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Testing for liver scarring at the diabetes annual review

Submission date
22/04/2022

Recruitment status
No longer recruiting

Registration date
27/04/2022

Overall study status
Completed

Last Edited
25/11/2024

Condition category
Digestive System

[X] Prospectively registered
[X] Protocol
[_] Statistical analysis plan
[_] Results
[_] Individual participant data
[X] Record updated in last year

Plain English summary of protocol

Background and study aims
Changes in the liver are common among people with diabetes and are mostly due to fat buildup. This condition is called non-alcoholic fatty liver disease (NAFLD) and is found in up to two-thirds of people living with type 2 diabetes (T2D). In some cases patients with NAFLD are not at particularly increased risk of developing serious liver disease, but in some patients NAFLD can take a more progressive form that involves inflammation and scarring in the liver (non-alcoholic steatohepatitis or NASH) that can progress to cirrhosis, liver failure and liver cancer. Sadly people with diabetes are at increased risk of developing NASH and scarring in the liver. Researchers want to identify people who will develop serious liver disease in the earlier stages, when something can be done to stop progression.
For most people, there are no symptoms of fatty liver, scarring or even cirrhosis until the latest stages of disease when treatment is less effective. Routine blood tests do not diagnose scarring or cirrhosis, but it is possible to calculate scores from these tests, such as the Fib-4 used in this study to accurately rule out significant disease. If Fib-4 is negative, we can be fairly confident that patients do not have significant fibrosis. If Fib-4 is positive, then patients should have further specialist investigations.
This study will focus on people in GP practices with T2D because they have an annual review that includes blood tests, to which a Fib-4 test will be added. Patients who have positive test results will be referred for a liver fibrosis scan either at their local hospital or GP practice. If Fib-4 testing in the annual review identifies more patients with fibrosis and is cost-effective, this test could be introduced across the NHS to target treatment and reduce the number of people who develop liver cancer or liver failure.

Who can participate?
Patients aged 18 years and over with type 2 diabetes who are registered at the GP practices participating in the study

What does the study involve?
Participants will not experience anything different at their annual review and blood samples will be taken in the normal way – only one blood draw is needed as normal for the annual review. Depending on the blood tests the practice does as standard, participants may not need to give any extra blood. If the Fib-4 blood test cannot exclude significant liver scarring, participants will

be told and invited to have a special scan of the liver called a Fibroscan. This is a quick test (10 minutes) that involves applying jelly to the abdomen and running a probe over the liver. It is not painful and there are no needles involved. This might take place at a local hospital or at a location in or near the GP practice.
A small number of people will be asked to take part in an optional interview and/or focus group to explore people's thoughts about liver screening alongside the diabetes annual review and the experience of being involved in this study. This interview and/or focus group would take place either in person at the GP practice, other NHS sites, or alternatively online/by telephone. This should take less than 90 minutes. The researchers wish to audio or video record this interview /focus group to record what is said. These recordings will then be destroyed after transcription to a written record. Transcription of interviews will be undertaken by the study team in an anonymised format. Afterwards the researchers may wish to contact participants to ask follow up questions based on comments from other patient interviews before completion of the study. Direct quotes from interviews may be published alongside the results of this study without any details that could identify participants.

What are the possible benefits and risks of participating?
If the results of the examinations performed in this study identify any abnormalities with the liver then participants will be referred to their local hospital liver clinic for routine clinical care.

Where is the study run from?
Barts Health NHS Trust (UK)

When is the study starting and how long is it expected to run for?
January 2020 to September 2024

Who is funding the study?
Gilead Sciences (USA)

Who is the main contact?
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Contact information

Type(s)
Scientific

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Additional identifiers

EudraCT/CTIS number
Nil known

IRAS number
299934

ClinicalTrials.gov number
Nil known

Secondary identifying numbers
CPMS 51136, IRAS 299934

Study information

Scientific Title
Feasibility and acceptability of a primary care liver fibrosis testing pathway centred on the diabetes annual review

Acronym
PRELUDE-1

Study objectives
Liver fibrosis screening using FIB-4 and Fibroscan will prove feasible in primary care as a component of the diabetes annual review.

Ethics approval required
Old ethics approval format

Ethics approval(s)
Approved 15/02/2022, East of England - Cambridge East Research Ethics Committee (The Old Chapel Royal Standard Place Nottingham NG1 6FS, UK; +44 (0)207 104 8102, +44 (0)2071048265; CambridgeEast.REC@hra.nhs.uk), ref: 21/EE/0269

Study design
Non-randomized; Both; Design type: Screening, Diagnosis, Process of Care, Management of Care, Cohort study

Primary study design
Interventional

Secondary study design
Non randomised study

Study setting(s)
Hospital

Study type(s)
Diagnostic

Participant information sheet
See trial outputs table

Health condition(s) or problem(s) studied
Liver fibrosis

Interventions
This is a prospective cohort study of automated fibrosis testing in patients with type 2 diabetes linked to a trial of hospital-based versus community-based second-tier testing. The overall strategy is to determine whether focussing on at-risk type 2 diabetes patients, without a priori recognition or suspicion of nonalcoholic fatty liver disease (NAFLD), is a feasible and acceptable approach to fibrosis testing in the community. This study takes advantage of the mature nationwide programme of annual diabetes review and the performance-based remuneration system in UK primary care.

Blood requests will be automatically generated at the review and the Fib-4 automatically calculated from these results and an action plan recommended based on the threshold of 1.3. Practices allocated to the hospital arm will send the referral to hospital as per existing local referral pathways. Practices in the community arm send electronic referrals to a dedicated NHS address and a member of the NHS care team will arrange an appointment for the patient at the community centre. Results from Fibroscans will be returned to the GP practice for coding in primary care records and clinical action.

Study procedures:
1. Practice-wide consent to take part in PRELUDE-1
2. Adoption and agreement to include Fib-4 test at diabetes annual review alongside standard biochemistry tests

3. Patients with indeterminate/high risk (Fib-4 >1.3) scores proceed to either community or hospital Fibroscan (pre-determined for each practice in this feasibility study)
4. Patients with Fibroscan >7.9 kPa referred to local hepatology services
5. Data extraction from EMIS 2021-22
6. Data extraction from EMIS 2022-23

The intervention builds on existing infrastructure and data extraction/audit tools that are already built into the routine care software packages that are in use in >90% of UK GP practices. This means that anonymised data can be extracted using Read codes (version CTV3) for "Diabetes Annual Review" or "Diabetes Type 2 Review" as the primary handle. The researchers will extract demographic and clinicopathological data to include ethnicity, social deprivation, partial postcode, medical history including alcohol consumption, medication use, blood and imaging results including liver aetiology screen. They will work with data using a remote secure server under the guidance of the the QMUL Research data access and management policy.

Cost-effectiveness
The researchers will undertake an exploratory cost-utility analysis of protocolled versus historic opportunistic testing for fibrosis in order to construct a Markov model of lifetime costs from a health and social care perspective and quality-adjusted life expectancy, considering current and potential novel drug therapies. The structure will be informed by a conceptual modelling phase, but is likely to include health states representing cirrhosis, decompensation and transplantation. The model will be parameterised following a structured literature search. Parameters on prevalence of fibrosis will be informed by the trial. The model will be probabilistic and results will be reported in the form of cost-effectiveness acceptability curves.

Identifying attitudes
The qualitative arm will comprise a semi-structured interview/focus group with primary care staff (GPs and practice nurses), and a semi-structured interview with patients taking part in the wider study. Purposive sampling across relevant key characteristics (e.g., job role, length of time in role, ethnicity, age, and gender) will be used to capture varying levels of staff clinical experience and knowledge, as well as diversity in sociodemographic factors. No sample size has been set as the target is saturation of themes. However, based on previous studies and to facilitate adequate purposive sampling, a minimum of 30 participants (15 staff and 15 patients) is a reasonable approximation. Interviews/focus groups will be scheduled to take place at the most convenient time for participants. Relevant routine departmental or practice meetings will be utilised where possible for staff focus groups to reduce burden on resources. Flexibility will be provided in cases where group participation is not possible, offering individual semi-structured interviews where preferred. Participation will involve a single session interview or focus group of approximately 60 minutes in duration.

The topic guides are devised from the study aims and from background literature on liver screening in primary care. PPI groups have also reviewed the study materials and methodologies and feedback has been incorporated accordingly. Topic guides will be used flexibly to facilitate the process of qualitative data collection, with scope for discussion of other topics that participants find salient. The staff topic guide focuses on attitudes towards non-alcoholic steatohepatitis (NASH) and liver fibrosis in diabetes, typical experiences of testing for fibrosis in primary care, and assessment guidelines. Specifically, the interviews will explore experiences of perceived advantages and disadvantages of the assessment strategy and the barriers and facilitators to implementing protocolled screening for liver fibrosis beyond the trial context. For patients, the topic guide focuses on overall experiences of taking part in the study, comprehension and impact of assessment, and knowledge of risk factors and health behaviours for NASH and fibrosis pre and post-test.

This work will inform the implementation strategy for the subsequent trial phase and help us understand why previous guidance has not resonated with the community.

Intervention Type
Other

Primary outcome measure
Proportion of individuals with type 2 diabetes with indeterminate or high-risk Fib-4 scores at the diabetes annual review

Secondary outcome measures
1. Proportion of patients referred for Fibroscan who attend in community vs hospital, measured at the end of the study
2. Exploratory cost-utility analysis of protocolled versus historic opportunistic testing for fibrosis, measured at the end of the study
3. Qualitative analysis of attitudes among primary care physicians towards NASH and liver fibrosis in diabetes, testing for fibrosis in primary care, and assessment guidelines, using structured interviews/focus groups at the end of the study
4. Proportion of individuals with indeterminate or high-risk Fib-4 who have raised fibroscan scores measured at the end of the study

Overall study start date
10/01/2020

Completion date
01/09/2024

Eligibility

Key inclusion criteria
1. General practice with >4000 registered patients
2. Practice lead, or representative, confirms agreement to participate in the study after reading the practice information sheet
3. Practice lead, or representative, confirms practice support introduction of Fib-4 testing for all patients with type 2 diabetes attending for annual review
4. Track record of >85% of patients with type 2 diabetes attending for diabetes review
5. Practice uses EMIS computer system
6. Referral route for fibroscan based on primary care non-invasive score agreed

Patient inclusion criteria:
1. Type 2 diabetes
2. Serum biochemistry sample taken alongside diabetes annual review

Participant type(s)
Patient

Age group
Adult

Sex

Both

Target number of participants
Planned Sample Size: 5300; UK Sample Size: 5300

Key exclusion criteria
1. Inclusion criteria not met
2. Practice participating in other screening or case-finding study related to liver fibrosis

Date of first enrolment
02/05/2022

Date of final enrolment
01/11/2023

Locations

Countries of recruitment
England

United Kingdom

Study participating centre
Barts Health NHS Trust
The Royal London Hospital
80 Newark Street
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E1 2ES

Study participating centre
Queen Mary University of London
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BS2 8HW

Study participating centre
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Sponsor type

University/education

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ROR
https://ror.org/026zzn846

Funder(s)

Funder type
Industry

Funder Name
Gilead Sciences

Alternative Name(s)
Gilead, Gilead Sciences, Inc.

Funding Body Type
Government organisation

Funding Body Subtype
For-profit companies (industry)

Location
United States of America

Results and Publications

Publication and dissemination plan
Planned publication of study protocol in coming months and then subsequent publication of trial data around 1 year after completion of the study in peer-reviewed journals

Intention to publish date
01/05/2025

Individual participant data (IPD) sharing plan
The data-sharing plans for the current study are unknown and will be made available at a later date

IPD sharing plan summary
Data sharing statement to be made available at a later date

Study outputs

Output type	Details	Date created	Date added	Peer reviewed?	Patient-facing?
Participant information sheet	version 1.4	11/03/2022	22/04/2022	No	Yes
Protocol article		19/05/2023	22/05/2023	Yes	No
HRA research summary			28/06/2023	No	No
Other publications	Baseline Data - conference Abstract	19/05/2023	25/11/2024	Yes	No
Other publications	aseline Data - conference Abstract	19/05/2023	25/11/2024	Yes	No
Other publications	qualitative process evaluation	13/10/2024	25/11/2024	Yes	No
Other publications	qualitative process evaluation	13/10/2024	25/11/2024	Yes	No