challenges with extrapolating prior models to a real-world intervention such as the NHSE pilot that aims to test a broader range of adults with T2DM for liver disease as part of routine care. Firstly, we don't know which patients respond to an invitation from primary care for liver assessment. For example, it is likely that patient age and comorbidities will influence their probability of having liver disease and their personal gain from an early diagnosis. Secondly, we don't know what proportion of this cohort meet clinical criteria for interventions that convey the advantage of early diagnosis, e.g. what proportion enter an HCC surveillance pathway and what proportion have CSPH and are started on beta blockers. Thirdly, we don't know the real-world performance of standard care in the UK. Most patients with T2DM do not get tested for liver disease, despite their heightened risk because they are not assessed for the additional risk factors that are needed to qualify for testing. For example, LFTs are not part of an annual diabetes check up in the UK and may or may not be measured when patients are considered for statin treatment; liver ultrasound is not a routine test, and alcohol consumption is not accurately or consistently assessed in primary care. Finally, previous economic evaluations are outdated as they use primary care-based assessments [e.g. history and examination] that do not incorporate tests for fibrosis [e.g. Fib-4 and VCTE]. Since the NICE NAFLD Guideline in 2016, tests for liver fibrosis are widely integrated into community diagnostic pathways for liver disease and therefore in future studies models of 'usual care' need to reflect this.

This study protocol describes a randomised controlled trial with a nested cost-effectiveness evaluation. The study aims to compare the number of participants referred for HCC surveillance between an intervention where patients with T2DM are universally offered screening for liver disease against usual care.

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Method and analysis

The trial is described in accordance with the SPIRIT checklist.[37] The design will be an unblinded randomised controlled trial with a nested cost-effectiveness evaluation comparing the offer of screening [i.e. offering testing to all patients with T2DM] for liver disease against standard care. We will proceed straight to an effectiveness evaluation rather than conducting a formal feasibility/pilot study. We justify this approach because the components of the intervention [used in testing for liver disease in patients with standard risk factors [e.g. abnormal blood results or harmful alcohol consumption]] are widely implemented. Additionally, data such as the attrition rate from the conventional diagnostic pathway is already known [see sample size section].[38] Undertaking a randomised controlled trial in this setting is very important as this provides the opportunity to have a contemporaneous usual care arm.

Primary outcome

i) The number of participants referred to secondary care with suspected liver disease within 12 months of randomisation who are subsequently referred for HCC surveillance.

As an unblinded trial it is important our primary outcome is as objective as possible and independent of the research team. In both study arms patients with high liver stiffness measurements will be referred to nearby hepatology services [with thresholds defined by local practice]. Via usual care an independent local clinician will then assess the severity of liver disease. In real-world practice this may include history, examination, no further tests or repeat VCTE, additional tests for fibrosis and in some case liver biopsy. Regardless of the clinical approach taken the primary outcome will be whether the clinician felt the disease was severe enough to warrant referral for HCC surveillance. Since the trial sites cover a variety of different regions across the south of England, this pragmatic approach is likely to closely reflect current UK practice.

Secondary outcomes

1. The test or combination of tests for liver cirrhosis with the lowest cost per case diagnosed*
2. The sub-group with the lowest cost per case diagnosed*
3. The incremental cost effectiveness ratio [ICER] of screening for liver cirrhosis in people with T2DM

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4. The number of cancer deaths avoided by screening [as per Markov modelling]
5. The number of patients diagnosed on VCTE with ≥F2 disease [defined as a liver stiffness of ≥8.2kpa][21]

*see i] for definition of a 'case'

Participants

Inclusion criteria

Any adult [≥18 years] patient with a known diagnosis of T2DM according to the primary care record in the Hampshire, Wiltshire, Dorset, and the Isle of Wight [all UK] areas will potentially be eligible to participate. Non-English speaking patients will be eligible for inclusion.

Exclusion criteria

- <18 years of age
- Evaluated for liver disease with either an ELF™ test or VCTE in the 2 years prior to the date of consent.
- A known prior clinical diagnosis of significant liver disease* due to any cause
- A known diagnosis of autoimmune hepatitis, primary biliary cholangitis, primary sclerosing cholangitis or viral hepatitis [irrespective of whether this has progressed to fibrosis or cirrhosis]

*Significant fibrosis or cirrhosis and in active hospital follow up

Setting

The study will be conducted in 16-20 Primary care practices and diabetes community care hubs in Wessex [including Hampshire, Wiltshire, the Isle of Wight and Dorset [UK]]. The setting of the study is important as it includes a range of existing community liver pathways which means the intervention is compared to a diverse representation of standard care – which are representative of diverse interpretations of the current NICE guidelines.[32]

Community hubs will be used for research data collection including VCTE and blood sampling. Primary care centres will be identified via the local Primary Care Network and the Primary Care NIHR clinical

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research network [CRN]. The number of practices we are using is justified in the later dedicated sections of the form.

Participant identification

Practices will identify potential participants from their patient records. The research team will provide these practices with a search query to run on their patient management systems [SystmOne or EMIS] [see supplementary material and trial website [reflexstudy.org]] Flagged patients will be screened for eligibility by practice staff. The patients on the list of potential participants will be sent a text 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 [see supplementary material].

Consent & Randomisation

If a participant contacts the research team they are sent an information sheet and given time to consider participation before providing written consent with the research team [see supplementary material]. After giving consent each participant will be randomised. 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 Biomedical research centre [BRC] team using randomisation software.[39]

Arm 1 – Screening

Participants in this arm will be referred by the research team directly for liver fibrosis assessment at a community hub. This assessment will include VCTE and venepuncture for an ELF™ test and a FIB-4 index. The result of the VCTE and any abnormalities identified in the blood tests will be managed in accordance with the local liver disease care pathway [as per the usual care arm described below]. VCTE will be performed by an experienced single operator after a minimum of a 3 hour fast and previously published criteria for a valid reading will be applied to each participant.[40]

Arm 2 – Standard care – NICE guidelines based – T2DM + additional risk factor testing

Participants in the standard care arm will not be contacted for VCTE. Usual care varies across the study area but is based on 2016 NICE guidance [**Figure 1**]. In the 2016 NICE NAFLD guideline, the presence of T2DM does not trigger an assessment for liver disease in the absence of other specific risk factors.[32]

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'Risk factors' to enter standard care vary in the study areas but broadly include: harmful alcohol consumption, an elevated ALT and a fatty liver on ultrasound examination. If risk factor thresholds are met then the usual care pathway varies further but in all areas involves VCTE with or without a biomarker for liver fibrosis [e.g. FIB-4 or ELF™] **[Figure 1]**. The variation in standard care is very important as it increases the external validity of our study by being representative of the heterogeneity across the UK.

After discussion with our PPI groups, participants included in the standard care arm will be given the opportunity to undergo VCTE and a biomarker test to assess them for liver fibrosis >12 months following randomisation [arranged at mutual convenience with the research team].

Data collection

Baseline data collection

All participants will give consent for access to their primary care records. These alongside a brief questionnaire will provide participant baseline data including demographics, medication and co-morbidities that cover the Charlson index[41] [giving an overall score for co-morbidity] and other prevalent co-morbidities in the study population **[Table 1]**.[42] Participants are not asked to complete further data collection activities as we want to minimise potential Hawthorne effect in our control group – we are concerned prolonged exposure to the research team may lead usual care participants to change behaviour and either seek or perhaps decline liver assessment.[43]

Primary Outcome data collection

The primary outcome - referral to HCC surveillance following a referral with suspected liver disease from primary care will be assessed by the research team from each participant's health care records. Participants will not need to be recontacted for outcome data. For usual care participants the GP care record will be reviewed for a referral letter to secondary care or a community liver assessment service that was sent within 12months of randomisation. For both trial arms records will be reviewed for evidence [e.g. a letter from hepatology services] that the patient has been enrolled in HCC surveillance. The GP record review will take place up to 36 months from randomisation to ensure enough time has elapsed for the patients to have been assessed by secondary care.

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Cost data collection

We will collect micro-costs[44] on the following components of the pathway:

- Item costs for ELF™ & FIB-4 tests and venepuncture cost
- Nursing time for: venepuncture, VCTE, results delivery and onward referral
- Cost per VCTE assessment including equipment, equipment servicing and training
- Community venue hire for liver assessment

Data management plan

Participant data will be managed according to the study data management plan which is available on the study website [reflexstudy.org]. Study data including participant identifiable data will be stored securely in accordance with ethical approvals.

Data analysis

Primary outcome

We will conduct an 'intention to diagnose' analysis for the primary outcome where all participants undergoing randomisation will be analysed within the group to which they were assigned, regardless of whether they engaged with the diagnostic process following referral within their study arm. Logistic regression will be used to compare the binary outcome between the standard care and intervention arms. Exact or penalized likelihood estimation methods will be used to avoid the small-sample bias that otherwise would be present with such small, expected outcome numbers. Loss to follow up [LTFU] and missing data will be managed in accordance with our LTFU management plan [see supplementary material].

Cost-effectiveness analysis

For the cost effectiveness evaluation, data from the study will be incorporated into a decision analytical model [developed in Microsoft Excel®]. These data include: the micro-costs of testing and follow up, drop-out rates from the diagnostic pathways [usual care and screening], the relative proportions of different stages of liver disease and the demographic characteristics of the cohorts.

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The model will consist of a decision tree for the diagnostic process and a Markov state transition model for the long term disease process [**Figure 2].** It will estimate the quality adjusted life years [QALYs] and costs associated with liver disease. The model structure will be similar to previous models for HCC surveillance.[e.g. [34,36]] and calculate the difference in costs and QALYs between different testing approaches and no testing. Patients with characteristics based on our study population and study outcomes will enter the model. The model will have one year cycles and a lifetime horizon [i.e until the cohort age is 100 years]. Costs will be calculated using an NHS and Personal Social Services perspective. Costs and utilities for the model health states will be taken from a targeted review of the medical literature.

Our base-case analysis will closely match real-world practice. In both cohorts patients identified with liver cirrhosis and referred for HCC surveillance will enter a separate health state – named F4_SURV. Based on recently published data, participants in this health state who develop HCC will have a higher chance of cure [i.e. return to their original F4 SURV health state] and a lower chance of progression to death or transplantation.[16] Similarly, a proportion of those in F4_SURV will have a lower risk of progressing to a decompensated state that reflects the real-world number of participants who commence B blockers in accordance with recent guidelines.[45,46] Participants identified with F2 or F3 disease will enter monitoring states [F2_Mon and F3_Mon] and undergo biannual assessment for progression to F4 disease. Monitoring will stop when participants in the model reach 80 years of age.

As part of our base case analysis, we will calculate the cost-effectiveness [cost per QALY] of four testing strategies that are broadly reflective of current testing strategies in the study region and the NHSE pilot [described in the background]. These will be compared against 'no testing' and presented as ICERs that can then be compared between strategies.

1. Usual care
2. Reflex testing with VCTE only [i.e. everyone offered VCTE]
3. FIB-4 then VCTE for patients with FIB-4 >3.25
4. ELF™ then VCTE for patients with an ELF™ >9.5

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We will conduct probabilistic sensitivity analyses where model parameters are probabilistically varied across pre-specified distributions and ranges. The results of the probabilistic sensitivity analyses will be presented as a scatter plot and a cost effectiveness acceptability curve.

Finally, we will conduct a one-way sensitivity analyses varying the input parameters in the model and scenarios around the main model assumptions. Specifically, we will test a scenario where we introduce a hypothetical anti-fibrotic agent that is given to patients in the F2_Mon and F3_Mon health states. As part of this we will conduct a threshold analysis where we will calculate ICERs for the hypothetical drug at different levels of therapeutic effectiveness. Anti-fibrotic therapy is not part of our base-case analysis as it is not currently part of usual care in England. **Figure 3** shows a Study flow chart showing how the study arms and nested cost-effectiveness evaluation are linked. The rationale for study sample size is also conveyed.

Sample Size

We will aim to recruit 320 patients into each arm of this study – 640 patients in total [**Figure 3**]. A sample of this size will enable us to address the primary outcome, with a minimum power of 80% after allowing for a very conservative 25% drop out rate from the diagnostic pathway in both arms. A more realistic drop out rate would be 5% which would give a power to test the primary outcome of >90%.

We are concerned that the conduct of our study may increase liver disease diagnosed via usual care due to Hawthorne effect on participants randomised to usual care or on primary care physicians who are more likely to request testing because they are, as a consequence of participation, more aware of liver disease.[43] Our sample size therefore also accounts for a doubling of background liver fibrosis testing in usual care. The background testing activity for liver disease in the study setting has been very important in calculating our samples size. We have estimated the background testing activity from what we know about the number of patients tested for liver fibrosis who have T2DM in a year and the total population of people with T2DM [Figure 3].

All sample size calculations were conducted using nQuery advisor 7.0.

Patient and public involvement

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To design the trial we have worked with two PPI representatives [one as PPI lead] and two PPI groups. Our PPI group was struck by the risk of liver cancer in people with diabetes. This was not something they were previously aware of. Both groups of contributors shared the views that cancer and specifically surveillance for liver cancer should be the focus of our research. Our groups are diverse - 8 participants in total; 2 female; two non-white British; one born in eastern Europe. The PPI groups have helped develop our study recruitment strategy and our participant facing study materials. Both groups raised some concerns about the use of a control arm. They advised us to ensure liver assessment was offered to all participants at the end of the study and this has been incorporated into our study procedures.

Discussion

The application, effectiveness and cost-effectiveness of screening for liver disease in patients with T2DM has not been well studied. Despite this it is now recommended practice in some countries and subject to national clinical pilots in others. We aim to fill this knowledge gap.

The robust assessment via a RCT of a screening intervention for liver disease in T2DM with an objective primary outcome that is assessed independently of the researchers will have a significant impact. If effective the trial would provide evidence toward justifying widespread screening in an enormous, and growing proportion of the global population with a knock-reduction in liver death. If not effective, it could prevent further roll out of a massive, costly programme of work that will have significant resource implications for health service systems. Looking forward the trial will also quantify the effect size required and suitable pricing for novel anti-fibrotic therapies to meet cost-effectiveness thresholds.

A strength of the study design is the incorporation of a usual care arm that is a diverse representation of standard practice where testing for liver disease is applied to a few, selected patients with T2DM. The design therefore allows for real-world comparisons between the status quo and [via the intervention arm] a close representation of what a screening programme for liver disease in patients with T2DM might look like.

Ethical approval and dissemination plans

The University of Southampton is the study sponsor, ERGO II submission ID 80205. Ethical approval was granted by the West of Scotland Research Ethics Service [WoSRES] on 2nd August 2023, REC reference 23/WS/0102. Any amendments to the study protocol will require authorisation from the ethical

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approvers. We expect that participants will be identified with liver disease as part of this study. We will work closely with clinicians in the study areas to ensure they are referred and reviewed in line with local practice. We also have academic clinicians within the study team [RB and CB] who can support participants if the need arises.

Our PPI group will explore the use of the internet, social media and involvement of community venues [e.g., mosques, churches, gurdwaras, community centres] to reach marginalised populations and convey the study findings. Our PPI lead will aim to publish articles in local newspapers and newsletters and explore possibilities for translation. We aim to submit our findings in abstract form to the European Liver conference in January 2026 and submit to a high impact liver medicine journal later that year.

Author contributions

Ryan M Buchanan is the guarantor. RMB, CB, KM, TR, JB, KC and SH conceived and planned the study design. RMB, KC & SH designed the data analysis plan. TR and CN designed and piloted data collection templates, all authors contributed to drafting the manuscript. All authors reviewed and commented on a final draft before submission. All authors agree to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

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Competing interest statement

TR received a one-off consultancy fee from Echosens LTD in 2023. Other authors have no other conflicts of interest to declare.

Data statement

Search codes of primary care data that are being used to identify participants are included as an appendix. As a protocol, this article does not present collected data and therefore a data repository is

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not included or needed. The final study dataset will held by the chief investigator and accessible to the co-investigators. The study funders will not have access to the data.

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Table 1 - **Baseline participant characteristics that will collected and where the data will be collected**

Baseline demographic characteristic	Collected at recruitment	Can be collected via EMIS/SystmOne*
Age, years	✓	
Sex, male [%]	✓	
Ethnicity [white European or minority ethnic group]	✓	
Alcohol consumption [AUDIT-C score]	✓	
Measured Height [cm]		
Measured weight [kg]	✓	
Smoking status [current, ex, never]		✓
Index of multiple deprivation [IMD] [from postcode]	✓	
Duration of diabetes, [years]		✓
Medical treatment for diabetes – tablets or insulin [currently, previously, never]	✓	
Currently prescribed medications		
Antiglycaemic treatment [any]	✓	
Sulphonylurea [e.g. gliclazide]	✓	
Metformin	✓	
Insulin	✓	
GLP-1 agonist [e.g. semaglutide]	✓	
Pioglitazone	✓	
SGL2 inhibitor [e.g …flozins]	✓	
Anticoagulants [DOAC or warfarin	✓	
Antihypertensives [any]	✓	
ACE [e.g. ramipril]	✓	
ARBs [e.g. candesartan]	✓	
B-blockers [e.g. bisoprolol]	✓	
Thiazides [e.g. BTZ]	✓	
Calcium channel blockers [e.g. amlodipine]	✓	
Antidepressants	✓	
Fibrates	✓	
Statins	✓	
Co-morbidities [to calculate Charlson co-morbidity index]		
Definitive or probable previous myocardial infarction	✓	✓
Congestive heart failure [dyspnoea with response to CHF medication]	✓	✓
Peripheral vascular disease [intermittent claudication, previous by-pass grafting]	✓	✓
Any end organ damage due to T2DM	✓	✓
Moderate to severe chronic kidney disease	✓	✓
Solid tumour [non, localized, metastatic]	✓	✓
Lymphoma [either cured, in remission or active]	✓	✓
Hemiplegia	✓	✓
AIDs	✓	✓
Peptic ulcer disease	✓	✓
Connective tissue disease [e.g. SLE, rheumatoid arthritis, not osteoarthritis]	✓	✓
Additional prevalent comorbidities in patients with T2DM	✓	✓
Hypertension	✓	✓
Asthma	✓	✓
Hypothyroidism	✓	✓

*EMIS and Systm1 are primary care software programmes used throughout England

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Figure legends

Figure 1
An overview of usual care for liver disease assessment and management within primary and secondary care liver services in study areas – highlighting the complexities and subtle variations in practice.

Figure 2
Markov model structure used to calculate incremental cost-effectiveness of different testing strategies. The findings from the trial will parameterise this model. Numbers 1-4 correspond to the benefits of early detection that will be incorporated into the modelling.

Figure 3
Study flow chart showing how the study arms and nested cost-effectiveness evaluation. Rationale for study sample size is also conveyed.

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BMJ Open: first published as 10.1136/bmjopen-2024-088043 on 6 March 2025. Downloaded from http://bmjopen.bmj.com/ on June 8, 2025 at Agence Bibliographique de l Enseignement Superieur (ABES) . Protected by copyright, including for uses related to text and data mining, AI training, and similar technologies.

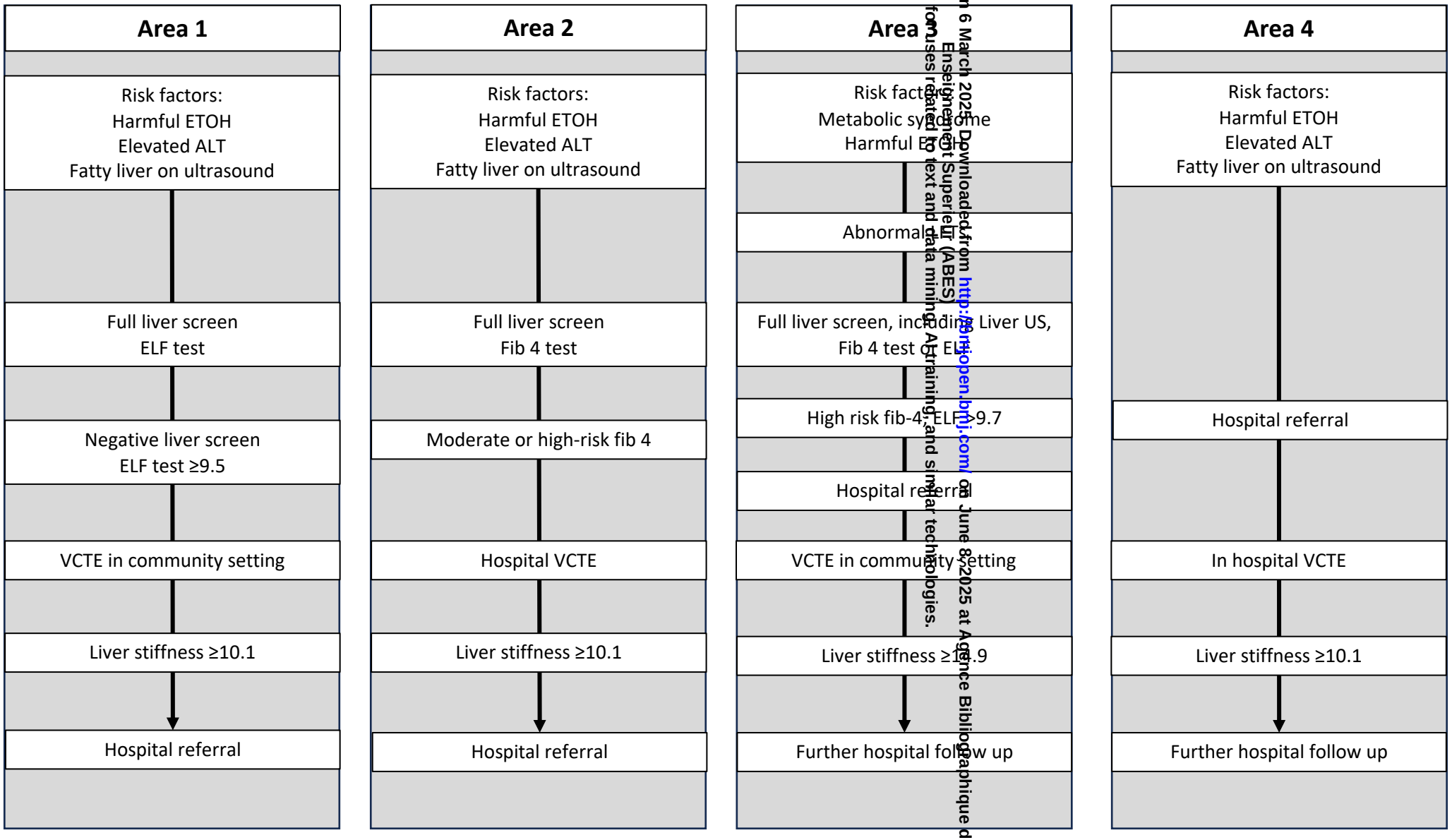

Figure 1

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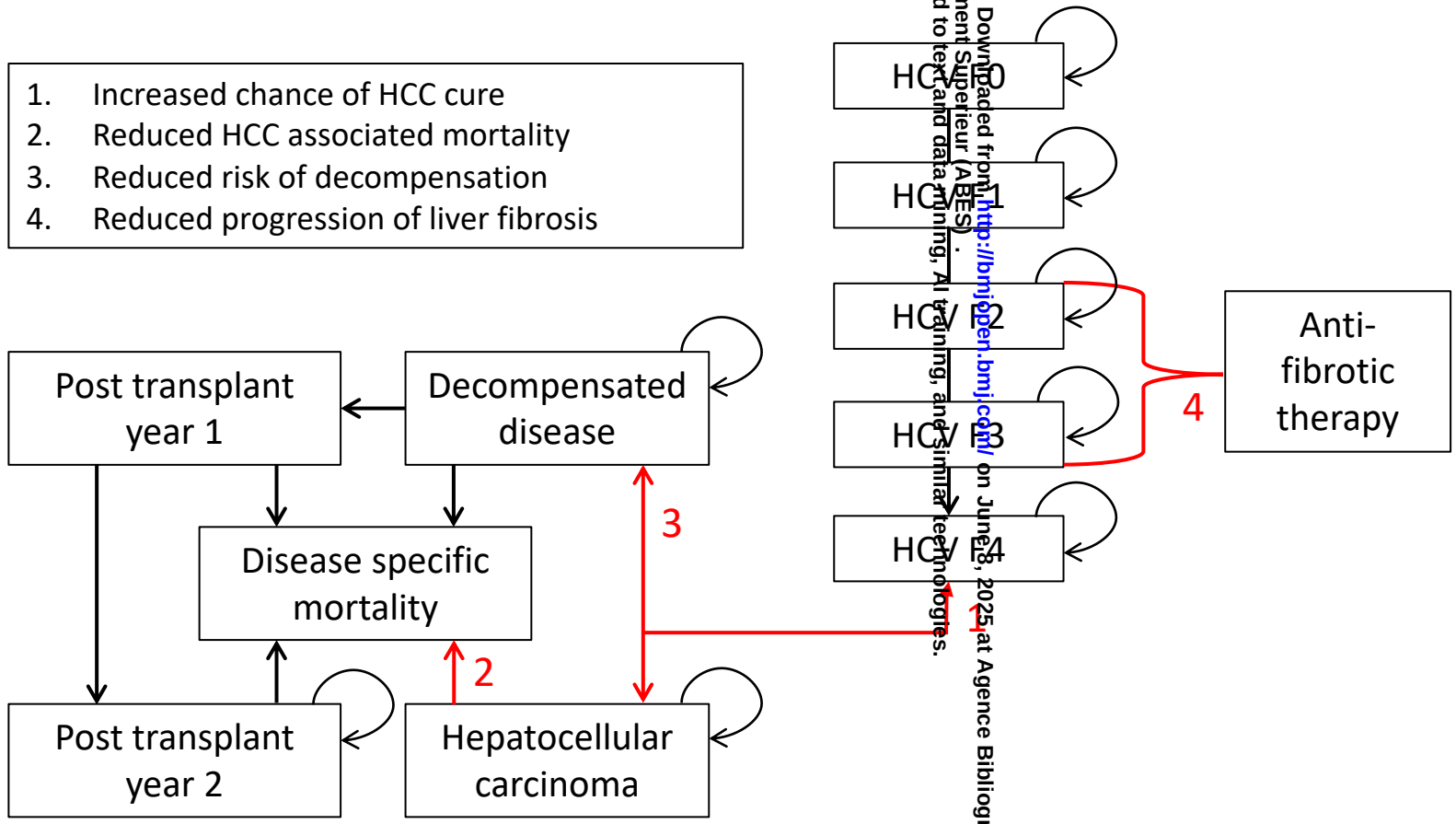

Figure 2

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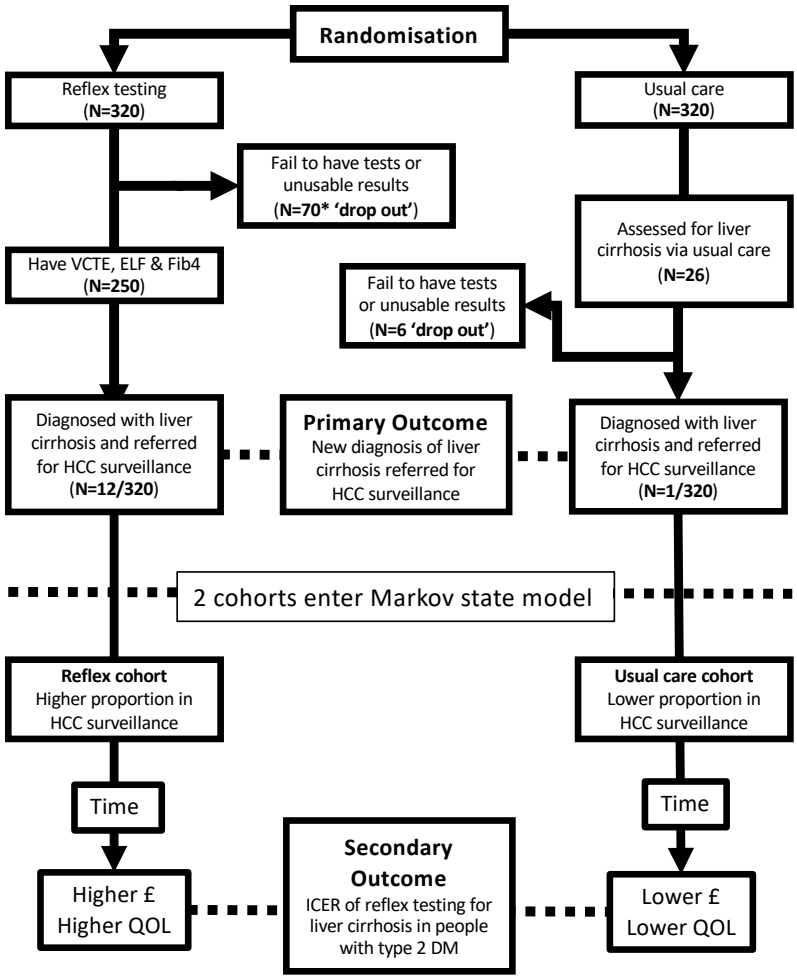

HCC – hepatocellular carcinoma, DM – diabetes mellitus, Qol – Quality of life, ICER – incremental cost effectiveness ratio, Kpa – kilopascals
*very conservative more likely to be ~34 people

Figure 3

BMJ Open: first published as 10.1136/bmjopen-2024-088043 on 6 March 2025. Downloaded from http://bmjopen.bmj.com/ on June 8, 2025 at Agence Bibliographique de l Enseignement Superieur (ABES) . Protected by copyright, including for uses related to text and data mining, AI training, and similar technologies.

REFLEX Supplementary Information

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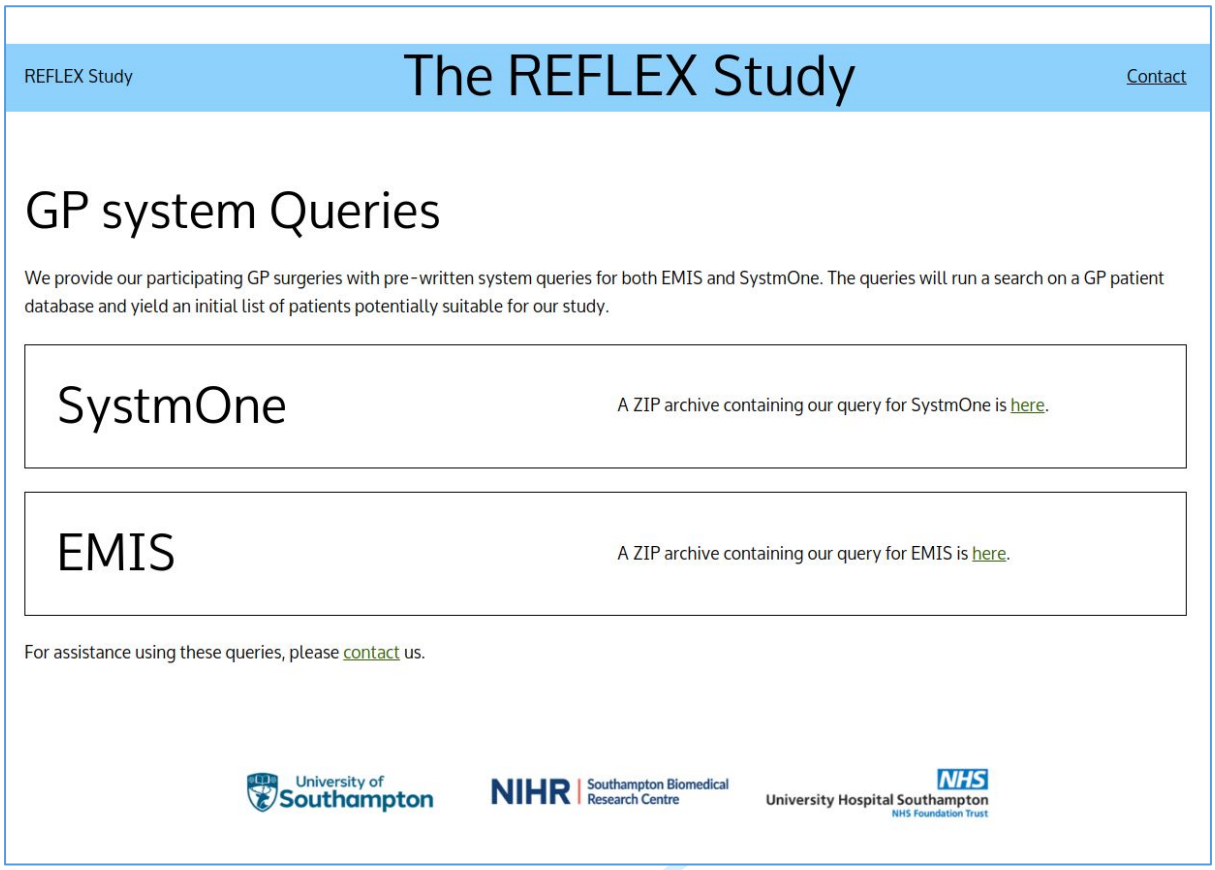
Supplementary 1 – Search Queries

https://www.reflexstudy.org/gp-system-queries/



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Supplementary 2 – EOI

https://www.reflexstudy.org/wp-content/uploads/2023/08/eoi.pdf

Appendix 5

Expressions of interest sent by participating GP practices via (a) text or (b)email/postal letters to potential participants:

(a) Text:

Dear *<insert patient name>*

<Insert name of GP surgery> has partnered with the University of Southampton to invite patients living with type 2 diabetes to take part in a study investigating liver health. Details of the study can be found at https://www.reflexstudy.org. Alternatively, you can call the research team directly on 07751 009483 / tina.reinson1@nhs.net for further information.

(b) Postal letter/email:

Dear *<insert patient name>*

<insert name of GP surgery> has partnered with the University of Southampton to invite patients living with type 2 diabetes to take part in a study investigating liver health.

We have *enclosed/attached* details about the study.

If you would like to take part in the study or have any questions, please contact the research team directly on 07751 009483 / tina.reinson1@nhs.net.

Yours sincerely

<insert name of GP surgery>

<Enc/attached>: Patient information sheet; consent form.

14 July 2023
A1_EOI_PotentialParticipants_V2.1
IRAS project ID: 326212
ERGO ID: 80205

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Supplementary 3 – Introductory Letter

https://www.reflexstudy.org/wp-content/uploads/2023/08/intro_letter.pdf

Professor Christopher Byrne
Professor of Endocrinology and Metabolism
University of Southampton
Human Development and Health Academic Unit
Faculty of Medicine
IDS, MP887
Southampton General Hospital
Tremona Road
Southampton, SO16 6YD

<insert date>

<Insert Patient name>
<Insert address>

Dear *<Insert patient name>*

Thank you for contacting the research team and requesting further information about our study that is investigating the liver health of people living with type 2 diabetes (The REFLEX Study).

Please find enclosed a patient information sheet (PIS_V3.5.1 and a consent form (ConsentForm_V3.2).

If you would like to participate or have any questions, please contact the research team on: 07751 009483 / tina.reinson1@nhs.net who will be happy to help.

Yours sincerely

Christopher Byrne
Professor of Endocrinology and Metabolism
and Chief Investigator of The REFLEX Study

Enc: Patient information Sheet
Patient Consent Form

14 July 2023
A2_EOI_IntroductoryLetter_V2.1
IRAS project ID: 326212
ERGO ID: 80205

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Supplementary 4 – Eligibility Questionnaire

https://www.reflexstudy.org/wp-content/uploads/2023/08/eligibility_qs.pdf

University of Southampton

Eligibility Questionnaire

Study title: Reflex testing for MAFLD in patients with type 2 diabetes

Chief Investigator: Professor Christopher Byrne **Participant Identification Number**: _____

Please ask each potential participant the following questions.

1. Do you have type 2 diabetes

Yes - go to question 2

No – go to statement 1.1

1.1 Thank the potential participant for their time and interest in the study and explain that they cannot take part because this study is looking to identify liver disease in participants living with type 2 diabetes.

2. Have you been diagnosed with liver cirrhosis?

Yes - go to statement 2.1

No – go to end statement

2.1 Thank the potential participant for their time and interest in the study and explain that they cannot take part because this study is looking to identify liver disease in participants who do **not** already have a diagnosis of advanced liver disease.

End statement

Thank you for answering our screening questions. You are eligible to take part in our study.

P0_EligibilityQuestionnaire_V2
26/3/2023

IRAS ID: 326212
ERGO ID 80205

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Supplementary 5 – Consent Form

https://www.reflexstudy.org/wp-content/uploads/2023/08/consent_form.pdf

University of Southampton

CONSENT FORM

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

ERGO ID: 80205 **IRAS ID:** 326212 **Chief Investigator**: Professor Christopher Byrne

Participant Identification Number*:* _____

1	I have read and understood the information sheet *<insert date /version no. of participant information sheet>* and have had the opportunity to ask questions about the study.	
2	I agree to take part in this research project and understand that I will be randomised to one of two groups. Group A or B.	
3	I consent to have a liver assessment using the FibroScan device and provide a blood sample.	
4	If randomised to Group B: (i) I understand that I will be offered my Fibroscan approximately 12 months after today (date of consent). I give permission for the research team to contact me to organise the liver assessment. (ii) I understand that the research team will need access my GP records over the next 12 months.	
5	I consent for my blood sample to be stored at the University of Southampton for the duration of this study	
5a	At the end of the study, I consent/do not consent for my left-over blood to be sent for archive storage at the Southampton Faculty of Medicine Tissue Bank (Human Tissue Authority Licence No: 12009) for use in future ethically approved health related studies.	
6	I understand that that all my details will be kept confidential, my name will not appear on any documents and I will not be directly identified in any reports of the research.	
7	I consent for the research team to access my patient records to obtain health data relevant to this study and for my data to be used for the purpose of this study .	
7a	I consent/do not consent for the research team to access my patients records to obtain health data for the next 10 years where it is relevant for research.	
8	I understand that where it is relevant to my taking part in this research, sections of my medical notes and data collected during the study may be looked at by the research team, regulatory authorities, the research sponsor or the NHS Trust. I give permission for these individuals to have access to my records.	
9	I understand that the results of my liver assessment will be overseen and monitored by clinicians at University Hospital Southampton who may need to contact me or refer me directly to liver health services that are local to me	
10	I consent for you to inform my GP of my liver assessment results.	
11	I understand my participation is voluntary and I may withdraw at any time for any reason without my participation rights, medical care or legal rights being affected.	
12	I would/would not be interested in receiving information about any future relevant liver studies (delete as appropriate). Please contact me via email/text/telephone/post (delete as appropriate) on: _____ _____	

Name of participant (print name): ..... Date: .....

Signature of participant: .....

Name of researcher (print name) ..... Date: .....

Signature of researcher .....

P1_ConsentForm_V3.2
14/07/2023
Copies to: participant; research file

IRAS ID: 326212

ERGO ID: 80205

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Supplementary 6 – Participant Initial Questionnaire

https://www.reflexstudy.org/wp-content/uploads/2023/08/initial_q.pdf

University of Southampton

Participant Initial Questionnaire

Study title: Reflex testing for MAFLD in patients with type 2 diabetes

Chief Investigator: Professor Christopher Byrne **Participant Identification Number**: _____

Date: _____ **Researcher:** _____

Date of Birth (day/month/year)	
Sex	
Ethnicity	
Current prescription medications	

AUDIT-C [1]

[1]Bush K, Kivlahan DR, et al (1998). The AUDIT alcohol consumption questions (AUDIT-C): An effective brief screening test for problem drinking. Ambulatory Care Quality Improvement Project (ACQUIP). Arch Intern Med. 158:1789-95)

How often do you have a drink containing alcohol?	Never	Monthly or less	2-4 times a month	2-3 times a week	4 or more times a week
How many standard drinks containing alcohol do you have on a typical day?	1 or 2	3 to 4	5 to 6	7 to 9	10 or more
How often do you have six or more drinks on one occasion?	Daily or almost daily	Weekly	Monthly	Less than monthly	Never
AUDIT-C score					
Venesection performed?	Yes / No				
Location and number of attempts					
Blood samples obtained?	Yes / No				
Refer patient elsewhere for venesection	Yes / No If yes, remember to provide patient with labels for test tubes				

Liver Assessment

Has the patient fasted? Y/N	Date:	Probe size: XL / M

P2_ParticipantInitialQuestionnaire_V1.1
13/7/2023

IRAS ID: 326212
ERGO ID 80205

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VCTE reading (kPa):	IQR/MED:	CAP (Db/m^2):
Patient advised of VCTE assessment? Y/N		
Additional information		

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Supplementary 7 – PIS

https://www.reflexstudy.org/wp-content/uploads/2023/08/pis.pdf

University of Southampton

Participant Information Sheet

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

Chief Investigator: Professor Christopher Byrne

ERGO ID: 80205 **IRAS ID:** 326212

You are being invited to take part in the above research study. To help you decide whether or not you would like to take part, it is important that you understand why the research is being done and what it will involve. Please read the information below carefully and ask questions if anything is not clear or you would like more information before you make your decision. You may like to discuss it with others but it is up to you to decide whether or not to take part. If you are happy to participate you will be asked to sign a consent form.

What is the research about?

Research, including our work, has shown that 15% of people living with type 2 diabetes are at risk of long-term complications to their health, including liver problems. However, we do not know what is the right way to monitor people living with type 2 diabetes for liver problems.

The aim of our study is to test a new way of identifying liver disease in people living with type 2 diabetes to see if it better than what we are currently doing.

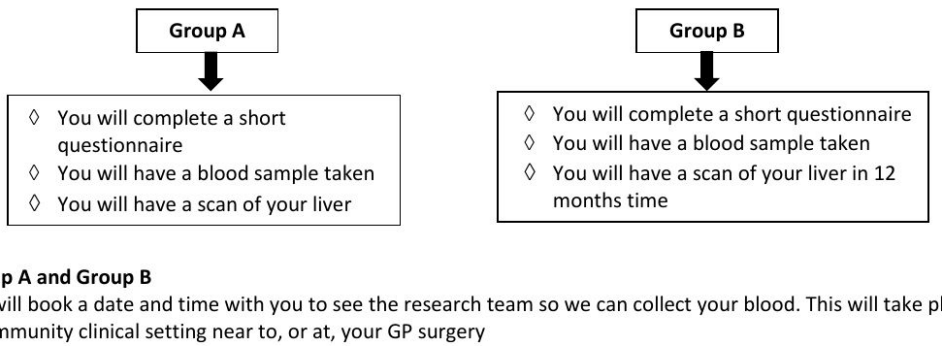
EchoSens, France, is funding this research. The University of Southampton is the study sponsor.

Why have I been asked to participate?

You have been asked to participate because you have type 2 diabetes. We are aiming to recruit 640 patients living with type 2 diabetes to the study.

What will happen to me if I take part?

You will be randomly put into one of two groups. The diagram below shows what will happen depending on which group you are put in.



Group A and Group B

We will book a date and time with you to see the research team so we can collect your blood. This will take place in a community clinical setting near to, or at, your GP surgery

Liver Scan

Group A will have their liver scanned directly following blood collection. Group B will be contacted in 12 months time to book their liver scan. The appointment will last approximately 20-30 minutes.

PIS_V3.5.1
14 July 2023

ERGO ID: 80205
IRAS Project ID: 326212

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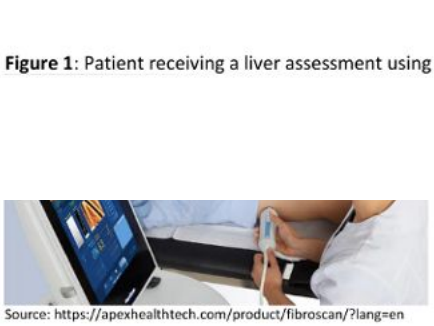
Figure 1: Patient receiving a liver assessment using the FibroScan machine



Source: https://apexhealthtech.com/product/fibroscan/?lang=en

he FibroScan uses ultrasound technology to measure the peed at which a sound wave returns from your liver. You ill need to lie down on your back and raise your right arm so that the FibroScan probe can be placed in a gap between your ribs (**Figure 1**). This scan doesn't break the skin, is painless and takes about 10 minutes.

Group B

We need to see what happens to you over the next 12 months. To do this we will need to access the results of any standard care tests you have had done within the 12 month period.

Your liver assessment results

The results of your FibroScan assessment and blood test scores will all be reviewed by the clinical team at University Hospital Southampton (UHS). Any additional tests will be organised by the clinical team at UHS who will contact you to discuss these. We will notify you of your liver assessment results and convey this information to your GP.

After your liver assessment there is no further follow up from the research team. However, if you have any questions at any time, please contact the study team on: *< insert contact details>.*

Are there any benefits in my taking part?

During the study all participants will have the opportunity to have their liver health assessed by blood tests and a scan. More broadly the information we get from the study will help us understand how best to monitor people with type 2 diabetes for complications to their health.

We would also like to offer you with a £15 voucher for taking the time to participate in our study.

Are there any risks involved?

The FibroScan assessment is a painless noninvasive procedure. Collecting blood involves using a needle stick which may hurt a bit – like a usual blood test. There is a small risk of bruising, a rare risk of infection, and you may feel lightheaded.

If you have any questions before or after your participation, then please contact the research team. See below for contact information.

What data will be collected?

The personal data we would like to collect includes: name, contact details (including email, home address, phone numbers), sex, ethnicity, NHS number, hospital number, date of birth, height, weight, alcohol consumption, and any current prescription medications you may be taking. We would also like to have access to your medical records.

Your blood sample will be sent to University Hospital Southampton for analysis. We will analyse your blood using two tests that are commonly used to assess liver health: the enhanced liver fibrosis (ELF™) test and Fibrosis-4 (FIB-4) test. We will archive your blood to use at a later date for measurement of cardio metabolic risks (e.g. cholesterol levels) and factors that are known to modify the severity of liver disease. Your blood will not be labelled with any identifiable data. For the duration of this study we will store your blood at the University of Southampton in -80'C freezers on Level A, in the Institute of Developmental Sciences (IDS) building.

On all the materials we collect from you we will put a unique number. This number will be used, instead of your name, to identify any data relating to you. Your data will be entered in to a password protected study database by

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a member of the research team. The study database will be stored on a secure server at the University of Southampton. There will be no identifying information stored with the research data we collect, this will be stored on a separate database and only the study principal investigator, or nominated representative, will have the key to unlocking and identifying patients.

Future research
At the end of the study, your blood will be sent for archive storage at the Southampton Faculty of Medicine Tissue Bank (Human Tissue Authority Licence No: 12009) for use in future ethically approved health related studies. Only non-identifiable samples will be shared with other researchers for future use.

As part of this study we want to better understand the progression of liver disease, so that the time span between liver assessments is optimal. However, liver disease develops slowly over many years, therefore we would like to remotely track any relevant changes to your health and continue to build our database of valuable liver disease information. We will therefore link your unique number onto an anonymised dataset and obtain any relevant information from NHS digital over the next 10 years regarding changes to your health. To do this we will need to share your name, date of birth and NHS number with NHS digital.

If you consent to be contacted for future studies, then we will keep your contact details separate from the study database and store them on the secure server at the University of Southampton.

Will my participation be confidential?
Your participation and the information we collect about you during the course of the research will be kept strictly confidential. Only the research team will have access to the research data. The study will be overseen and monitored by the University of Southampton, where the study Chief Investigator Christopher Byrne is Professor of Endocrinology & Metabolism.

Only members of the research team and responsible members of the University of Southampton may be given access to data about you for monitoring purposes and/or to carry out an audit of the study to ensure that the research is complying with applicable regulations. Individuals from regulatory authorities (people who check that we are carrying out the study correctly) may require access to your data. All of these people have a duty to keep your information, as a research participant, strictly confidential.

Do I have to take part?
No, it is entirely up to you to decide whether or not to take part. If you decide you want to take part, you will need to sign a consent form *<insert date and version number>* to show you have agreed to take part.

What happens if I change my mind?
You have the right to change your mind and withdraw at any time without giving a reason and without your participant rights or routine care being affected.

If you wish to withdraw from the study, please contact the research team *<insert contact details>.*

If you withdraw from the study, we will keep the information about you that we have already obtained for the purposes of achieving the objectives of the study only.

What will happen to the results of the research?
Your personal details will remain strictly confidential. Research findings made available in any reports or publications will not include information that can directly identify you without your specific consent.

The results of this study will be published. All participant details will remain strictly confidential and no patient identifiable information will be used.

Where can I get more information?
You can contact the research team on *<insert research team contact details>.*

PIS_V3.5.1
14 July 2023

ERGO ID: 80205
IRAS Project ID: 326212

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The British Liver Trust and Diabetes UK have plenty of useful information. You can speak directly to a liver nurse on: 0800 652 7330 or go to their website: www.britishlivertrust.org.uk. Contact details for Diabetes UK: 0345 123 2399 / www.diabetes.co.uk

What happens if there is a problem?

If you have a concern about any aspect of this study, you should speak to the researchers who will do their best to answer your questions.

If you remain unhappy or have a complaint about any aspect of this study, please contact the University of Southampton Research Integrity and Governance Manager (023 8059 5058, rgoinfo@soton.ac.uk).

Data Protection Privacy Notice

The University of Southampton conducts research to the highest standards of research integrity. As a publicly-funded organisation, the University has to ensure that it is in the public interest when we use personally-identifiable information about people who have agreed to take part in research. This means that when you agree to take part in a research study, we will use information about you in the ways needed, and for the purposes specified, to conduct and complete the research project. Under data protection law, 'Personal data' means any information that relates to and is capable of identifying a living individual. The University's data protection policy governing the use of personal data by the University can be found on its website (https://www.southampton.ac.uk/legalservices/what-we-do/data-protection-and-foi.page).

This Participant Information Sheet tells you what data will be collected for this project and whether this includes any personal data. Please ask the research team if you have any questions or are unclear what data is being collected about you.

Our privacy notice for research participants provides more information on how the University of Southampton collects and uses your personal data when you take part in one of our research projects and can be found at http://www.southampton.ac.uk/assets/sharepoint/intranet/ls/Public/Research%20and%20Integrity%20Privacy%20Notice/Privacy%20Notice%20for%20Research%20Participants.pdf

Any personal data we collect in this study will be used only for the purposes of carrying out our research and will be handled according to the University's policies in line with data protection law. If any personal data is used from which you can be identified directly, it will not be disclosed to anyone else without your consent unless the University of Southampton is required by law to disclose it.

Data protection law requires us to have a valid legal reason ('lawful basis') to process and use your Personal data. The lawful basis for processing personal information in this research study is for the performance of a task carried out in the public interest. Personal data collected for research will not be used for any other purpose.

For the purposes of data protection law, the University of Southampton is the 'Data Controller' for this study, which means that we are responsible for looking after your information and using it properly. The University of Southampton will keep identifiable information about you for 10 years after the study has finished after which time any link between you and your information will be removed.

To safeguard your rights, we will use the minimum personal data necessary to achieve our research study objectives. Your data protection rights – such as to access, change, or transfer such information - may be limited, however, in order for the research output to be reliable and accurate. The University will not do anything with your personal data that you would not reasonably expect.

If you have any questions about how your personal data is used, or wish to exercise any of your rights, please consult the University's data protection webpage (https://www.southampton.ac.uk/legalservices/what-we-do/data-protection-and-foi.page) where you can make a request using our online form. If you need further assistance, please contact the University's Data Protection Officer (data.protection@soton.ac.uk).

Thank you for taking the time to read this information sheet and considering taking part in the research.

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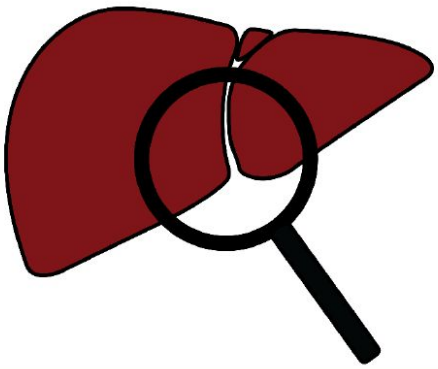
Supplementary 8 – Poster

https://www.reflexstudy.org/wp-content/uploads/2023/08/poster.pdf

Participants needed

REFLEX is a study investigating liver health in people living with type 2 diabetes



Who do we need?

People living with type 2 diabetes, 18 years +

What's involved?

A single 20-30 appointment where we will collect a blood sample and assess the health of your liver with a machine that uses ultrasound based technology.

Contact for more information

CONTACT REFLEX

☎ 07751 009483

✉ Tina.reinson1@nhs.net

REFLEX STUDY

ERGO II ID: 80205
IRAS ID: 326212
Poster_V2.2_14/07/2023

University of Southampton

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Supplementary 9 – Summary PIS

https://www.reflexstudy.org/wp-content/uploads/2023/08/summary_pis.pdf

Participants needed

REFLEX is a study investigating liver health in people living with type 2 diabetes

Who do we need?

People living with type 2 diabetes, 18 years +

Research, including our work, has shown that 15% of people living with type 2 diabetes are at risk of long-term complication to their health, including liver problems. However, we do not know what is the right way to monitor people living with type 2 diabetes for liver problems.

What will happen to me if I take part?

You will be randomly put into one of two groups. Both groups will complete a short questionnaire and have a blood sample taken. Group A will have a scan of their liver straight away, Group B will have a scan of their liver in 12 months time. The appointments will take place in a community clinical setting near to, or at, your GP surgery. The appointment will between 20 and 30 minutes.

Figure 1: Patient receiving a liver assessment using the FibroScan machine

Source: https://apexhealthtech.com/product/fibroscan/?lang=en

The FibroScan uses ultrasound technology to measure the speed at which a sound wave returns from your liver. You will need to lie down on your back and raise your right arm so that the FibroScan probe can be placed in a gap between your ribs (**Figure 1**). This procedure is non-invasive, painless and takes about 10 minutes.

Are there any benefits in my taking part?

During the study all participants will have the opportunity to have their liver health assessed by blood tests and a scan. More broadly the information we get from the study will help us understand how best to monitor people with type 2 diabetes for complications to their health.

Are there any risks involved?

The FibroScan assessment is a painless noninvasive procedure. Collecting blood involves using a needle stick which may hurt a bit – like a usual blood test. There is a small risk of bruising, a rare risk of infection, and you may feel lightheaded.

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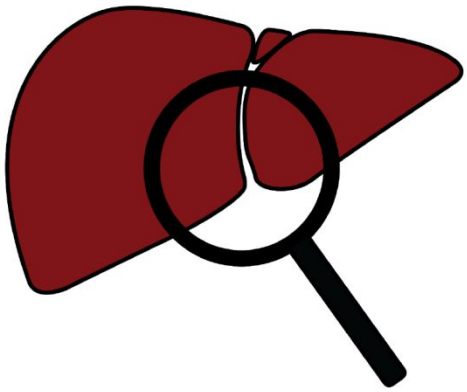
Supplementary 10 – TV Feed

https://www.reflexstudy.org/wp-content/uploads/2023/08/TV_feed.pdf

We have partnered with the University of Southampton on The REFLEX Study that is investigating the liver health of people living with type 2 diabetes

University of Southampton

REFLEX_PowerPointPresentionV2.2
13 July 2023; ERGO ID 80205; IRAS ID 326212



We do not know the most effective way to assess patients for complications of type 2 diabetes

REFLEX_PowerPointPresentionV2.2

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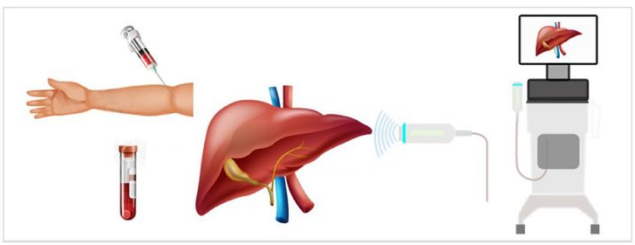
If you are living with type 2 diabetes and over the age of 18 years you may be eligible to take part in our study

University of Southampton

REFLEX_PowerPointPresentionV2.2

Our study involves one single 20-30 minute appointment
In this time we will:

- Collect a blood sample
- Assess the health of your liver with a machine that uses ultrasound technology



Source: https://www.internationaldrugmart.com/blog/liver-function-test/

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If you would like further information about The REFLEX Study please contact the research team on:

07751 009483

Tina.reinson1@nhs.net

Or visit the study website:

REFLEXstudy.org

University of Southampton

REFLEX_PowerPointPresentionV2.2

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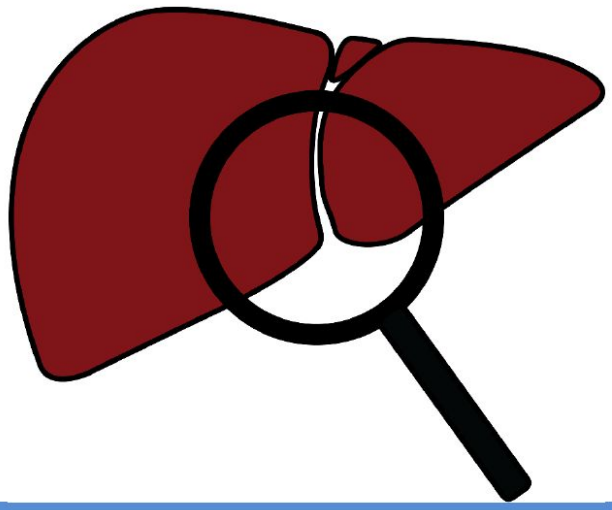
Supplementary 11 – GP Website

https://www.reflexstudy.org/wp-content/uploads/2023/08/gp_website.pdf

We have partnered with the University of Southampton on a study investigating liver disease in people living with type 2 diabetes – The REFLEX study



What's involved?

A single 20-30 minute appointment where we will collect a blood sample and assess the health of your liver with a machine that uses ultrasound based technology.

Contact for more information

REFLEX STUDY

Further information can be found at:

https://www.reflexstudy.org

07751 009483

tina.reinson1@nhs.net

CONTACT REFLEX

REFLEX_PracticeWebsite_V3.2
14/07/2023
ERGO ID: 80205
IRAS Project ID: 326212

University of Southampton

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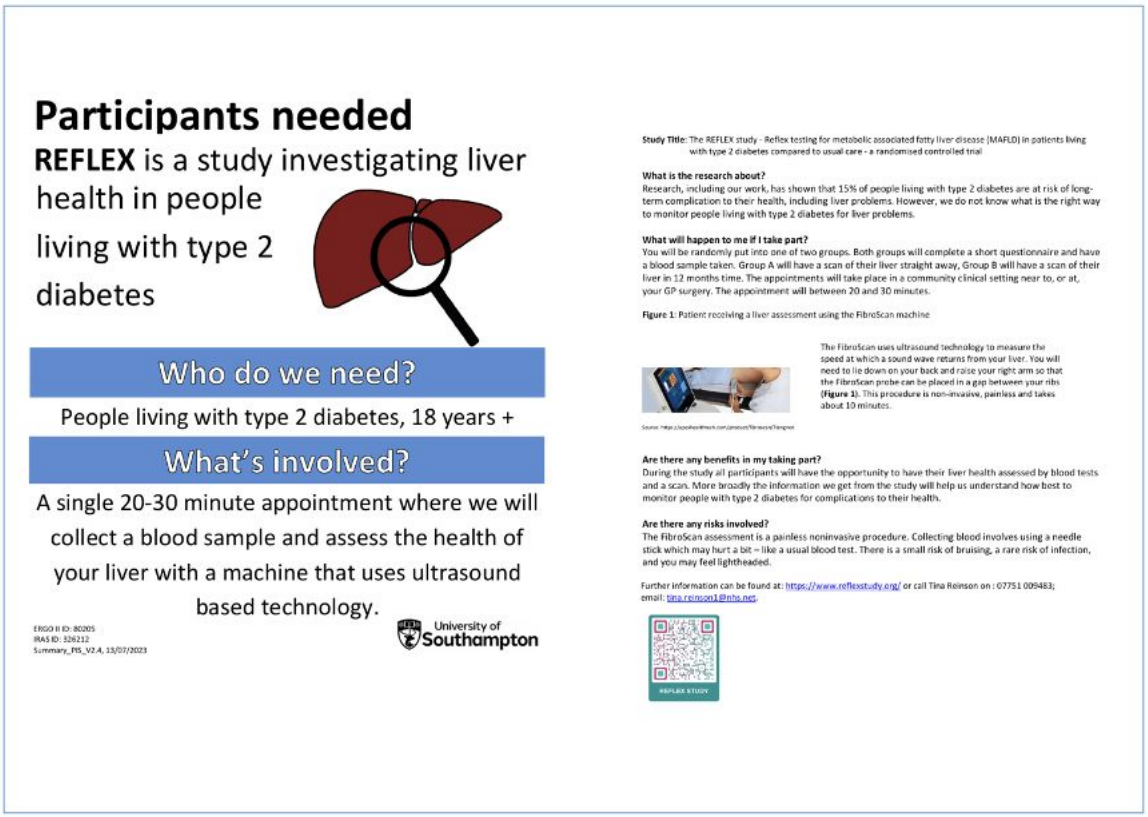
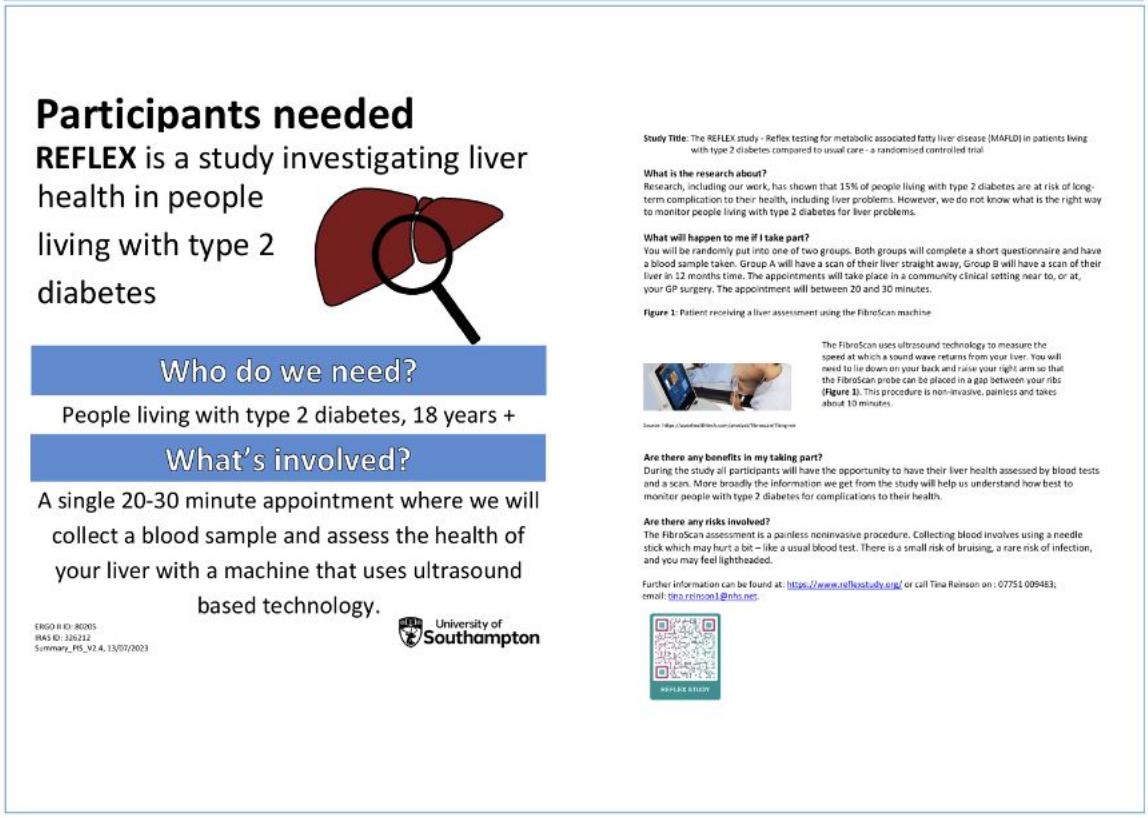
Supplementary 12 – Flyer





https://www.reflexstudy.org/wp-content/uploads/2023/08/Appendix_3_SummaryPIS_V2.4_double_page.pdf

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Supplementary 13 – Patient Letter

https://www.reflexstudy.org/wp-content/uploads/2023/08/patient_letter.pdf

<Insert UHS logo>

University of Southampton

<insert name of clinician>
<Address>
Southampton, SO16 6YD
<email>

<insert date>

<Insert GP name>
<Insert GP address>

Dear Dr <insert GP name>

Reference patient: <insert patient name; NHS number and date of birth>

The above patient took part in the REFLEX testing for metabolic associated fatty liver disease (MAFLD) in patients with type 2 diabetes study on <insert date>.

<Insert patient name> agreed that we may inform you of their liver assessment finding:

FibroScan result: <insert liver stiffness and steatosis readings, and IQR/MED>

Table 1: Interpretation of FibroScan results

Liver stiffness reading interpretation[1]			CAP (controlled attenuation parameter) score interpretation[2]		
Fibroscan reading	Fibrosis stage[a]	Interpretation	CAP score	Steatosis stage	Accumulated fat in the liver
<6.0 kPa	F0	No scarring	<250 dB/m²	S0	<11%
≥6.0 kPa to 8.1 kPa	F1	Mild fibrosis	>250 dB/m² and <301 dB/m²	S1	11% and 33%
≥8.2 kPa to 9.6 kPa	F2	Moderate fibrosis	>301 dB/m² and <325 dB/m²	S2	34% and 66%
≥9.7 kPa to 13.5 kPa	F3	Severe fibrosis	>325 dB/m²	S3	>66%
≥13.6 kPa	F4	Advanced fibrosis or cirrhosis			

[a]Liver biopsy validated fibrosis stages; [1]Eddowes PJ, Sasso M, Allison M, et al. Accuracy of FibroScan Controlled Attenuation Parameter and Liver Stiffness Measurement in Assessing Steatosis and Fibrosis in Patients With Nonalcoholic Fatty Liver Disease. Gastroenterology. 2019 May;156(6):1717-1730. doi: 10.1053/j.gastro.2019.01.042; [2]PLoS One. 2014 Jun 5;9(6):e98689. doi: 10.1371/journal.pone.0098689. eCollection 2014.

Diagnosis: <insert diagnosis and interpretation>
Action: Please <insert any relevant clinical notes as advised by study clinicians at the time of assessment>

At the time of the VCTE assessment <insert patient name> was advised of <his/her/their> VCTE result.

Patient follow up has now finished.

If you have any queries, please contact the study team on: <insert telephone number and email address>

With kind regards

<Insert clinician name and position>

Cc: ***<insert patient name>***

26 March 2023
B1_PatientLetter_V2
IRAS project ID: 326212
ERGO ID: 80205

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Supplementary 14 – Missing data plan

Sensitivity Analysis Plan to Manage Loss to Follow-Up (LTFU) in REFLEX

Objective:
The purpose of this sensitivity analysis is to assess the robustness of the primary trial results to different assumptions about missing data caused by loss to follow-up (LTFU). The analysis will help determine how the outcomes would change under various scenarios related to the handling of missing data.

---

1. Overview of Loss to Follow-Up and missing data

Loss to follow-up (LTFU) can introduce bias if the participants lost to follow-up differ systematically from those who remain in the study. Sensitivity analysis will help address potential biases and provide a range of plausible outcomes based on different assumptions about missing data.

Potential scenarios where missing data may affect our study

1. A participant randomised to the intervention arm does not attend for liver assessment
2. A participant found to have a high liver stiffness does not attend for further clinical assessment and therefore the primary outcome (referral to HCC surveillance) is not assessed

2. Primary Analysis Approach

The primary analysis will use an **Intent-to-diagnose (ITD)** approach, including all randomised participants, regardless of whether they completed the study. For participants with missing outcome data due to LTFU, we will apply multiple imputation methods in the primary analysis to account for the uncertainty of missing data.

Alongside this we will present available data describing LTFU participants and compare them with participants who completed the study. This will be available as a supplementary table. The comparison will allow us to consider if LTFU was 'non-random' and how it may have influenced our conclusions.

Multiple Imputation (MI)

- **Description:** Multiple imputation will be used to impute missing values based on observed data, assuming that data are Missing at Random (MAR). Imputed datasets will be created using covariates that predict both missingness and the outcome.
- **Rationale:** MI allows us to handle uncertainty in the missing data and provides a range of plausible values, assuming the MAR assumption holds.
- **Interpretation:** Compare the results from MI with the complete case analysis. Large deviations would suggest sensitivity of the results to the MAR assumption.

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3. Sensitivity Analysis Approaches

Subsequently several sensitivity analyses will be conducted to explore the impact of LTFU on the trial's results. These will include:

a. Complete Case Analysis

- **Description:** Analyse only participants who complete the trial and for whom outcome data are available.
- **Rationale:** This represents a "best-case" scenario where LTFU is assumed to be random and does not introduce bias. However, if LTFU is not random, this could lead to biased results.
- **Interpretation:** The results from this analysis will be compared with the primary analysis (including MI for LTFU) to identify any major differences caused by the exclusion of participants lost to follow-up.

b. Worst-Case/Best-Case Imputation

- **'Worst-Case' Scenario:**
  - Assume that all participants lost to follow-up in the REFLEX group did not have the primary outcome (entry into HCC surveillance), while those in usual care did.
- **Best-Case Scenario:**
  - Assume the opposite: participants lost to follow-up in the REFLEX group were entered into HCC surveillance, while those in usual care were not.
- **Rationale:** These extreme-case analyses provide boundaries for the possible impact of missing data. If the conclusions remain similar to the primary analysis, the results are considered robust to LTFU.
- **Interpretation:** Significant changes between the worst-case/best-case scenario and the primary results would indicate that LTFU might have substantially influenced the trial's findings.

4. Assumptions and Limitations

- **Missing at Random (MAR) vs. Missing Not at Random (MNAR):** The primary analysis assumes MAR, which means that the probability of being lost to follow-up depends only on observed characteristics. The sensitivity analyses (e.g., worst-case/best-case imputation) will allow us to assess how results change if data are MNAR.
- **Limitations:** Each method has its own limitations. Complete case analysis may introduce bias if LTFU is not random, and extreme-case scenarios may not reflect realistic assumptions. However, taken together, the sensitivity analyses will provide a range of outcomes under different assumptions.

5. Reporting

Results from the sensitivity analyses will be reported alongside the primary analysis. We will summarise:

- How each analysis affects the estimated treatment effect.
- Whether the conclusions of the trial (e.g., statistical significance, effect size) change under different assumptions about LTFU.
- Any substantial differences between the sensitivity analyses and the primary analysis, highlighting potential areas of concern regarding missing data.

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7. Managing missing data in the cost-effectiveness evaluation

In our cost-effectiveness model the characteristics of the cohorts entering the model at time 0 will be based on ITD with MI for missing values. However, whether a patient in the model is engaged with HCC surveillance or other treatments will be determined by whether they engaged with liver assessment as part of the trial and usual care (if referred to hepatology services after assessment).

For example, if a participant is randomised but does not attend for liver assessment the stage of that participants liver disease will be determined by MI. But in the model (if via MI their liver stiffness is high) they will be assumed to have engaged with liver services so will not enter HCC surveillance or experience other benefits of engagement with care. Similarly, if a participant attends for liver assessment as part of the trial and has a high liver stiffness but does not engage with liver services they will not enter HCC surveillance or experience other benefits of engagement with care.

8. Conclusion

The sensitivity analysis will ensure that the trial's conclusions are robust to assumptions about missing data and LTFU. By considering multiple scenarios, the analysis will provide confidence in the validity of the results, or indicate areas where LTFU may have introduced bias. By taking these approaches we will ensure our cost-effectiveness results are cognisant with real-world levels of engagement with the liver diagnostic care cascade and doesn't make the mistake of assuming 100% engagement.

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BMJ Open

Screening to identify people with type 2 diabetes at risk of liver cancer in primary care - a randomised controlled trial PROTOCOL

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Primary Subject Heading:	Gastroenterology and hepatology
Secondary Subject Heading:	Health economics, Health services research
Keywords:	Randomized Controlled Trial, Hepatobiliary tumours < ONCOLOGY, Health Care Costs, Diabetes & endocrinology < INTERNAL MEDICINE, Hepatology < INTERNAL MEDICINE

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Screening to identify people with type 2 diabetes at risk of liver cancer in primary care - a randomised controlled trial PROTOCOL

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Key words: Hepatology, Diabetes & endocrinology, Health care costs, Randomized Controlled Trial, Hepatobiliary cancer.

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Abstract

Introduction

Hepatocellular carcinoma [HCC] is expected to become the 3rd most common cause of cancer death world-wide by 2030. The increase in HCC is in large part due to the rising prevalence of risk factors such as type 2 diabetes [T2DM]. Up to 1 in 20 people living with T2DM have liver cirrhosis and they have a 1-2% incidence of HCC per year.

Patients with cirrhosis enter surveillance for HCC to identify early-stage, curable tumours. A diagnosis of T2DM does not mandate testing to identify patients with cirrhosis with testing restricted to those with additional risks. There has never been a trial and nested cost-effectiveness evaluation comparing screening all patients with T2DM for cirrhosis against usual care.

Methods and analysis

The study will use a multi-centre, unblinded individual randomised controlled trial design. The aim will be to determine the effectiveness and cost-effectiveness of screening all adults with T2DM to identify those at high risk of HCC.

The recruitment strategy has been supported by patient and public involvement [PPI]. Participants will be identified via an automated search of primary care records and invited to participate via text. 320 participants will be randomised to screening. Screening will include measurement of bio-markers for liver fibrosis [ELF™ and Fib-4] and vibration controlled transient elastography. Another 320 participants will be randomised to standard care.

Demographic and medical history data will be collected at baseline from all participants. Outcome data will be collected remotely from healthcare records. The primary outcome is the proportion of participants in each arm who are referred into HCC surveillance following testing for liver disease within 12months of randomisation. The results will be used to calculate the incremental cost-effectiveness ratio of screening via a Markov model.

Ethics and dissemination

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The results of this study will be presented directly to NHS England. Additional dissemination via conference proceedings and publication will be supported by our PPI team. Ethical approval was granted by the West of Scotland Research Ethics Service [WoSRES] on 2nd August 2023, REC reference 23/WS/0102.

Trial registration: ISRCTN17017677

Article summary

Strengths and limitations of this study

- First comparison via an RCT between risk factor-based testing for liver disease in people with T2DM [usual care in the United Kingdom] and screening offered to all adults with T2DM.
- Provides definitive cost-effectiveness of both approaches and impact on liver cancer diagnosis and survival in a real-world setting.
- Will delineate relative cost-effectiveness of different non-invasive tests to identify significant liver disease in people with T2DM.
- Trial limited to United Kingdom so usual care may not be internationally representative.
- Short study time-horizon therefore observation of clinical outcomes subject of modelling rather than real-world observation.

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Introduction

Cancer is the leading cause of mortality in patients with type 2 diabetes mellitus [T2DM][1] and T2DM is strongly associated with site-specific cancers including hepatocellular carcinoma [HCC].[2] 830,200 people died from HCC in 2020 and the incidence of HCC is expected to increase by 55% in the next 20 years.[3] HCC is now the fastest growing indication for liver transplantation[4] and it is expected to become the 3rd most common cause of cancer death worldwide by 2030.[5] HCC has a very poor prognosis with a 5-year survival of ~20%.[6] However, if cases are identified at an early stage curative treatments are available which include surgical resection, liver transplant or tumour ablation.[6]

A major driver for the increasing number of deaths from HCC is the increasing global prevalence of T2DM.[3,5,7] T2DM causes liver steatosis, inflammation, fibrosis and liver cirrhosis and patients with significant liver fibrosis or cirrhosis are at risk of HCC.[8,9] There is a high prevalence of all stages of liver disease in people living with T2DM.[10–14].

International guidance recommends biannual surveillance for HCC in patients with liver cirrhosis via ultrasound imaging however, less than one third of incident cases of HCC in patients with T2DM are identified via surveillance.[15] Identification of HCC via surveillance is important as cancers that are identified in patients who are undergoing regular surveillance have better outcomes.[16] To engage patients with T2DM with HCC surveillance it is necessary to first identify patients with cirrhosis. In the past liver disease was hard to identify because it progresses without signs or symptoms. However, several approaches have now been validated in patients with T2DM to identify asymptomatic disease. These include utilization of blood tests such as the Fibrosis-4 test [FIB-4][17] and the Enhanced Liver Fibrosis [ELF™] test [18], as well as a simple scan of the liver which uses vibration controlled transient elastography [VCTE] to assess the liver stiffness[17,19–21] as a validated marker of fibrosis.

In addition to HCC surveillance early-diagnosis of liver disease can facilitate positive interventions aimed at improving patient outcomes. These include optimisation of blood glucose control in people with T2DM, dietary modification and treatments to facilitate weight loss, moderation, or complete abstinence from alcohol [a co-factor in liver disease progression for these patients[22]] and potentially pharmacotherapy that reduces fibrogenesis. With respect to the latter, on 14th March 2024, Resmetirom[23] was given conditional approval by the US Food and Drug Administration [FDA] for the

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treatment of adults with noncirrhotic non-alcoholic steatohepatitis [NASH] with moderate to advanced liver scarring [fibrosis] alongside diet and exercise. Furthermore, selected patients could be prescribed beta blocker therapy to reduce mortality from bleeding oesophageal varices and to reduce risk of liver decompensation.[24]

In addition to being recommended in the USA[25,26], screening for liver disease in patients with T2DM and obesity has recently been adopted as a national pilot in England that has been funded by the National Health Service England [NHSE] cancer service.[27] The national pilot uses a primary care based search algorithm for T2DM as well as other risk factors for liver disease [such as hazardous alcohol consumption] and then invites patients into a cascade of non-invasive tests for fibrosis.

Whilst patients with T2DM are known to have an increased risk of fibrosis and cirrhosis[28] there is a lack of empirical evidence supporting implementation of this NHSE programme. Just three studies have tested a diagnostic pathway for liver disease against a contemporaneous control[29–31] and just one specifically focussed on liver disease in patients with T2DM.[30]

The NHSE pilot is different from the current national [NICE] guidelines in the UK which recommends testing for liver disease is restricted to patients with risk factors for liver cirrhosis including a fatty liver on ultrasound imaging, abnormal liver enzyme levels and potentially harmful levels of alcohol consumption.[32] T2DM alone is not a risk factor that currently mandates assessment. The reason for these narrow criteria is a lack of cost-effectiveness data supporting wider eligibility for testing.[33]

The NICE NAFLD guideline [ng49] was published in 2016[32] and since its publication researchers have modelled the cost-effectiveness of testing for liver disease in patients with T2DM[34–36]. Published models have compared testing strategies that include novel biomarkers and VCTE against standard care where standard care includes history, physical examination, liver 'function' tests [LFTs] and an ultrasound scan. The sensitivity and specificity of each approach is pre-defined and parameterises models that calculate the health gain for patients correctly categorised with liver disease and offsets this against the cost of the different testing approaches by calculating an incremental cost-effectiveness ratio [ICER].[34,36] Most recently, Forlano et al. modelled the ICER for screening in patients with T2DM. The model was parameterised using cross-sectional data from a cohort of patients with T2DM living in London [UK] that were all tested for liver cirrhosis using with FIB-4, ELF™, VCTE and in 19/249 cases,

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liver biopsy. The costs and outcomes associated with testing this cohort were compared to a usual care [primary care diagnosis] that was less accurate. In the base case analysis the ICER was well below NICE cost-effectiveness thresholds with the additional costs of testing being offset by the gain from an accurate early diagnosis.

However, there are challenges with extrapolating prior models to a real-world intervention such as the NHSE pilot that aims to test a broader range of adults with T2DM for liver disease as part of routine care. Firstly, we don't know the characteristics of patients who will respond to an invitation from primary care for liver assessment. These characteristics are important - it is likely that patient age and comorbidities will influence their probability of having liver disease and their personal gain from an early diagnosis. Secondly, we don't know what proportion of this cohort meet clinical criteria for interventions that convey the advantage of early diagnosis, e.g. what proportion enter an HCC surveillance pathway and what proportion have CSPH and are started on beta blockers. Thirdly, we don't know the real-world performance of standard care in the UK. Most patients with T2DM do not get tested for liver disease, despite their heightened risk because they are not assessed for the additional risk factors that are needed to qualify for testing. For example, LFTs are not part of an annual diabetes check up in the UK and may or may not be measured when patients are considered for statin treatment; liver ultrasound is not a routine test, and alcohol consumption is not accurately or consistently assessed in primary care. Finally, previous economic evaluations are outdated as they use primary care-based assessments [e.g. history and examination] that do not incorporate tests for fibrosis [e.g. Fib-4 and VCTE]. Since the NICE NAFLD Guideline in 2016, tests for liver fibrosis are widely integrated into community diagnostic pathways for liver disease and therefore in future studies models of 'usual care' need to reflect this.

This study protocol describes a randomised controlled trial with a nested cost-effectiveness evaluation. The study aims to compare the number of participants referred for HCC surveillance between an intervention where patients with T2DM are universally offered screening for liver disease against usual care.

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Method and analysis

The trial is described in accordance with the SPIRIT checklist.[37] The design will be an unblinded randomised controlled trial with a nested cost-effectiveness evaluation comparing the offer of screening to all patients with T2DM for liver disease against standard care. We will proceed straight to an effectiveness evaluation rather than conducting a formal feasibility/pilot study. We justify this approach because the components of the intervention [used in testing for liver disease in patients with standard risk factors [e.g. abnormal blood results or harmful alcohol consumption]] are widely implemented. Additionally, data such as the attrition rate from the conventional diagnostic pathway is already known [see sample size section].[38] Undertaking a randomised controlled trial in this setting is very important as this provides contemporaneous standard care arm as a counterfactual.

Primary outcome

i) The number of participants referred to secondary care with suspected liver disease within 12 months of randomisation who are subsequently referred for HCC surveillance.

As an unblinded trial it is important our primary outcome is as objective as possible and independent of the research team. In both study arms patients with high liver stiffness measurements will be referred to nearby hepatology services [with thresholds defined by local practice]. Via usual care an independent local clinician will then assess the severity of liver disease. In real-world practice this may include history, examination, no further tests or repeat VCTE, additional tests for fibrosis and in some case liver biopsy. Regardless of the clinical approach taken the primary outcome will be whether the clinician felt the disease was severe enough to warrant referral for HCC surveillance. Since the trial sites cover a variety of different regions across the south of England, this pragmatic approach is likely to closely reflect current UK practice.

Secondary outcomes

1. The test or combination of tests for liver cirrhosis with the lowest cost per case diagnosed*
2. The sub-group with the lowest cost per case diagnosed*
3. The incremental cost effectiveness ratio [ICER] of screening for liver cirrhosis in people with T2DM

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4. The number of cancer deaths avoided by screening [as per Markov modelling]
5. The number of patients diagnosed on VCTE with ≥F2 disease [defined as a liver stiffness of ≥8.2kpa][21]

*see i) for definition of a 'case'

Participants

Inclusion criteria

Any adult [≥18 years] patient with a known diagnosis of T2DM according to the primary care record in the Hampshire, Wiltshire, Dorset, and the Isle of Wight [all UK] areas will potentially be eligible to participate. Non-English speaking patients will be eligible for inclusion.

Exclusion criteria

- <18 years of age
- Evaluated for liver disease with either an ELF™ test or VCTE in the 2 years prior to the date of consent.
- A known prior clinical diagnosis of significant liver disease* due to any cause
- A known diagnosis of autoimmune hepatitis, primary biliary cholangitis, primary sclerosing cholangitis or viral hepatitis [irrespective of whether this has progressed to fibrosis or cirrhosis]

*Significant fibrosis or cirrhosis and in active hospital follow up

Setting

The study will be conducted in 16-20 Primary care practices and diabetes community care hubs in Wessex [including Hampshire, Wiltshire, the Isle of Wight and Dorset [UK]]. The setting of the study is important as it includes a range of existing community liver pathways which means the intervention is compared to a diverse representation of standard care – which are representative of diverse interpretations of the current NICE guidelines.[32]

Community hubs will be used for research data collection including VCTE and blood sampling. Primary care centres will be identified via the local Primary Care Network and the Primary Care NIHR clinical

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research network [CRN]. The number of practices we are using is justified in the later dedicated sections of the form.

Recruitment will take place from January 2024 and will be complete by April 2025. Outcome data collection will be completed by June 2026 and the cost-effectiveness analysis will be complete by the study end date - 1st September 2026.

Participant identification

Primary care centres will identify potential participants from their patient records. The research team will provide these practices with a search query to run on their patient management systems [SystmOne or EMIS] [see supplementary material and trial website [reflexstudy.org]] Flagged patients will be screened for eligibility by practice staff. The patients on the list of potential participants will be sent a text 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 [see supplementary material].

Consent & Randomisation

If a participant contacts the research team they will be sent an information sheet and given time to consider participation before providing written consent with the research team [see supplementary material]. After giving consent each participant will be randomised. 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 Biomedical research centre [BRC] team using randomisation software.[39]

Arm 1 – Screening

Participants in this arm will be referred by the research team directly for liver fibrosis assessment at a community hub. This assessment will include VCTE and venepuncture for an ELF™ test and a FIB-4 index. The result of the VCTE and any abnormalities identified in the blood tests will be managed in accordance with the local liver disease care pathway [as per the usual care arm described below]. VCTE will be performed by an experienced single operator after a minimum of a 3 hour fast and previously published criteria for a valid reading will be applied to each participant.[40]

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Arm 2 – Standard care – NICE guidelines based – T2DM + additional risk factor testing

Participants in the standard care arm will not be contacted for VCTE and following baseline data collection will have no further contact from the research team during the follow up period – outcomes will be collected remotely from the medical record [see below].

Standard care varies across the study area but is based on 2016 NICE guidance (NG49) [**Figure 1**].[32] In the 2016 NICE NAFLD guideline, the presence of T2DM does not trigger an assessment for liver disease in the absence of other specific risk factors.[32] 'Risk factors' to enter standard care vary in the study areas but broadly include: harmful alcohol consumption, an elevated ALT and a fatty liver on ultrasound examination. If risk factor thresholds are met then the usual care pathway varies further but in all areas involves VCTE with or without a biomarker for liver fibrosis [e.g. FIB-4 or ELF™] **[Figure 1]**. The variation in standard care is very important as it increases the external validity of our study by being representative of the heterogeneity across the UK.

After discussion with our PPI groups, participants included in the standard care arm will be given the opportunity to undergo VCTE and a biomarker test to assess them for liver fibrosis >12 months following randomisation [arranged at mutual convenience with the research team].

Data collection

Baseline data collection

All participants will give consent for access to their primary care records. These alongside a brief questionnaire will provide participant baseline data including demographics, medication and co-morbidities that cover the Charlson index[41] [giving an overall score for co-morbidity] and other prevalent co-morbidities in the study population **[Table 1]**.[42] Participants are not asked to complete further data collection activities during the 12 month follow up period as we want to minimise potential Hawthorne effect in our control group. We are concerned prolonged exposure to the research team could lead usual care participants to change behaviour and either seek or perhaps decline liver assessment.[43]

Primary Outcome data collection

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The primary outcome - referral to HCC surveillance following a referral with suspected liver disease from primary care will be assessed by the research team from each participant's health care records. Participants will not need to be recontacted for outcome data. For standard care participants the primary care record will be reviewed for a referral letter to secondary care or a community liver assessment service that was sent within 12months of randomisation. For both trial arms records will be reviewed for evidence [e.g. a letter from hepatology services] that the patient has been enrolled in HCC surveillance. The primary care record review will take place up to 30 months from randomisation to ensure enough time for definitive decisions regarding HCC surveillance to have been made by the clinical team.

Cost data collection

We will collect micro-costs[44] on the following components of the pathway:

- Item costs for ELF™ & FIB-4 tests and venepuncture cost
- Nursing time for: venepuncture, VCTE, results delivery and onward referral
- Cost per VCTE assessment including equipment, equipment servicing and training
- Community venue hire for liver assessment

Data management plan

Participant data will be managed according to the study data management plan which is available on the study website [reflexstudy.org]. Study data including participant identifiable data will be stored securely in accordance with ethical approvals.

Data analysis

Primary outcome

We will conduct an 'intention to diagnose' analysis for the primary outcome where all participants undergoing randomisation will be analysed within the group to which they were assigned, regardless of whether they engaged with the diagnostic process following referral within their study arm. Logistic regression will be used to compare the binary outcome between the standard care and intervention arms. Exact or penalized likelihood estimation methods will be used to avoid the small-sample bias that otherwise would be present with such small, expected outcome numbers. Loss to follow up [LTFU] and

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missing data will be managed in accordance with our LTFU management plan [see supplementary material].

Cost-effectiveness analysis

For the cost effectiveness evaluation, data from the study will be incorporated into a decision analytical model [developed in Microsoft Excel®]. These data include: the micro-costs of testing and follow up, drop-out rates from the diagnostic pathways [usual care and screening], the relative proportions of different stages of liver disease and the demographic characteristics of the cohorts.

The model will consist of a decision tree for the diagnostic process and a Markov state transition model for the long term disease process [**Figure 2].** It will estimate the quality adjusted life years [QALYs] and costs associated with liver disease. The model structure will be similar to previous models for HCC surveillance.[e.g. [34,36]] and calculate the difference in costs and QALYs between different testing approaches and no testing. Patients with characteristics based on our study population and study outcomes will enter the model. The model will have one year cycles and a lifetime horizon [i.e until the cohort age is 100 years]. Costs will be calculated using an NHS and Personal Social Services perspective. Costs and utilities for the model health states will be taken from a targeted review of the medical literature.

Our base-case analysis will closely match real-world practice. In both cohorts patients identified with liver cirrhosis and referred for HCC surveillance will enter a separate health state – named F4_SURV. Based on recently published data, participants in this health state who develop HCC will have a higher chance of cure [i.e. return to their original F4 SURV health state] and a lower chance of progression to death or transplantation.[16] Similarly, a proportion of those in F4_SURV will have a lower risk of progressing to a decompensated state that reflects the real-world number of participants who commence B blockers in accordance with recent guidelines.[45,46] Participants identified with F2 or F3 disease will enter monitoring states [F2_Mon and F3_Mon] and undergo biannual assessment for progression to F4 disease. Monitoring will stop when participants in the model reach 80 years of age.

As part of our base case analysis, we will calculate the cost-effectiveness [cost per QALY] of four testing strategies that are broadly reflective of current testing strategies in the study region and the NHSE pilot

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[described in the background]. These will be compared against 'no testing' and presented as ICERs that can then be compared between strategies.

1. Usual care
2. Reflex testing with VCTE only [i.e. everyone offered VCTE]
3. FIB-4 then VCTE for patients with FIB-4 >3.25
4. ELF™ then VCTE for patients with an ELF™ >9.5

We will conduct probabilistic sensitivity analyses where model parameters are probabilistically varied across pre-specified distributions and ranges. The results of the probabilistic sensitivity analyses will be presented as a scatter plot and a cost effectiveness acceptability curve.

Finally, we will conduct a one-way sensitivity analyses varying the input parameters in the model and scenarios around the main model assumptions. Specifically, we will test a scenario where we introduce a hypothetical anti-fibrotic agent that is given to patients in the F2_Mon and F3_Mon health states. As part of this we will conduct a threshold analysis where we will calculate ICERs for the hypothetical drug at different levels of therapeutic effectiveness. Anti-fibrotic therapy is not part of our base-case analysis as it is not currently part of usual care in England. **Figure 3** shows a Study flow chart showing how the study arms and nested cost-effectiveness evaluation are linked. The rationale for study sample size is also conveyed.

Sample Size

We will aim to recruit 320 patients into each arm of this study – 640 patients in total [**Figure 3**]. A sample of this size will enable us to address the primary outcome, with a minimum power of 80% after allowing for a very conservative 25% drop out rate from the diagnostic pathway in both arms. A more realistic drop out rate would be 5% which would give a power to test the primary outcome of >90%.

We are concerned that the conduct of our study may increase liver disease diagnosed via usual care due to Hawthorne effect on participants randomised to usual care or on primary care physicians who are more likely to request testing because they are, as a consequence of participation, more aware of liver disease.[43] Our sample size therefore also accounts for a doubling of background liver fibrosis testing in usual care. The background testing activity for liver disease in the study setting has been very important

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in calculating our samples size. We have estimated the background testing activity from what we know about the number of patients tested for liver fibrosis who have T2DM in a year and the total population of people with T2DM [Figure 3].

All sample size calculations were conducted using nQuery advisor 7.0.

Patient and public involvement

To design the trial we have worked with two PPI representatives [one as PPI lead] and two PPI groups. Our PPI group was struck by the risk of liver cancer in people with diabetes. This was not something they were previously aware of. Both groups of contributors shared the views that cancer and specifically surveillance for liver cancer should be the focus of our research. Our groups are diverse - 8 participants in total; 2 female; two non-white British; one born in eastern Europe. The PPI groups have helped develop our study recruitment strategy and our participant facing study materials. Both groups raised some concerns about the use of a control arm. They advised us to ensure liver assessment was offered to all participants at the end of the study and this has been incorporated into our study procedures.

Discussion

The application, effectiveness and cost-effectiveness of screening for liver disease in patients with T2DM has not been well studied. Despite this it is now recommended practice in some countries and subject to national clinical pilots in others. We aim to fill this knowledge gap.

The robust assessment via a RCT of a screening intervention for liver disease in T2DM with an objective primary outcome that is assessed independently of the researchers will have a significant impact. If effective the trial would provide evidence toward justifying widespread screening in an enormous, and growing proportion of the global population with a knock-reduction in liver death. If not effective, it could prevent further roll out of a massive, costly programme of work that will have significant resource implications for health service systems. Looking forward the trial will also quantify the effect size required and suitable pricing for novel anti-fibrotic therapies to meet cost-effectiveness thresholds.

A strength of the study design is the incorporation of a usual care arm that is a diverse representation of standard practice where testing for liver disease is applied to a few, selected patients with T2DM. The design therefore allows for real-world comparisons between the status quo and [via the intervention

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arm] a close representation of what a screening programme for liver disease in patients with T2DM might look like.

Ethical approval and dissemination plans

The University of Southampton is the study sponsor, ERGO II submission ID 80205. Ethical approval was granted by the West of Scotland Research Ethics Service [WoSRES] on 2nd August 2023, REC reference 23/WS/0102. Any amendments to the study protocol will require authorisation from the ethical approvers. We expect that participants will be identified with liver disease as part of this study. We will work closely with clinicians in the study areas to ensure they are referred and reviewed in line with local practice. We also have academic clinicians within the study team [RB and CB] who can support participants if the need arises.

Our PPI group will explore the use of the internet, social media and involvement of community venues [e.g., mosques, churches, gurdwaras, community centres] to reach marginalised populations and convey the study findings. Our PPI lead will aim to publish articles in local newspapers and newsletters and explore possibilities for translation. We aim to submit our findings in abstract form to the European Liver conference in January 2026 and submit to a high impact liver medicine journal later that year.

Author contributions

Ryan M Buchanan is the guarantor. RMB, CB, KM, TR, JB, KC and SH conceived and planned the study design. RMB, KC & SH designed the data analysis plan. TR and CN designed and piloted data collection templates, all authors contributed to drafting the manuscript. All authors reviewed and commented on a final draft before submission. All authors agree to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

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Competing interest statement

TR received a one-off consultancy fee from Echosens LTD in 2023. Other authors have no other conflicts of interest to declare.

Data availability statement

Search codes of primary care data that are being used to identify participants are included as an appendix. As a protocol, this article does not present collected data and therefore a data repository is not included or needed. As part of publication of the completed trial all relevant trial data will be available via a publicly accessible online repository.

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Table 1 - **Baseline participant characteristics that will collected and where the data will be collected**

Baseline demographic characteristic	Collected at recruitment	Can be collected via EMIS/SystmOne*
Age, years	✓	
Sex, male [%]	✓	
Ethnicity [white European or minority ethnic group]	✓	
Alcohol consumption [AUDIT-C score]	✓	
Measured Height [cm]		
Measured weight [kg]	✓	
Smoking status [current, ex, never]		✓
Index of multiple deprivation [IMD] [from postcode]	✓	
Duration of diabetes, [years]		✓
Medical treatment for diabetes – tablets or insulin [currently, previously, never]	✓	
Currently prescribed medications		
Antiglycaemic treatment [any]	✓	
Sulphonylurea [e.g. gliclazide]	✓	
Metformin	✓	
Insulin	✓	
GLP-1 agonist [e.g. semaglutide]	✓	
Pioglitazone	✓	
SGL2 inhibitor [e.g …flozins]	✓	
Anticoagulants [DOAC or warfarin	✓	
Antihypertensives [any]	✓	
ACE [e.g. ramipril]	✓	
ARBs [e.g. candesartan]	✓	
B-blockers [e.g. bisoprolol]	✓	
Thiazides [e.g. BTZ]	✓	
Calcium channel blockers [e.g. amlodipine]	✓	
Antidepressants	✓	
Fibrates	✓	
Statins	✓	
Co-morbidities [to calculate Charlson co-morbidity index]		
Definitive or probable previous myocardial infarction	✓	✓
Congestive heart failure [dyspnoea with response to CHF medication]	✓	✓
Peripheral vascular disease [intermittent claudication, previous by-pass grafting]	✓	✓
Any end organ damage due to T2DM	✓	✓
Moderate to severe chronic kidney disease	✓	✓
Solid tumour [non, localized, metastatic]	✓	✓
Lymphoma [either cured, in remission or active]	✓	✓
Hemiplegia	✓	✓
AIDs	✓	✓
Peptic ulcer disease	✓	✓
Connective tissue disease [e.g. SLE, rheumatoid arthritis, not osteoarthritis]	✓	✓
Additional prevalent comorbidities in patients with T2DM	✓	✓
Hypertension	✓	✓
Asthma	✓	✓
Hypothyroidism	✓	✓

*EMIS and Systm1 are primary care software programmes used throughout England

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Figure legends

Figure 1
An overview of usual care for liver disease assessment and management within primary and secondary care liver services in study areas – highlighting the complexities and subtle variations in practice.

Figure 2
Markov model structure used to calculate incremental cost-effectiveness of different testing strategies. The findings from the trial will parameterise this model. Numbers 1-4 correspond to the benefits of early detection that will be incorporated into the modelling.

Figure 3
Study flow chart showing how the study arms and nested cost-effectiveness evaluation. Rationale for study sample size is also conveyed.

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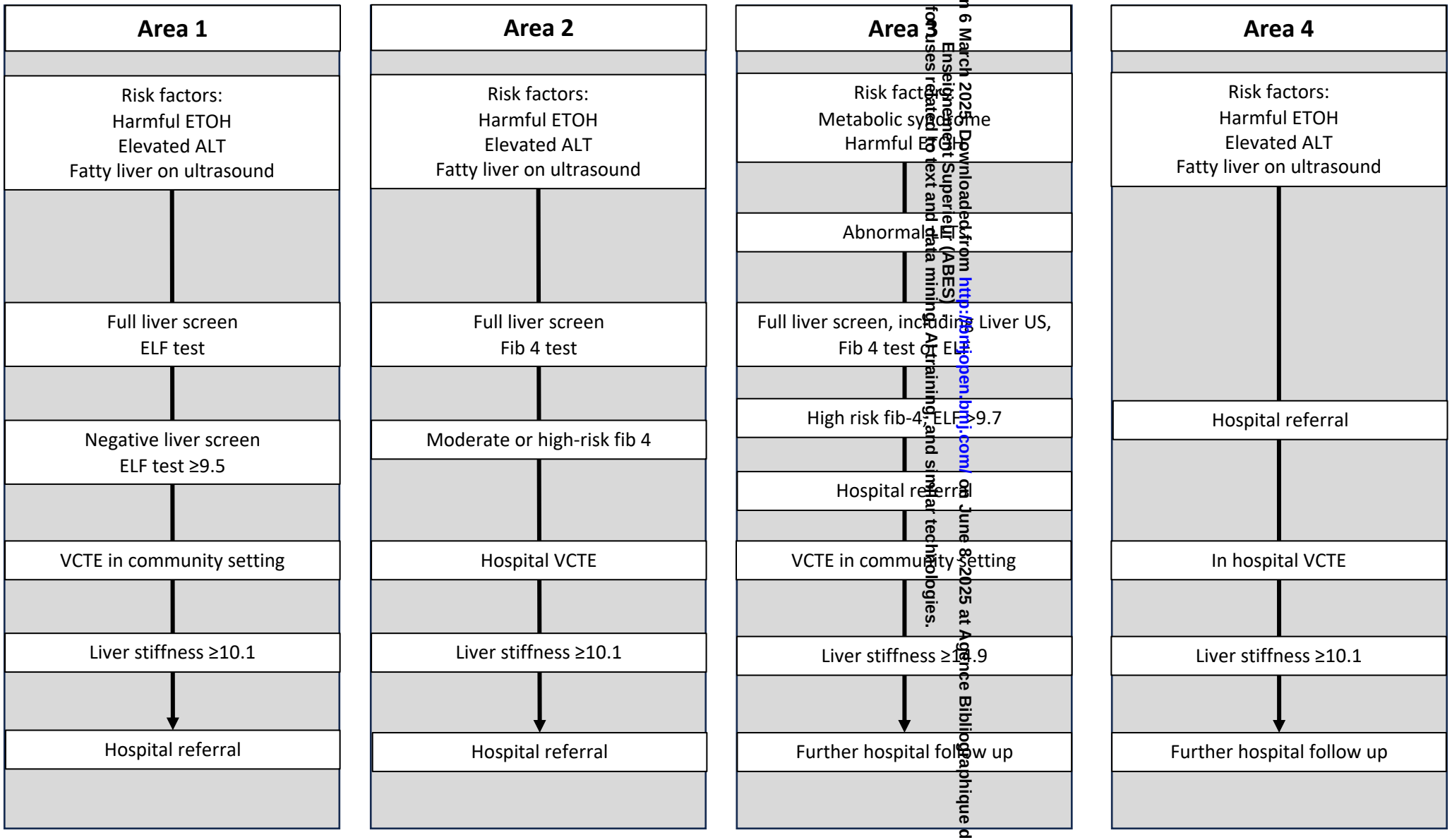

Figure 1

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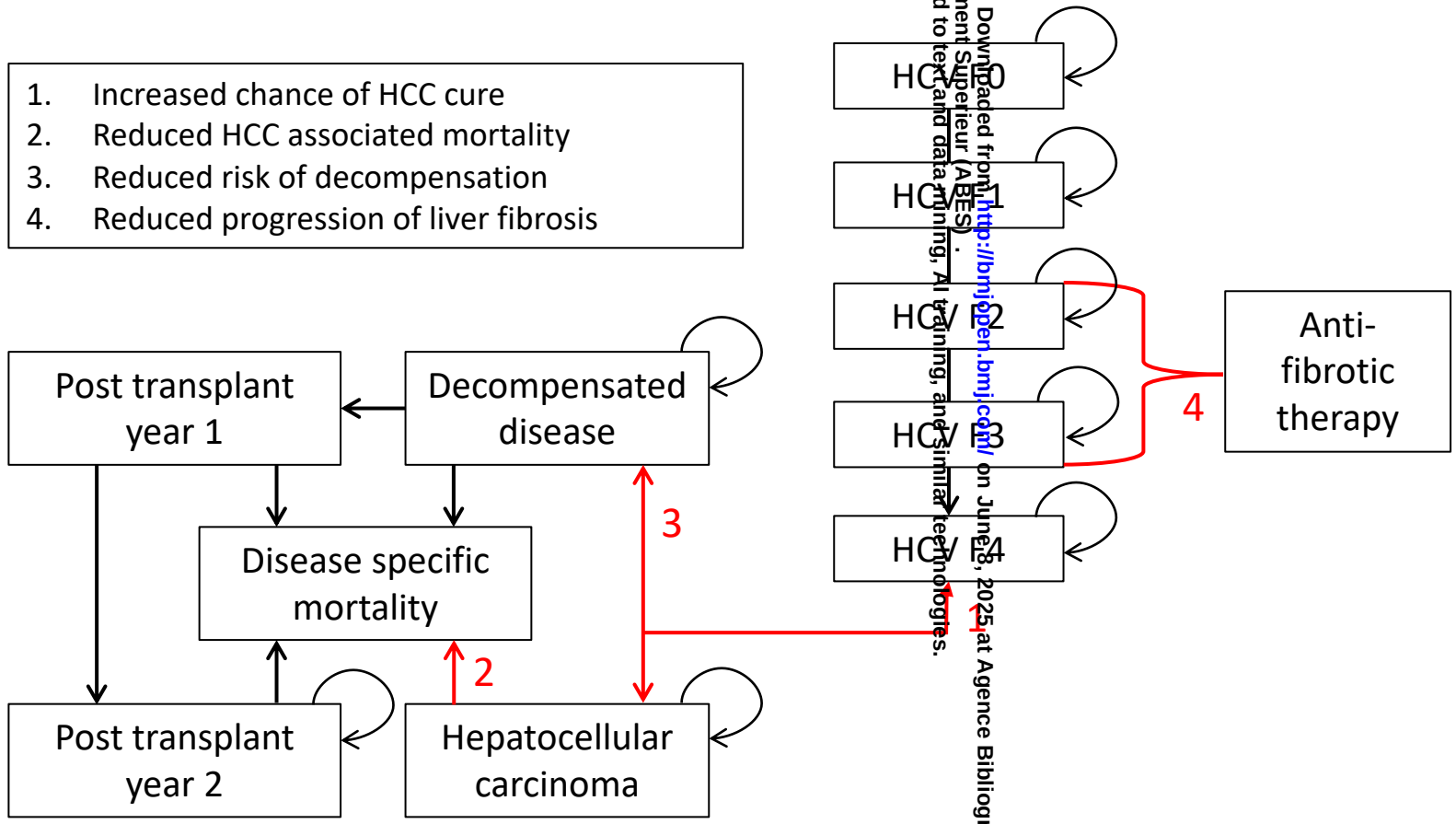

Figure 2

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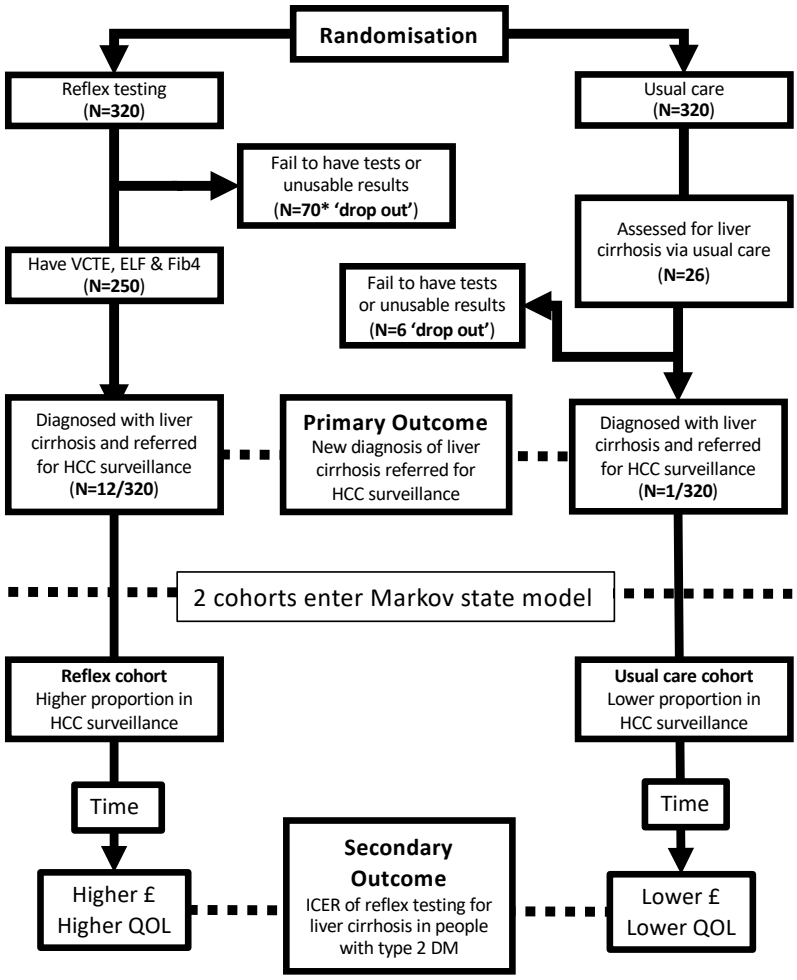

HCC – hepatocellular carcinoma, DM – diabetes mellitus, Qol – Quality of life, ICER – incremental cost effectiveness ratio, Kpa – kilopascals
*very conservative more likely to be ~34 people

Figure 3

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REFLEX Supplementary Information

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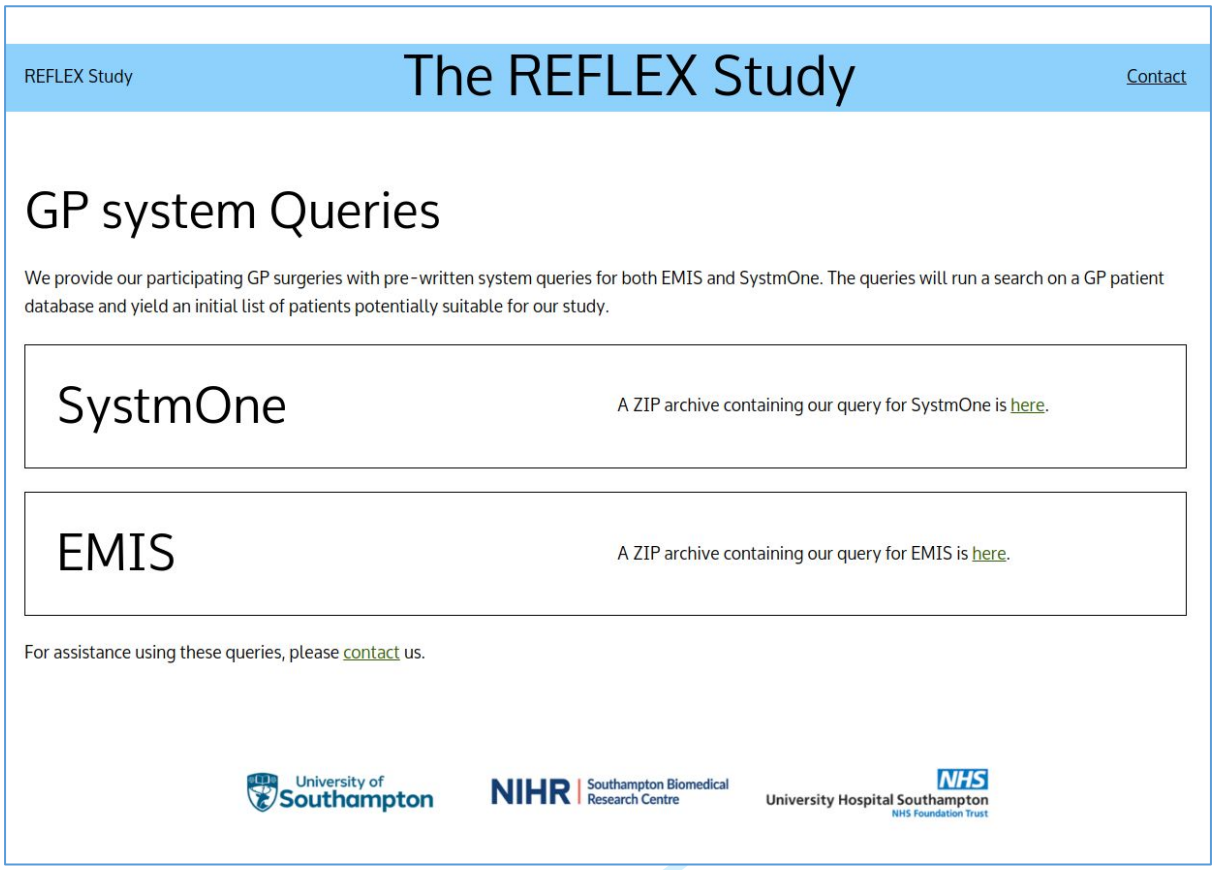
Supplementary 1 – Search Queries

https://www.reflexstudy.org/gp-system-queries/



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Supplementary 2 – EOI

https://www.reflexstudy.org/wp-content/uploads/2023/08/eoi.pdf

Appendix 5

Expressions of interest sent by participating GP practices via (a) text or (b)email/postal letters to potential participants:

(a) Text:

Dear *<insert patient name>*

<Insert name of GP surgery> has partnered with the University of Southampton to invite patients living with type 2 diabetes to take part in a study investigating liver health. Details of the study can be found at https://www.reflexstudy.org. Alternatively, you can call the research team directly on 07751 009483 / tina.reinson1@nhs.net for further information.

(b) Postal letter/email:

Dear *<insert patient name>*

<insert name of GP surgery> has partnered with the University of Southampton to invite patients living with type 2 diabetes to take part in a study investigating liver health.

We have *enclosed/attached* details about the study.

If you would like to take part in the study or have any questions, please contact the research team directly on 07751 009483 / tina.reinson1@nhs.net.

Yours sincerely

<insert name of GP surgery>

<Enc/attached>: Patient information sheet; consent form.

14 July 2023
A1_EOI_PotentialParticipants_V2.1
IRAS project ID: 326212
ERGO ID: 80205

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Supplementary 3 – Introductory Letter

https://www.reflexstudy.org/wp-content/uploads/2023/08/intro_letter.pdf

Professor Christopher Byrne
Professor of Endocrinology and Metabolism
University of Southampton
Human Development and Health Academic Unit
Faculty of Medicine
IDS, MP887
Southampton General Hospital
Tremona Road
Southampton, SO16 6YD

<insert date>

<Insert Patient name>
<Insert address>

Dear *<Insert patient name>*

Thank you for contacting the research team and requesting further information about our study that is investigating the liver health of people living with type 2 diabetes (The REFLEX Study).

Please find enclosed a patient information sheet (PIS_V3.5.1 and a consent form (ConsentForm_V3.2).

If you would like to participate or have any questions, please contact the research team on: 07751 009483 / tina.reinson1@nhs.net who will be happy to help.

Yours sincerely

Christopher Byrne
Professor of Endocrinology and Metabolism
and Chief Investigator of The REFLEX Study

Enc: Patient information Sheet
Patient Consent Form

14 July 2023
A2_EOI_IntroductoryLetter_V2.1
IRAS project ID: 326212
ERGO ID: 80205

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Supplementary 4 – Eligibility Questionnaire

https://www.reflexstudy.org/wp-content/uploads/2023/08/eligibility_qs.pdf

University of Southampton

Eligibility Questionnaire

Study title: Reflex testing for MAFLD in patients with type 2 diabetes

Chief Investigator: Professor Christopher Byrne **Participant Identification Number**: _____

Please ask each potential participant the following questions.

1. Do you have type 2 diabetes

Yes - go to question 2

No – go to statement 1.1

1.1 Thank the potential participant for their time and interest in the study and explain that they cannot take part because this study is looking to identify liver disease in participants living with type 2 diabetes.

2. Have you been diagnosed with liver cirrhosis?

Yes - go to statement 2.1

No – go to end statement

2.1 Thank the potential participant for their time and interest in the study and explain that they cannot take part because this study is looking to identify liver disease in participants who do **not** already have a diagnosis of advanced liver disease.

End statement

Thank you for answering our screening questions. You are eligible to take part in our study.

P0_EligibilityQuestionnaire_V2
26/3/2023

IRAS ID: 326212
ERGO ID 80205

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Supplementary 5 – Consent Form

https://www.reflexstudy.org/wp-content/uploads/2023/08/consent_form.pdf

University of Southampton

CONSENT FORM

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

ERGO ID: 80205 **IRAS ID:** 326212 **Chief Investigator**: Professor Christopher Byrne

Participant Identification Number*:* _____

1	I have read and understood the information sheet *<insert date /version no. of participant information sheet>* and have had the opportunity to ask questions about the study.	
2	I agree to take part in this research project and understand that I will be randomised to one of two groups. Group A or B.	
3	I consent to have a liver assessment using the FibroScan device and provide a blood sample.	
4	If randomised to Group B: (i) I understand that I will be offered my Fibroscan approximately 12 months after today (date of consent). I give permission for the research team to contact me to organise the liver assessment. (ii) I understand that the research team will need access my GP records over the next 12 months.	
5	I consent for my blood sample to be stored at the University of Southampton for the duration of this study	
5a	At the end of the study, I consent/do not consent for my left-over blood to be sent for archive storage at the Southampton Faculty of Medicine Tissue Bank (Human Tissue Authority Licence No: 12009) for use in future ethically approved health related studies.	
6	I understand that that all my details will be kept confidential, my name will not appear on any documents and I will not be directly identified in any reports of the research.	
7	I consent for the research team to access my patient records to obtain health data relevant to this study and for my data to be used for the purpose of this study .	
7a	I consent/do not consent for the research team to access my patients records to obtain health data for the next 10 years where it is relevant for research.	
8	I understand that where it is relevant to my taking part in this research, sections of my medical notes and data collected during the study may be looked at by the research team, regulatory authorities, the research sponsor or the NHS Trust. I give permission for these individuals to have access to my records.	
9	I understand that the results of my liver assessment will be overseen and monitored by clinicians at University Hospital Southampton who may need to contact me or refer me directly to liver health services that are local to me	
10	I consent for you to inform my GP of my liver assessment results.	
11	I understand my participation is voluntary and I may withdraw at any time for any reason without my participation rights, medical care or legal rights being affected.	
12	I would/would not be interested in receiving information about any future relevant liver studies (delete as appropriate). Please contact me via email/text/telephone/post (delete as appropriate) on: _____ _____	

Name of participant (print name): ..... Date: .....

Signature of participant: .....

Name of researcher (print name) ..... Date: .....

Signature of researcher .....

P1_ConsentForm_V3.2
14/07/2023
Copies to: participant; research file

IRAS ID: 326212

ERGO ID: 80205

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Supplementary 6 – Participant Initial Questionnaire

https://www.reflexstudy.org/wp-content/uploads/2023/08/initial_q.pdf

University of Southampton

Participant Initial Questionnaire

Study title: Reflex testing for MAFLD in patients with type 2 diabetes

Chief Investigator: Professor Christopher Byrne **Participant Identification Number**: _____

Date: _____ **Researcher:** _____

Date of Birth (day/month/year)	
Sex	
Ethnicity	
Current prescription medications	

AUDIT-C [1]

[1]Bush K, Kivlahan DR, et al (1998). The AUDIT alcohol consumption questions (AUDIT-C): An effective brief screening test for problem drinking. Ambulatory Care Quality Improvement Project (ACQUIP). Arch Intern Med. 158:1789-95)

How often do you have a drink containing alcohol?	Never	Monthly or less	2-4 times a month	2-3 times a week	4 or more times a week
How many standard drinks containing alcohol do you have on a typical day?	1 or 2	3 to 4	5 to 6	7 to 9	10 or more
How often do you have six or more drinks on one occasion?	Daily or almost daily	Weekly	Monthly	Less than monthly	Never
AUDIT-C score					
Venesection performed?	Yes / No				
Location and number of attempts					
Blood samples obtained?	Yes / No				
Refer patient elsewhere for venesection	Yes / No If yes, remember to provide patient with labels for test tubes				

Liver Assessment

Has the patient fasted? Y/N	Date:	Probe size: XL / M

P2_ParticipantInitialQuestionnaire_V1.1
13/7/2023

IRAS ID: 326212
ERGO ID 80205

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University of Southampton

VCTE reading (kPa):	IQR/MED:	CAP (Db/m^2):
Patient advised of VCTE assessment? Y/N		
Additional information		

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Supplementary 7 – PIS

https://www.reflexstudy.org/wp-content/uploads/2023/08/pis.pdf

University of Southampton

Participant Information Sheet

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

Chief Investigator: Professor Christopher Byrne

ERGO ID: 80205 **IRAS ID:** 326212

You are being invited to take part in the above research study. To help you decide whether or not you would like to take part, it is important that you understand why the research is being done and what it will involve. Please read the information below carefully and ask questions if anything is not clear or you would like more information before you make your decision. You may like to discuss it with others but it is up to you to decide whether or not to take part. If you are happy to participate you will be asked to sign a consent form.

What is the research about?

Research, including our work, has shown that 15% of people living with type 2 diabetes are at risk of long-term complications to their health, including liver problems. However, we do not know what is the right way to monitor people living with type 2 diabetes for liver problems.

The aim of our study is to test a new way of identifying liver disease in people living with type 2 diabetes to see if it better than what we are currently doing.

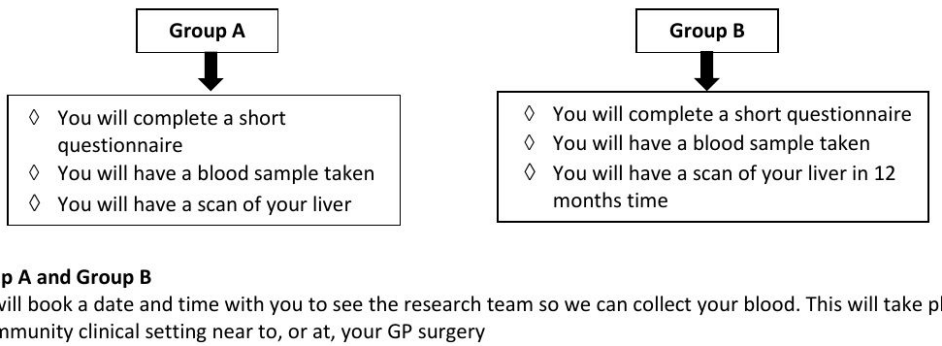
EchoSens, France, is funding this research. The University of Southampton is the study sponsor.

Why have I been asked to participate?

You have been asked to participate because you have type 2 diabetes. We are aiming to recruit 640 patients living with type 2 diabetes to the study.

What will happen to me if I take part?

You will be randomly put into one of two groups. The diagram below shows what will happen depending on which group you are put in.



Group A and Group B

We will book a date and time with you to see the research team so we can collect your blood. This will take place in a community clinical setting near to, or at, your GP surgery

Liver Scan

Group A will have their liver scanned directly following blood collection. Group B will be contacted in 12 months time to book their liver scan. The appointment will last approximately 20-30 minutes.

PIS_V3.5.1
14 July 2023

ERGO ID: 80205
IRAS Project ID: 326212

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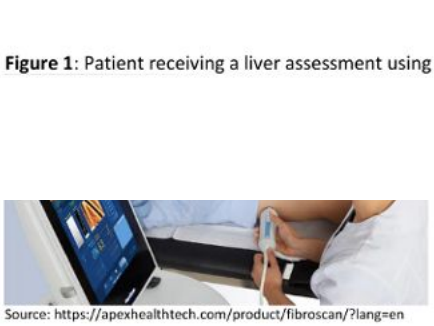
Figure 1: Patient receiving a liver assessment using the FibroScan machine



Source: https://apexhealthtech.com/product/fibroscan/?lang=en

he FibroScan uses ultrasound technology to measure the peed at which a sound wave returns from your liver. You ill need to lie down on your back and raise your right arm so that the FibroScan probe can be placed in a gap between your ribs (**Figure 1**). This scan doesn't break the skin, is painless and takes about 10 minutes.

Group B

We need to see what happens to you over the next 12 months. To do this we will need to access the results of any standard care tests you have had done within the 12 month period.

Your liver assessment results

The results of your FibroScan assessment and blood test scores will all be reviewed by the clinical team at University Hospital Southampton (UHS). Any additional tests will be organised by the clinical team at UHS who will contact you to discuss these. We will notify you of your liver assessment results and convey this information to your GP.

After your liver assessment there is no further follow up from the research team. However, if you have any questions at any time, please contact the study team on: *< insert contact details>.*

Are there any benefits in my taking part?

During the study all participants will have the opportunity to have their liver health assessed by blood tests and a scan. More broadly the information we get from the study will help us understand how best to monitor people with type 2 diabetes for complications to their health.

We would also like to offer you with a £15 voucher for taking the time to participate in our study.

Are there any risks involved?

The FibroScan assessment is a painless noninvasive procedure. Collecting blood involves using a needle stick which may hurt a bit – like a usual blood test. There is a small risk of bruising, a rare risk of infection, and you may feel lightheaded.

If you have any questions before or after your participation, then please contact the research team. See below for contact information.

What data will be collected?

The personal data we would like to collect includes: name, contact details (including email, home address, phone numbers), sex, ethnicity, NHS number, hospital number, date of birth, height, weight, alcohol consumption, and any current prescription medications you may be taking. We would also like to have access to your medical records.

Your blood sample will be sent to University Hospital Southampton for analysis. We will analyse your blood using two tests that are commonly used to assess liver health: the enhanced liver fibrosis (ELF™) test and Fibrosis-4 (FIB-4) test. We will archive your blood to use at a later date for measurement of cardio metabolic risks (e.g. cholesterol levels) and factors that are known to modify the severity of liver disease. Your blood will not be labelled with any identifiable data. For the duration of this study we will store your blood at the University of Southampton in -80'C freezers on Level A, in the Institute of Developmental Sciences (IDS) building.

On all the materials we collect from you we will put a unique number. This number will be used, instead of your name, to identify any data relating to you. Your data will be entered in to a password protected study database by

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a member of the research team. The study database will be stored on a secure server at the University of Southampton. There will be no identifying information stored with the research data we collect, this will be stored on a separate database and only the study principal investigator, or nominated representative, will have the key to unlocking and identifying patients.

Future research
At the end of the study, your blood will be sent for archive storage at the Southampton Faculty of Medicine Tissue Bank (Human Tissue Authority Licence No: 12009) for use in future ethically approved health related studies. Only non-identifiable samples will be shared with other researchers for future use.

As part of this study we want to better understand the progression of liver disease, so that the time span between liver assessments is optimal. However, liver disease develops slowly over many years, therefore we would like to remotely track any relevant changes to your health and continue to build our database of valuable liver disease information. We will therefore link your unique number onto an anonymised dataset and obtain any relevant information from NHS digital over the next 10 years regarding changes to your health. To do this we will need to share your name, date of birth and NHS number with NHS digital.

If you consent to be contacted for future studies, then we will keep your contact details separate from the study database and store them on the secure server at the University of Southampton.

Will my participation be confidential?
Your participation and the information we collect about you during the course of the research will be kept strictly confidential. Only the research team will have access to the research data. The study will be overseen and monitored by the University of Southampton, where the study Chief Investigator Christopher Byrne is Professor of Endocrinology & Metabolism.

Only members of the research team and responsible members of the University of Southampton may be given access to data about you for monitoring purposes and/or to carry out an audit of the study to ensure that the research is complying with applicable regulations. Individuals from regulatory authorities (people who check that we are carrying out the study correctly) may require access to your data. All of these people have a duty to keep your information, as a research participant, strictly confidential.

Do I have to take part?
No, it is entirely up to you to decide whether or not to take part. If you decide you want to take part, you will need to sign a consent form *<insert date and version number>* to show you have agreed to take part.

What happens if I change my mind?
You have the right to change your mind and withdraw at any time without giving a reason and without your participant rights or routine care being affected.

If you wish to withdraw from the study, please contact the research team *<insert contact details>.*

If you withdraw from the study, we will keep the information about you that we have already obtained for the purposes of achieving the objectives of the study only.

What will happen to the results of the research?
Your personal details will remain strictly confidential. Research findings made available in any reports or publications will not include information that can directly identify you without your specific consent.

The results of this study will be published. All participant details will remain strictly confidential and no patient identifiable information will be used.

Where can I get more information?
You can contact the research team on *<insert research team contact details>.*

PIS_V3.5.1
14 July 2023

ERGO ID: 80205
IRAS Project ID: 326212

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The British Liver Trust and Diabetes UK have plenty of useful information. You can speak directly to a liver nurse on: 0800 652 7330 or go to their website: www.britishlivertrust.org.uk. Contact details for Diabetes UK: 0345 123 2399 / www.diabetes.co.uk

What happens if there is a problem?

If you have a concern about any aspect of this study, you should speak to the researchers who will do their best to answer your questions.

If you remain unhappy or have a complaint about any aspect of this study, please contact the University of Southampton Research Integrity and Governance Manager (023 8059 5058, rgoinfo@soton.ac.uk).

Data Protection Privacy Notice

The University of Southampton conducts research to the highest standards of research integrity. As a publicly-funded organisation, the University has to ensure that it is in the public interest when we use personally-identifiable information about people who have agreed to take part in research. This means that when you agree to take part in a research study, we will use information about you in the ways needed, and for the purposes specified, to conduct and complete the research project. Under data protection law, 'Personal data' means any information that relates to and is capable of identifying a living individual. The University's data protection policy governing the use of personal data by the University can be found on its website (https://www.southampton.ac.uk/legalservices/what-we-do/data-protection-and-foi.page).

This Participant Information Sheet tells you what data will be collected for this project and whether this includes any personal data. Please ask the research team if you have any questions or are unclear what data is being collected about you.

Our privacy notice for research participants provides more information on how the University of Southampton collects and uses your personal data when you take part in one of our research projects and can be found at http://www.southampton.ac.uk/assets/sharepoint/intranet/ls/Public/Research%20and%20Integrity%20Privacy%20Notice/Privacy%20Notice%20for%20Research%20Participants.pdf

Any personal data we collect in this study will be used only for the purposes of carrying out our research and will be handled according to the University's policies in line with data protection law. If any personal data is used from which you can be identified directly, it will not be disclosed to anyone else without your consent unless the University of Southampton is required by law to disclose it.

Data protection law requires us to have a valid legal reason ('lawful basis') to process and use your Personal data. The lawful basis for processing personal information in this research study is for the performance of a task carried out in the public interest. Personal data collected for research will not be used for any other purpose.

For the purposes of data protection law, the University of Southampton is the 'Data Controller' for this study, which means that we are responsible for looking after your information and using it properly. The University of Southampton will keep identifiable information about you for 10 years after the study has finished after which time any link between you and your information will be removed.

To safeguard your rights, we will use the minimum personal data necessary to achieve our research study objectives. Your data protection rights – such as to access, change, or transfer such information - may be limited, however, in order for the research output to be reliable and accurate. The University will not do anything with your personal data that you would not reasonably expect.

If you have any questions about how your personal data is used, or wish to exercise any of your rights, please consult the University's data protection webpage (https://www.southampton.ac.uk/legalservices/what-we-do/data-protection-and-foi.page) where you can make a request using our online form. If you need further assistance, please contact the University's Data Protection Officer (data.protection@soton.ac.uk).

Thank you for taking the time to read this information sheet and considering taking part in the research.

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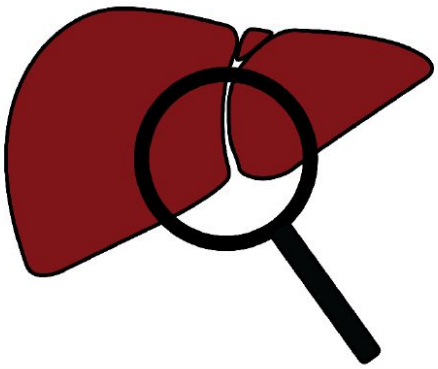
Supplementary 8 – Poster

https://www.reflexstudy.org/wp-content/uploads/2023/08/poster.pdf

Participants needed

REFLEX is a study investigating liver health in people living with type 2 diabetes



Who do we need?

People living with type 2 diabetes, 18 years +

What's involved?

A single 20-30 appointment where we will collect a blood sample and assess the health of your liver with a machine that uses ultrasound based technology.

Contact for more information

CONTACT REFLEX

☎ 07751 009483

✉ Tina.reinson1@nhs.net

REFLEX STUDY

ERGO II ID: 80205
IRAS ID: 326212
Poster_V2.2_14/07/2023

University of Southampton

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Supplementary 9 – Summary PIS

https://www.reflexstudy.org/wp-content/uploads/2023/08/summary_pis.pdf

Participants needed

REFLEX is a study investigating liver health in people living with type 2 diabetes

Who do we need?

People living with type 2 diabetes, 18 years +

Research, including our work, has shown that 15% of people living with type 2 diabetes are at risk of long-term complication to their health, including liver problems. However, we do not know what is the right way to monitor people living with type 2 diabetes for liver problems.

What will happen to me if I take part?

You will be randomly put into one of two groups. Both groups will complete a short questionnaire and have a blood sample taken. Group A will have a scan of their liver straight away, Group B will have a scan of their liver in 12 months time. The appointments will take place in a community clinical setting near to, or at, your GP surgery. The appointment will between 20 and 30 minutes.

Figure 1: Patient receiving a liver assessment using the FibroScan machine

Source: https://apexhealthtech.com/product/fibroscan/?lang=en

The FibroScan uses ultrasound technology to measure the speed at which a sound wave returns from your liver. You will need to lie down on your back and raise your right arm so that the FibroScan probe can be placed in a gap between your ribs (**Figure 1**). This procedure is non-invasive, painless and takes about 10 minutes.

Are there any benefits in my taking part?

During the study all participants will have the opportunity to have their liver health assessed by blood tests and a scan. More broadly the information we get from the study will help us understand how best to monitor people with type 2 diabetes for complications to their health.

Are there any risks involved?

The FibroScan assessment is a painless noninvasive procedure. Collecting blood involves using a needle stick which may hurt a bit – like a usual blood test. There is a small risk of bruising, a rare risk of infection, and you may feel lightheaded.

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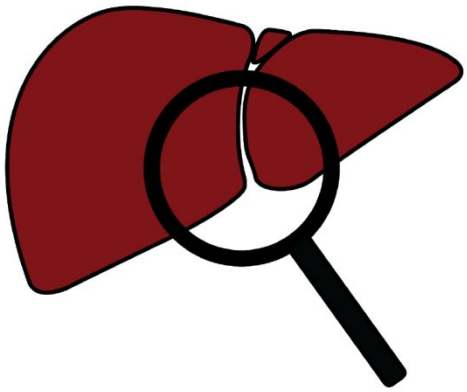
Supplementary 10 – TV Feed

https://www.reflexstudy.org/wp-content/uploads/2023/08/TV_feed.pdf

We have partnered with the University of Southampton on The REFLEX Study that is investigating the liver health of people living with type 2 diabetes

University of Southampton

REFLEX_PowerPointPresentionV2.2
13 July 2023; ERGO ID 80205; IRAS ID 326212



We do not know the most effective way to assess patients for complications of type 2 diabetes

REFLEX_PowerPointPresentionV2.2

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If you are living with type 2 diabetes and over the age of 18 years you may be eligible to take part in our study

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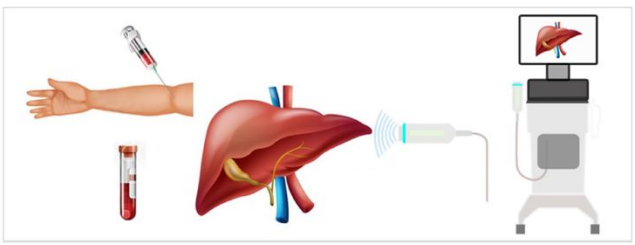
REFLEX_PowerPointPresentionV2.2

Our study involves one single 20-30 minute appointment
In this time we will:

- Collect a blood sample
- Assess the health of your liver with a machine that uses ultrasound technology



Source: https://www.internationaldrugmart.com/blog/liver-function-test/

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If you would like further information about The REFLEX Study please contact the research team on:

07751 009483

Tina.reinson1@nhs.net

Or visit the study website:

REFLEXstudy.org

University of Southampton

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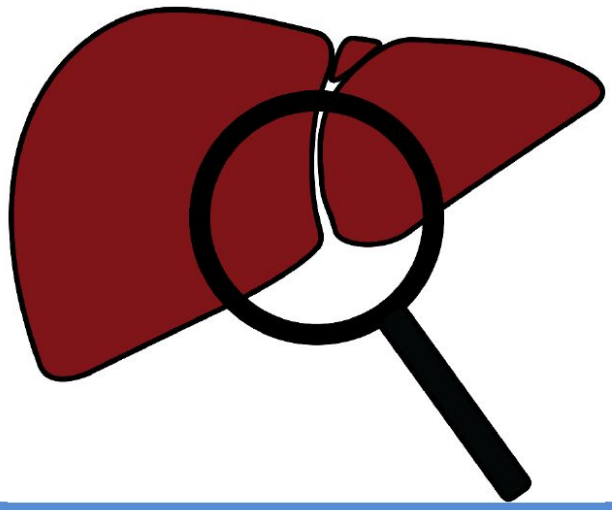
Supplementary 11 – GP Website

https://www.reflexstudy.org/wp-content/uploads/2023/08/gp_website.pdf

We have partnered with the University of Southampton on a study investigating liver disease in people living with type 2 diabetes – The REFLEX study



What's involved?

A single 20-30 minute appointment where we will collect a blood sample and assess the health of your liver with a machine that uses ultrasound based technology.

Contact for more information

REFLEX STUDY

Further information can be found at:

https://www.reflexstudy.org

07751 009483

tina.reinson1@nhs.net

CONTACT REFLEX

REFLEX_PracticeWebsite_V3.2
14/07/2023
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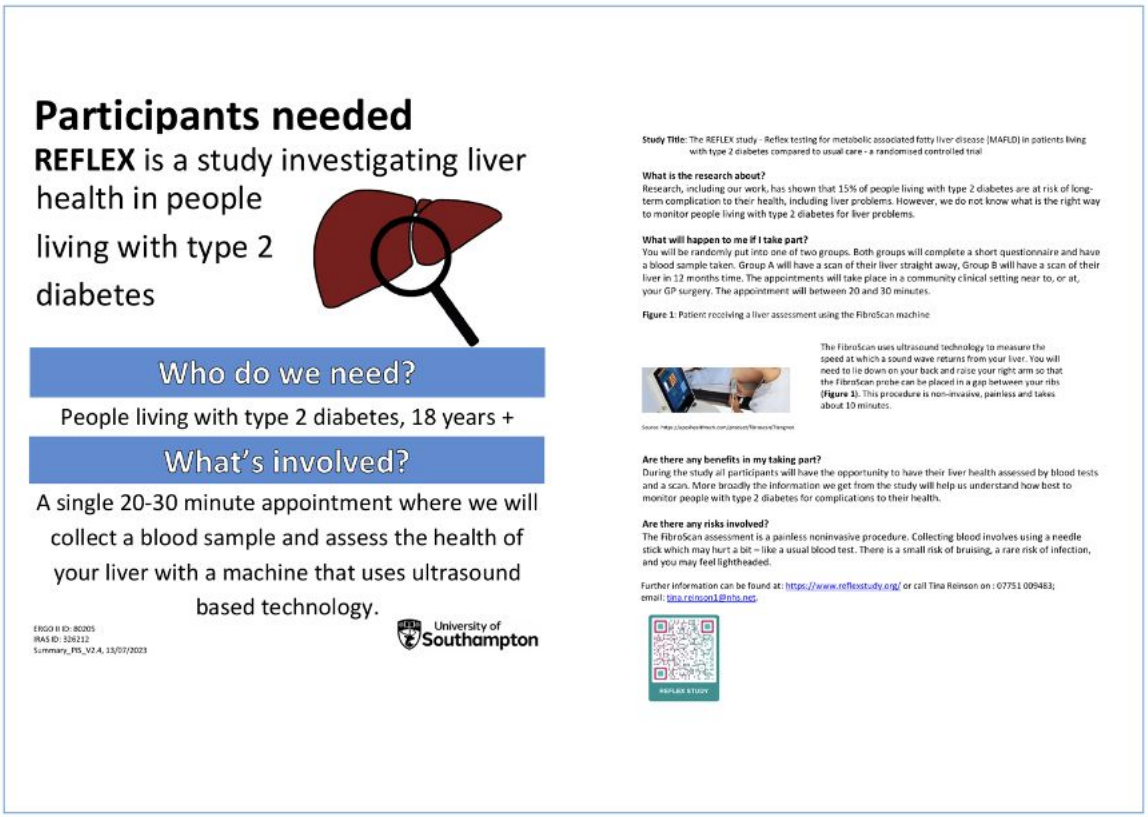
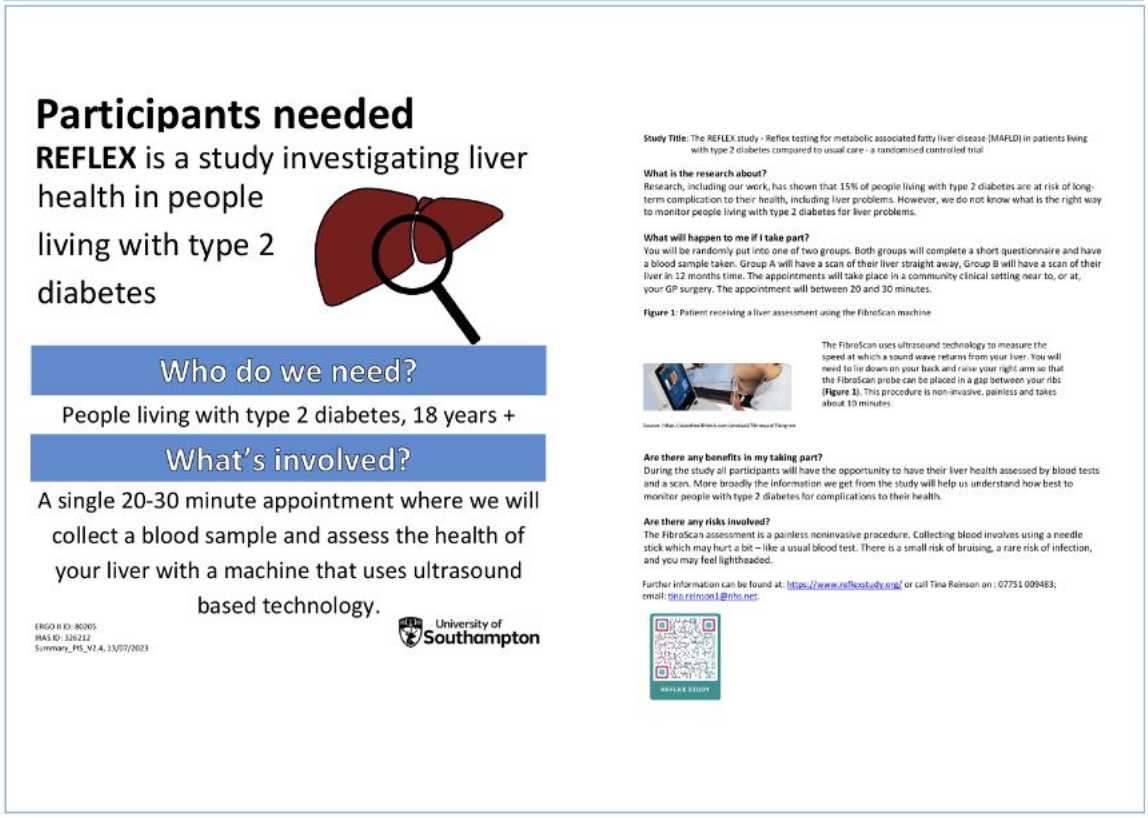
Supplementary 12 – Flyer





https://www.reflexstudy.org/wp-content/uploads/2023/08/Appendix_3_SummaryPIS_V2.4_double_page.pdf

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Supplementary 13 – Patient Letter

https://www.reflexstudy.org/wp-content/uploads/2023/08/patient_letter.pdf

<Insert UHS logo>

University of Southampton

<insert name of clinician>
<Address>
Southampton, SO16 6YD
<email>

<insert date>

<Insert GP name>
<Insert GP address>

Dear Dr <insert GP name>

Reference patient: <insert patient name; NHS number and date of birth>

The above patient took part in the REFLEX testing for metabolic associated fatty liver disease (MAFLD) in patients with type 2 diabetes study on <insert date>.

<Insert patient name> agreed that we may inform you of their liver assessment finding:

FibroScan result: <insert liver stiffness and steatosis readings, and IQR/MED>

Table 1: Interpretation of FibroScan results

Liver stiffness reading interpretation[1]			CAP (controlled attenuation parameter) score interpretation[2]		
Fibroscan reading	Fibrosis stage[a]	Interpretation	CAP score	Steatosis stage	Accumulated fat in the liver
<6.0 kPa	F0	No scarring	<250 dB/m²	S0	<11%
≥6.0 kPa to 8.1 kPa	F1	Mild fibrosis	>250 dB/m² and <301 dB/m²	S1	11% and 33%
≥8.2 kPa to 9.6 kPa	F2	Moderate fibrosis	>301 dB/m² and <325 dB/m²	S2	34% and 66%
≥9.7 kPa to 13.5 kPa	F3	Severe fibrosis	>325 dB/m²	S3	>66%
≥13.6 kPa	F4	Advanced fibrosis or cirrhosis			

[a]Liver biopsy validated fibrosis stages; [1]Eddowes PJ, Sasso M, Allison M, et al. Accuracy of FibroScan Controlled Attenuation Parameter and Liver Stiffness Measurement in Assessing Steatosis and Fibrosis in Patients With Nonalcoholic Fatty Liver Disease. Gastroenterology. 2019 May;156(6):1717-1730. doi: 10.1053/j.gastro.2019.01.042; [2]PLoS One. 2014 Jun 5;9(6):e98689. doi: 10.1371/journal.pone.0098689. eCollection 2014.

Diagnosis: <insert diagnosis and interpretation>
Action: Please <insert any relevant clinical notes as advised by study clinicians at the time of assessment>

At the time of the VCTE assessment <insert patient name> was advised of <his/her/their> VCTE result.

Patient follow up has now finished.

If you have any queries, please contact the study team on: <insert telephone number and email address>

With kind regards

<Insert clinician name and position>

Cc: ***<insert patient name>***

26 March 2023
B1_PatientLetter_V2
IRAS project ID: 326212
ERGO ID: 80205

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Supplementary 14 – Missing data plan

Sensitivity Analysis Plan to Manage Loss to Follow-Up (LTFU) in REFLEX

Objective:
The purpose of this sensitivity analysis is to assess the robustness of the primary trial results to different assumptions about missing data caused by loss to follow-up (LTFU). The analysis will help determine how the outcomes would change under various scenarios related to the handling of missing data.

---

1. Overview of Loss to Follow-Up and missing data

Loss to follow-up (LTFU) can introduce bias if the participants lost to follow-up differ systematically from those who remain in the study. Sensitivity analysis will help address potential biases and provide a range of plausible outcomes based on different assumptions about missing data.

Potential scenarios where missing data may affect our study

1. A participant randomised to the intervention arm does not attend for liver assessment
2. A participant found to have a high liver stiffness does not attend for further clinical assessment and therefore the primary outcome (referral to HCC surveillance) is not assessed

2. Primary Analysis Approach

The primary analysis will use an **Intent-to-diagnose (ITD)** approach, including all randomised participants, regardless of whether they completed the study. For participants with missing outcome data due to LTFU, we will apply multiple imputation methods in the primary analysis to account for the uncertainty of missing data.

Alongside this we will present available data describing LTFU participants and compare them with participants who completed the study. This will be available as a supplementary table. The comparison will allow us to consider if LTFU was 'non-random' and how it may have influenced our conclusions.

Multiple Imputation (MI)

- **Description:** Multiple imputation will be used to impute missing values based on observed data, assuming that data are Missing at Random (MAR). Imputed datasets will be created using covariates that predict both missingness and the outcome.
- **Rationale:** MI allows us to handle uncertainty in the missing data and provides a range of plausible values, assuming the MAR assumption holds.
- **Interpretation:** Compare the results from MI with the complete case analysis. Large deviations would suggest sensitivity of the results to the MAR assumption.

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3. Sensitivity Analysis Approaches

Subsequently several sensitivity analyses will be conducted to explore the impact of LTFU on the trial's results. These will include:

a. Complete Case Analysis

- **Description:** Analyse only participants who complete the trial and for whom outcome data are available.
- **Rationale:** This represents a "best-case" scenario where LTFU is assumed to be random and does not introduce bias. However, if LTFU is not random, this could lead to biased results.
- **Interpretation:** The results from this analysis will be compared with the primary analysis (including MI for LTFU) to identify any major differences caused by the exclusion of participants lost to follow-up.

b. Worst-Case/Best-Case Imputation

- **'Worst-Case' Scenario:**
  - Assume that all participants lost to follow-up in the REFLEX group did not have the primary outcome (entry into HCC surveillance), while those in usual care did.
- **Best-Case Scenario:**
  - Assume the opposite: participants lost to follow-up in the REFLEX group were entered into HCC surveillance, while those in usual care were not.
- **Rationale:** These extreme-case analyses provide boundaries for the possible impact of missing data. If the conclusions remain similar to the primary analysis, the results are considered robust to LTFU.
- **Interpretation:** Significant changes between the worst-case/best-case scenario and the primary results would indicate that LTFU might have substantially influenced the trial's findings.

4. Assumptions and Limitations

- **Missing at Random (MAR) vs. Missing Not at Random (MNAR):** The primary analysis assumes MAR, which means that the probability of being lost to follow-up depends only on observed characteristics. The sensitivity analyses (e.g., worst-case/best-case imputation) will allow us to assess how results change if data are MNAR.
- **Limitations:** Each method has its own limitations. Complete case analysis may introduce bias if LTFU is not random, and extreme-case scenarios may not reflect realistic assumptions. However, taken together, the sensitivity analyses will provide a range of outcomes under different assumptions.

5. Reporting

Results from the sensitivity analyses will be reported alongside the primary analysis. We will summarise:

- How each analysis affects the estimated treatment effect.
- Whether the conclusions of the trial (e.g., statistical significance, effect size) change under different assumptions about LTFU.
- Any substantial differences between the sensitivity analyses and the primary analysis, highlighting potential areas of concern regarding missing data.

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7. Managing missing data in the cost-effectiveness evaluation

In our cost-effectiveness model the characteristics of the cohorts entering the model at time 0 will be based on ITD with MI for missing values. However, whether a patient in the model is engaged with HCC surveillance or other treatments will be determined by whether they engaged with liver assessment as part of the trial and usual care (if referred to hepatology services after assessment).

For example, if a participant is randomised but does not attend for liver assessment the stage of that participants liver disease will be determined by MI. But in the model (if via MI their liver stiffness is high) they will be assumed to have engaged with liver services so will not enter HCC surveillance or experience other benefits of engagement with care. Similarly, if a participant attends for liver assessment as part of the trial and has a high liver stiffness but does not engage with liver services they will not enter HCC surveillance or experience other benefits of engagement with care.

8. Conclusion

The sensitivity analysis will ensure that the trial's conclusions are robust to assumptions about missing data and LTFU. By considering multiple scenarios, the analysis will provide confidence in the validity of the results, or indicate areas where LTFU may have introduced bias. By taking these approaches we will ensure our cost-effectiveness results are cognisant with real-world levels of engagement with the liver diagnostic care cascade and doesn't make the mistake of assuming 100% engagement.

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