Feasibility and acceptability of a primary care liver fibrosis testing pathway centred on the diabetes annual review: PRELUDE1 prospective cohort study protocol

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ABSTRACT
Introduction Non-alcoholic fatty liver disease is the most common chronic liver disease worldwide affecting 20%–25% in the USA and Europe with a 60%–80% lifetime prevalence for people with type 2 diabetes (T2D). Fibrosis has repeatedly been demonstrated to be the major determinant of liver disease morbidity and mortality and there is currently no routine screening for liver fibrosis in at-risk T2D population.

Methods and analysis This 12-month prospective study of automated fibrosis testing uses the fibrosis-4 score (FIB-4) in patients with T2D linked to the investigation of hospital-based versus community-based second-tier transient elastography (TE) testing. We plan to include >5000 participants across 10 General Practitioner (GP) practices in East London and Bristol. This will determine the rate of undiagnosed significant liver fibrosis in a T2D population, the feasibility of two-tier liver fibrosis screening using FIB-4 at the diabetes annual review and subsequent TE delivered either in the community or secondary care settings. This will include an intention-to-treat analysis for all those invited to attend for diabetes annual review. A qualitative substudy regarding the acceptability of the fibrosis screening pathway will comprise semistructured interviews/focus groups with primary care staff (GPs and practice nurses), and patients taking part in the wider study.

Ethics and dissemination This study received a favourable opinion from the Cambridge East research ethics committee. The results of this study will be disseminated in peer-reviewed scientific journals, conference presentations and local diabetes lay panel meetings.

Trial registration number ISRCTN14585543.

INTRODUCTION
Non-alcoholic fatty liver disease (NAFLD) is the most common chronic liver disease worldwide affecting 20%–25% in the West\(^1\),\(^2\) and 60%–80% of people with type 2 diabetes (T2D).\(^3\)\(^4\) NAFLD is defined by excess liver fat and has a multidirectional relationship with the different elements of metabolic syndrome and comorbidities. Not all patients with NAFLD progress to advanced liver disease: approximately 1 in 6 people with NAFLD has the progressive form, non-alcoholic steatohepatitis (NASH).\(^5\) NASH is characterised by hepatocyte injury with inflammation leading to fibrosis in approximately 20% of cases.\(^6\) T2D is a key risk factor for NASH and fibrosis, and among patients with NASH, diabetes predicts end-stage liver disease\(^7\) and increases the risk of hepatocellular carcinoma threefold.\(^8\)

Evidence including systematic reviews indicates that fibrosis is the major determinant of liver disease-related outcomes and mortality.\(^9\)–\(^13\) Guidelines recommend that patients with little or no fibrosis are best managed in primary care, where the team attend to metabolic risk factors, educate and encourage lifestyle change to reduce cardiovascular risk.\(^14\)–\(^15\) Secondary care assessment and therapy can be reserved for patients with NASH/fibrosis, who may additionally benefit from specialist testing behaviour and lifestyle interventions and optimising medical therapy for associated comorbidities including T2D and cardiovascular risk factors and access to treatments including clinical trials.\(^16\)–\(^18\)
NAFLD is largely an asymptomatic disease and there are no standardised diagnostic care pathways. As a result, the prevalence of recorded NAFLD diagnoses in the primary care records of 18 million Europeans is 1.85% and not the 20%–25% expected from meta-analyses. It is not possible to identify patients on a benign versus progressive disease course from clinical assessment or serum transaminase levels alone. A liver biopsy is needed to reliably and accurately diagnose NASH and fibrosis. It is neither feasible nor desirable to biopsy everyone with NAFLD; it is invasive, costly and has associated morbidity. Non-invasive scores can be calculated from routine clinical blood results to give a proxy estimate of the risk of fibrosis in patients with a clinical diagnosis of NAFLD. Non-invasive test scores correlate with outcomes, and identify those likely to have advanced fibrosis or those in whom significant fibrosis can be excluded (low-risk scores). Most scores have high specificity with areas under receiver–operator curves for advanced fibrosis over 0.8. Fibrosis-4 (FIB-4), based on alanine transaminase (ALT), aspartate aminotransferase (AST), platelet count and age will be used in this study.

This study focuses on patients with T2D in primary care because of the risks of undiagnosed liver fibrosis in this group and the role of T2D as a risk factor for impaired quality of life, disease progression and all-cause mortality in patients with NAFLD. Joint guidance from European Societies of Liver, Diabetes and Obesity states that ‘NAFLD should be looked for’ in all patients with T2D, although existing non-invasive tests are currently not used routinely in primary care. Within The Health Improvement Network UK primary care database, only 14% of patients with a recorded diagnosis of NAFLD had the blood results needed to calculate FIB-4, but we do not know whether it is actually calculated or used to guide care. Key barriers include liver function tests providing either ALT or AST but not both unless specifically requested and awareness of NAFLD, fibrosis and its complications among primary care and diabetes clinicians is low.

This study explores a strategy to automate fibrosis assessment in patients with diabetes. We and others have assessed pathways for patients with abnormal liver tests (eg, Birmingham and Lambeth Liver Evaluation Testing Strategies [BALLETS] study) or with coded NAFLD diagnoses. The intelligent liver function test (iLFT) pathway is an elegant and innovative approach to efficiently determining the aetiology and severity of liver disease if a physician suspects liver disease. However, knowledge and awareness are reported to be limited among non-liver specialists. An Italian study of n=1527 patients with diabetes and fatty liver index-identified NAFLD has been used to estimate the change in non-invasive scores over a 3-year time period, but does not offer a solution to the problem of undiagnosed advanced fibrosis in patients with diabetes. All of these approaches depend on a priori consideration of risk factors, and knowledge of liver disease on the part of primary care physicians. Yet we know that NAFLD is under-recognised, poorly coded and that abnormal liver tests do not result in risk stratification. This problem is not unique to the UK with low rates of fibrosis testing in the Netherlands, Spain and Italy too.

In Europe, most patients with diabetes are managed by primary care teams who, in some territories, are financially incentivised to conduct a diabetes annual review of glycaemic control, complications, comorbidities and cardiovascular risk profile. These reviews are conducted by trained health professionals who follow a proforma and request a bundle of tests that are usually computer-generated, allowing the FIB-4 score to be automatically requested. The FIB-4 score is calculated in the laboratory and returned to the patient’s records in the usual results system accompanied by recommended action—to refer for TE if the score is >1.3. A recent UK pilot study used routine primary care FIB-4 testing in people with T2D (n=467) and subsequent assessment by TE in those with elevated FIB-4 results, >1.3 or >2.0 in those over 65 years of age. This pathway identified a new diagnosis of advanced liver disease in 4.5% (n=20) of the cohort, 45.5% of whom had an ALT level within the normal range and may have not been screened for hepatic fibrosis otherwise.

We have designed a multicentre study including 10 primary care sites in London and Bristol to determine whether this approach is feasible in multiple settings within the UK’s National Health Service. There is a debate about the optimal cut-off for FIB-4 in different patient populations. McPherson et al have proposed a higher cut-off for those over the age of 65, however, Boursier et al reported that a cut-off 1.3 did not significantly affect the sensitivity in the T2D population.

Therefore a universal FIB-4 cut-off of 1.3 was selected to maximise sensitivity to identify at-risk individuals to be referred for TE and strengthen the negative predictive value of the FIB-4 result. In summary, the strategy tested here is to identify patients at risk of fibrosis from among those with the clinical characteristic that most strongly predicts progressive disease and poor outcomes; T2D.

**METHODS AND ANALYSIS**

This is a 12-month prospective cohort study in which automated fibrosis testing in patients with T2D is linked to a comparison of hospital-based versus community-based second-tier testing. The study commenced in September 2022 with expected completion date of September 2024, due to the staggered activation of primary care sites. The overall strategy is to determine whether focussing on at-risk patients with T2D, regardless of a priori recognition or suspicion of NAFLD fibrosis, is a feasible and acceptable approach to fibrosis testing in the community. This study takes advantage of the established programme of annual diabetes review and the performance-based remuneration system in UK primary care and will sit alongside current routine clinical care.
Inclusion criteria
- General practice with >4000 registered patients.
- Practice lead confirms, on behalf of physicians, agreement to participate in the study after reading the practice information sheet.
- Practice lead confirms physicians support the introduction of FIB-4 testing for all patients attending for annual review.
- Track record of >85% of patients with T2D attending for diabetes review.
- Practice uses Egton Medical Information Systems (EMIS) software.
- Referral route for transient elastography based on primary care non-invasive score agreed.

Patient participant inclusion criteria
- Adults >18 years.
- T2D.

Exclusion criteria
- Inclusion criteria not met.
- Practice participating in other screening or case-finding studies related to liver fibrosis.

GP practices will be identified through the National Institute for Health and Care Research (NIHR) Clinical Research Networks. There will be practice-wide consent to take part in PRELUDE1. The study will involve all adults (≥18 years) in a practice diagnosed with T2D. We will therefore seek to inform all patients over the course of the year about the study. This will include strategically placed information posters for example, at phlebotomy stations. Patients will be sign-posted to opt-out if they wish in these various ways of communication. We will proactively explain the study to any patient groups associated with each practice as well as all staff including nurses and receptionists. A study website with educational material on the trial has been created and is freely available (https://www.prelude1.org/). Patients and healthcare professionals taking part in the qualitative aspect of the project will complete written consent.

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 appropriate Systematized Nomenclature of Medicine Clinical Terms (SNOMED) clinical terms. We will extract fully anonymised data including demographic and clinicopathological data to include ethnicity, partial postcode, medical history including alcohol consumption, medication use, blood and imaging results including liver aetiology screen.

The appropriate blood requests will be generated after selecting ‘FIB-4’ within the primary care pathology system at the annual diabetic review. The FIB-4 result is automatically calculated from these results and returned to the primary care clinician with appropriate advice. Individual platelet count, AST and ALT values will not be returned to the primary care clinician limiting additional clinical input actioning abnormal results.

A low FIB-4 result (<1.3) advises the primary care clinician to discuss lifestyle modification with repeat FIB-4 testing in 3 years if NAFLD is suspected. For an intermediate or high FIB-4 result (>1.3), the primary care clinician is prompted to refer for TE assessment themselves to be done via the PRELUDE1 pathway in the of an electronic referral to National Health Service (NHS) administrators. We will capture the proportion of individuals with elevated FIB-4 results (identified through the data capture) who are not referred for or do not attend TE. It will be predetermined for each practice whether their patients will be offered a hospital appointment or assessment at the GP practice where the study team undertake scanning with a portable Fibroscan machine. All TE operators will be hospital-based clinical or research staff and will undergo training delivered by Echosens. Results from TE will be returned to the GP practice for coding in primary care records within an EMIS template designed for the PRELUDE1 study and onward clinical action. The scanning team will refer individuals with TE ≥8kPa, uninterpretable or technically challenging elastography readings directly to Hepatology services in line with local standard operating procedures for community TE. Predicting the number of patients who will require a liver biopsy is difficult. However, a meta-analysis of non-invasive tests, including FIB-4 and TE in NAFLD, has shown that the number of individuals who could require a liver biopsy (TE ≥8kPa) could be successfully reduced from 33% to 19% by using TE cut-off of 20kPa for cirrhosis although individual clinician practice and diagnostic uncertainty will affect this rate.35

We estimate that 1065 people will be referred for TE. In this group, decision making around biopsy will depend on that result, assessment in secondary care and discussion with each individual patient. We estimate that a third will have low-risk liver stiffness, a further third will have features of advanced fibrosis or cirrhosis where biopsy is not required.35 We estimate that 50% of patients will agree to a biopsy without first waiting for a trial of lifestyle change resulting in approximately 175 biopsies performed as a direct result of this study. This equates to fewer than two a week for each secondary care hepatology service.

Liver biopsy is invasive but relatively safe. An NHS cohort study using hospital episode statistics followed outcomes of over 61 000 elective percutaneous liver biopsies. Bleeding requiring transfusion of blood products occurred in 0.65% and all-cause mortality was 0.2%.36 Patients diagnosed with significant liver fibrosis or cirrhosis after review in hepatology clinic will remain under the care of secondary care hepatology as per standard clinical care.

Patients within the study, alongside primary care staff, including doctors, nurses and allied health professionals, will be approached by researchers and consented to an additional qualitative arm that further explores the
acceptability of the FIB-4 test and TE. This will comprise a semistructured interview/focus group with primary care staff (GPs and practice nurses), and patients taking part in the wider study. Purposive sampling across relevant key characteristics (eg, job role, length of time in the 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. Interviews/focus groups will be scheduled to take place at the most convenient time for participants. Relevant routine departmental or practice meetings will be used where possible for staff focus groups to reduce the burden on resources. Flexibility will be provided in cases where group participation is not possible, offering individual semistructured interviews where preferred. Participation will involve a single-session interview or focus group of approximately 60 min in duration.

**Patient and public involvement and engagement (PPIE)**

A topic guide was devised from the study aims and from background literature on liver screening in primary care. PPIE 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 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 the 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-test and post-test.

**Estimation of sample size and power**

We require sufficient numbers of patients to detect a difference in attendance between hospital-based and community-based TE testing. In an Australian mixed primary and secondary care study, 33% of 857 patients with indeterminate or high-risk scores, accepted the invitation for hospital-based follow-up assessment.\(^7\) In order to detect a difference of 10% (which we would consider clinically meaningful) between the intervention arms with a two-sided 𝑝=0.05 and power 0.9, we will include n=494 patients in each arm: total n=988 patients with diabetes and indeterminate/high-risk FIB-4. In order to recruit sufficient participants a total of 10 GP practices will be enrolled in the study; five in London and five in Bristol.

We base this on the following assumptions:

- 8.6% of UK adults have diabetes\(^36\) of whom we expect 85% to attend the diabetes annual review. We assume an average practice size in the UK is circa 7250 patients, therefore the expected population of people in practices with T2D is 5300.

- 68% of people with T2D are expected to have NAFLD.

- In our study of 18 million European adults, 36.7% of FIB-4 scores were ‘indeterminate’ or ‘high’ risk (‘positive’ for the purposes of this study)\(^7\,\,33\) Srivastava and colleagues showed that 29.7% of adults with diagnosed NAFLD in primary care have a ‘positive’ FIB-4 score (>1.3) although we acknowledge that the current study population will include people with T2D rather than all NAFLD and so the true positive rate is likely to be higher. We estimate this to be 45%.

- We conservatively estimate that the intervention will result in two-thirds of positive FIB-4 scores being detected or n=1065 who will be invited to participate in the second phase of the study.

Qualitative arm: No sample size has been set as the target is theme saturation. 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.

To determine the primary outcome, we will express the number of patients who have indeterminate or high-risk FIB-4 scores as a proportion of those (1) all patients with a diagnostic code of T2D (equivalent to ‘intention-to-treat’) and (2) patients with a diagnostic code of T2D who attend for diabetes review (’per-protocol’). Secondary outcomes include determining (1) the proportions of patients referred for TE who attend in community versus hospital and (2) the number of patients who attend their TE appointment as a proportion of those with a positive FIB-4 result. Following testing for normality, appropriate statistical tests will be used to compare with data from the preceding 12 months. Comparative statistics will be used to assess the secondary outcomes. Two-sided significance will be determined by a p value of <0.05.

Qualitative arm: Thematic analysis will be used to code and identify recurring and salient themes that are conceptually significant. Results will also be compared across and within groups to explore any differences. A hierarchy of themes will be constructed. NVivo software will also be used to explore and graphically present themes.

The Trial Committee (quorum is 3 members of study investigators) will meet prior to recruitment, at 3 months and 6 months into recruitment and 1 year after initiation of the study. If the recruitment is below target, additional meetings will be convened. As there is no investigative intervention in this study no regular monitoring schedule will be devised. Reports of a serious adverse event will trigger discussion with the study sponsor whether a trial monitoring should be commenced. Any concerns regarding the delivery of the study highlighted at the trial committees can also instigate formal monitoring procedures by the sponsor.
REFERENCES
