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Reflex testing for metabolic-associated fatty liver disease in patients with type 2 diabetes

Submission date	**Recruitment status**	[X] Prospectively registered
26/03/2023	No longer recruiting	[X] Protocol
Registration date	**Overall study status**	[_] Statistical analysis plan
26/04/2023	Ongoing	[_] Results
Last Edited	**Condition category**	[_] Individual participant data
20/08/2025	Digestive System	[_] Record updated in last year

Plain English summary of protocol

Background and study aims
Research has shown that 15% of people living with type 2 diabetes (T2DM) have liver scarring (fibrosis) equivalent to the histological grade of F2 fibrosis (called moderate liver fibrosis). A further 4% of patients living with T2DM will have severe liver fibrosis (equivalent to F3/F4 fibrosis). These people are at high risk of more severe liver disease (cirrhosis and primary liver cancer). Identifying liver fibrosis brings benefits for patients because they can make key lifestyle changes; start medications that can stop the disease from getting worse; or have regular liver surveillance to detect and treat the development of potentially fatal liver cancer. Despite this, assessment of liver disease in patients living with T2DM is not currently recommended. The aim of this study is to test a new way of identifying liver disease in people living with T2DM.

Who can participate?
Patients aged over 18 years with T2DM in the Wessex Clinical Research Network (CRN) region

What does the study involve?
The researchers will compare testing everyone with T2DM for liver disease using a blood test and non-invasive liver scan (vibration-controlled transient elastography [VCTE], also called FibroScan) against the existing care pathway where only those with another risk factor get tested.

What are the possible benefits and risks of participating?
Taking part in this study means that participants will find out how healthy their liver is. They will also help provide information which may lead to routine testing for liver disease in all patients living with type 2 diabetes.

Where is the study run from?
University of Southampton (UK)

When is the study starting and how long is it expected to run for?
February 2022 to August 2035

Who is funding the study?
Echosens (France)

Who is the main contact?
Dr Tina Reinson, t.reinson@soton.ac.uk

Contact information

Type(s)
Scientific

Contact name
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Additional identifiers

Integrated Research Application System (IRAS)
326212

Central Portfolio Management System (CPMS)
55453

Protocol serial number
80205

Study information

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

Acronym
REFLEX

Study objectives
The aim of this study is to test a new way of identifying liver disease in people living with type 2 diabetes (T2DM). The researchers will compare testing everyone with T2DM for liver disease using a blood test and non-invasive liver scan (vibration-controlled transient elastography (VCTE) also called FibroScan) against the existing care pathway - where only those with another risk factor get tested.

Ethics approval required
Ethics approval required

Ethics approval(s)
Approved 02/08/2023, West of Scotland REC 3 (Ground Floor Ward 11, Dykebar Hospital, Grahamston Road, Paisley, PA2 7DE, United Kingdom; +44 (0)141 314 0212; WoSREC3@ggc.scot.nhs.uk), ref: 23/WS/0102

Primary study design
Interventional

Study design
Randomized controlled trial

Study type(s)
Diagnostic, Prevention

Health condition(s) or problem(s) studied
Identifying significant liver disease in patients living with type 2 diabetes

Interventions
To ensure equal numbers of patients within each arm of the study the researchers will use block randomization with a block size of 4. Blocks will be used to ensure a balance between the participants in each arm of the study - strata will be sex, age group and alcohol consumption. This will be managed by the Southampton NIHR BRC using randomisation software.

Intervention arm: Vibration-controlled transient elastography (VCTE) assessment and blood test (for enhanced liver fibrosis test (ELF) and Fibrosis-4 score (FIB-4)

Control arm: Manage in accordance with the standard care offered at their GP practice. However, 12 months after consent to the study the researchers will invite these patients for a liver assessment as for the intervention arm.

Intervention Type
Other

Primary outcome(s)
Current primary outcome measure as of 07/02/2025:
The number of participants referred to specialist services with suspected liver disease within 12 months of randomisation who are subsequently enrolled in HCC surveillance. The clinical decision to refer for HCC surveillance is made by hospital-based specialists who are independent of the research team.

Previous primary outcome measure:
1. The number of patients diagnosed with moderate or significant liver disease within a year of randomisation (defined as ≥8.2 kPa on VCTE)
2. The number of patients with significant liver disease (defined as ≥12.1 kPa* on VCTE) and referred for HCC surveillance

Both measured using vibration-controlled transient elastography (VCTE) at the following timepoints:
Intervention arm: one time only, at the time of liver assessment, there is no additional follow-up
Control arm: 12 months after consent (via patient records, one time only)

Key secondary outcome(s)
Current secondary outcome measures as of 07/02/2025:
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 (incremental cost-effectiveness is calculated from a Markov model)
4. The number of cancer deaths avoided by screening (as per Markov modelling)
5. The number of patients diagnosed on VCTE at baseline with ≥F2 disease (liver stiffness is measured in kPa using VCTE, ≥F2 is measured as a liver stiffness of ≥8.2 kPa)

*Measured using micro-costs in pound sterling (£) of the following components of the pathway:
1. Item costs for ELF™ & FIB-4 tests and venepuncture cost
2. Nursing time for venepuncture, VCTE, results delivery and onward referral
3. Cost per VCTE assessment including equipment, equipment servicing and training
4. Community venue hire for liver assessment

Previous secondary outcome measures:
1. 'Costs per case' of moderate and significant liver disease identified via reflex testing (i.e. testing all people living with T2DM as part of their routine diabetes care) for liver disease and usual care
2. The test or combination of tests for liver fibrosis with the lowest cost per case
3. The incremental cost-effectiveness ratio (ICER) of reflex testing and HCC surveillance for liver disease in people living with T2DM

Measured using micro-costs in pound sterling (£) of the following components of the pathway:
1. Item costs for ELF™ & FIB-4 tests and venepuncture cost
2. Nursing time for venepuncture, VCTE, results delivery and onward referral
3. Cost per VCTE assessment including equipment, equipment servicing and training
4. Community venue hire for liver assessment

Analysed 12 months after the last patient is recruited to the control arm.

Completion date
31/08/2035

Eligibility

Key inclusion criteria
Current inclusion criteria as of 07/02/2025:
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.

Previous inclusion criteria:
1. >18 years of age
2. Diagnosis of type 2 diabetes
3. In the Wessex Clinical Research Network (CRN) region
4. Able to provide informed consent

Participant type(s)
Patient

Healthy volunteers allowed
No

Age group
Adult

Lower age limit
18 Years

Sex
All

Total final enrolment
640

Key exclusion criteria
Current exclusion criteria as of 07/02/2025:
1. <18 years of age
2. Evaluated for liver disease with either an ELF™ test or VCTE in the 2 years prior to the date of consent
3. A known prior clinical diagnosis of significant liver disease* due to any cause
4. 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

Previous exclusion criteria:
1. <18 years of age
2. Unable to provide informed consent
3. A known prior diagnosis of cirrhosis due to any cause

Date of first enrolment
01/09/2023

Date of final enrolment
07/10/2024

Locations

Countries of recruitment
United Kingdom

England

Study participating centre
Clinical Research Network (CRN) Wessex
Unit 7, Berrywood Business Village
Tollbar Way
Hedge End
Southampton
United Kingdom
SO30 2UN

Sponsor information

Organisation
University of Southampton

ROR
https://ror.org/01ryk1543

Funder(s)

Funder type
Industry

Funder Name
Echosens

Results and Publications

Individual participant data (IPD) sharing plan
Current IPD sharing plan as of 07/02/2025:
Search codes of primary care data that are being used to identify participants will be included as an appendix in the published protocol.** As part of publication of the completed trial all relevant trial data will be available via a publicly accessible online repository.
**(DOI for publication will follow)

Previous IPD sharing plan:
All data collected will be anonymised and it will not be publically available as raw collected data. The anonymised data will be analysed and the researchers will publish the summary analysis in the results publication.

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

IPD sharing plan summary

Stored in publicly available repository

Study outputs

Output type	Details	Date created	Date added	Peer reviewed?	Patient-facing?
Protocol article		06/03/2025	20/08/2025	Yes	No
Participant information sheet	Participant information sheet	11/11/2025	11/11/2025	No	Yes
Study website	Study website	11/11/2025	11/11/2025	No	Yes