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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	[_] Protocol
Registration date	**Overall study status**	[_] Statistical analysis plan
26/04/2023	Ongoing	[_] Results
Last Edited	**Condition category**	[_] Individual participant data
07/02/2025	Digestive System	[X] 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 2025

Who is funding the study?
Echosens (France)

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

Study website
https://www.reflexstudy.org/

Contact information

Type(s)
Scientific

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Additional identifiers

EudraCT/CTIS number

IRAS number
326212

ClinicalTrials.gov number
Nil known

Secondary identifying numbers
80205, IRAS 326212, CPMS 55453

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

Study design
Randomized controlled trial

Primary study design
Interventional

Secondary study design
Randomised controlled trial

Study setting(s)
Community, Internet/virtual, Medical and other records, Telephone, University/medical school /dental school, Other

Study type(s)
Diagnostic, Prevention

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

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 measure
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)

Secondary outcome measures
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.

Overall study start date
01/02/2022

Completion date
31/08/2025

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

Age group
Adult

Lower age limit
18 Years

Sex
Both

Target number of participants
640

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
England

United Kingdom

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

Sponsor information

Organisation
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Sponsor type
University/education

Website
http://www.southampton.ac.uk/

ROR
https://ror.org/01ryk1543

Funder(s)

Funder type
Industry

Funder Name
Echosens

Results and Publications

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

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

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

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

Intention to publish date
01/09/2026

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