LOCATE NAFLD

LOCal Assessment & Triage Evaluation of NAFLD

Study Protocol

26th October 2020

Version: 1.3

This protocol uses the 2013 Standard Protocol Items: Recommendations for Interventional Trials (SPIRIT) Checklist

AusHSI Australian Centre for Health Services Innovation

USC

The University of Queensland Australia

QIMR Berghofer Medical Research Institute

An NHMRC MRFF Keeping Australians Out of Hospital Project (GNT1175567)

Led by the Australian Centre for Health Services Innovation at Queensland University of Technology with University of the Sunshine Coast, The University of Queensland and the QIMR Berghofer Medical Research Institute

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Items from the World Health Organization Trial Registration Data Set:

Data category	Information
Primary registry and trial identifying number	Australian New Zealand Clinical Trials Registry (ANZCTR) – ACTRN12620000158965p
Date of registration in primary registry	13/02/2020
Secondary identifying numbers	Universal Trial Number: U1111-1247-1295
Source(s) of monetary or material support	National Health and Medical Research Council (NHMRC), Medical Research Future Fund Keeping Australians Out of Hospital, APP1175567
Primary sponsor	Queensland University of Technology
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Contact for scientific queries	As above
Public title	LOCal Assessment and Triage Evaluation of Non-Alcoholic Fatty Liver Disease (LOCATE-NAFLD)
Scientific title	LOCal Assessment and Triage Evaluation of Non-Alcoholic Fatty Liver Disease (LOCATE-NAFLD): a randomised trial testing a community fibrosis assessment service for patients with suspected non-alcoholic fatty liver disease
Countries of recruitment	Australia
Health condition(s) or problem(s) studied	Non-alcoholic fatty liver disease
Intervention(s)	Alternative model of care for triaging patients with NAFLD in the community
Placebo comparator	Usual care
Key inclusion and exclusion criteria	Ages eligible for study: ≥18 years Sexes eligible for study: both Accepts healthy volunteers: No Inclusion criteria:

	• Have had NAFLD diagnosed or suspected by their General Practitioner (GP), or suspicion of NAFLD by triaging hepatologist, from a GP referral letter. • Aged ≥ 18 years • Understand the consent procedures and give their full consent (See Section 11.1). Exclusion criteria: • Are pregnant. • Have advanced cardiac disease or another terminal illness. • Have high current alcohol consumption, defined as two or more standard drinks per day. • Require priority review at the Hepatology Clinic • Have Hepatitis B or C (extracted from the GP referral letter). • Have been evaluated in a specialist hepatology clinic in the previous 12 months. • Have plans to leave the area within the next 12 months.
Study type	Interventional Allocation: randomised at individual level Intervention model: pre-post change to model of care Masking: unblinded Primary purpose: prevention Phase III
Target sample size	156 (minimum)
Primary outcome(s)	Time to first diagnosis of high-risk non-alcoholic fatty liver disease
Key secondary outcomes	• Time to referral of other specialists • Time to additional screening/tests related to metabolic syndromes • Validation of results in intervention arm • Time to first successful scan • Admissions to hospital • Presentations to an emergency department • Health-related quality of life

Protocol version and changes

Version 1.2, xx-August-2020

Version	Date	Changes
1.2	21-08-2020	Added additional screening question. Removed MBS/PBS data and consent. Added additional questions to baseline and 12-month follow-up to replace MBS/PBS data.
1.3	26-10-2020	Added additional wording to inclusion criteria to allow triaging clinicians to determine eligibility into study

Contents

1. BACKGROUND

1.1 Introduction

Non-alcoholic fatty liver disease (NAFLD) is the most common type of chronic liver disease in Australia and its recent increase mirrors the obesity and type 2 diabetes epidemics (1,2). The prevalence of disease in Australia is comparable to other developed countries, impacting approximately 30% of adults (3). NAFLD-associated morbidity and mortality is expected to further burden the hospital system, particularly as obesity rates grow. The economic burden of NAFLD is also expected to increase, although few studies have reported economic outcomes. NAFLD reduces health-related quality of life, particularly for those with severe disease who have higher complication risks.

There is an unmet need for an integrated system that can provide unified, high quality care for those affected by NAFLD. Such a system would provide accurate stratification of disease risk, timely identification of those with advanced disease, and structured, evidence-based support and guidance for GPs to enable the majority of those with mild disease to be managed in the community.

We propose that a community fibrosis assessment service will provide NAFLD patients with an integrated model of care. Gathering evidence from a prospective implementation study will address critical knowledge gaps in the Australian evidence-base and enhance the likelihood that the new findings will be implemented into routine practice. The study will be conducted in Queensland, including regional areas where patients often travel long distances to receive care and hence will greatly benefit from a better planned model of care.

1.2 NAFLD

As the number of NAFLD cases increase, the health system will incur increased costs associated with its diagnosis, management and disease progression (4). It has been estimated that the annual cost of liver diseases in Australia is $51 billion, of which NAFLD accounts for a considerable share (5). Due to the ongoing epidemic of obesity the total number of patients with NAFLD is likely to increase by 50% by 2030 (6). Hence there is soon likely to be a need for improved health services for dealing with liver disease.

The large number of patients sets NAFLD apart from other liver diseases. The major initial focus of clinical care is classifying disease phase, detecting cirrhosis, and identifying those at highest risk of progressive disease (7). Most patients with NAFLD do not have advanced liver disease, but those that do have an increased rate of decompensated chronic liver disease, hepatocellular carcinoma, and death (7). The traditional gold standard in liver disease assessment is biopsy, however, biopsies have issues with costs, safety, availability, and patient experience (8,9). Non-invasive tests for fibrosis, such as transient elastography (TE) using a Fibroscan machine, have been developed which, in combination with serum-based tests, can accurately identify patients at risk of disease progression (10–12).

Currently, many patients who present to primary care with abnormal liver function tests or steatosis on liver ultrasound are referred for assessment in secondary care. Due to the large number of patients with NAFLD, this results in long waits for clinical and fibrosis assessment, placing unnecessary burden on the public hospital system. Depending on the presence of risk factors such as diabetes, 60 to 90% of patients with NAFLD do not have advanced fibrosis, are not at risk of chronic liver disease complications, and can be safely managed in primary care. At the other end of the risk scale, recent community-based studies have suggested that as many as 12 to 17% of primary care patients with NAFLD and type 2 diabetes may have clinically significant liver disease (13,14). Due to

the lack of risk stratification at primary care level coupled with poor general practitioner knowledge about NAFLD, many patients with advanced disease may not undergo timely referral into secondary care. This exposes them to the risk of disease progression, decompensation and avoidable hospital admissions (15,16).

1.3 Previous economic studies

The economic burden of NAFLD is an area that is under-researched. There has only been one economic evaluation of NAFLD that has been conducted in Australia (17). While this study was led by an Australian-based team, it used data drawn from elsewhere in the world to parameterise the model used to draw conclusions. It was also only concerned with the cost-effectiveness of a specific treatment strategy, rather than defining the economic impact of NAFLD on the wider health system and the economic benefits that could be realised by reducing avoidable admissions and keeping Australians out of hospital.

The economic burden of NAFLD will likely increase over time due to the continued increase in obesity. There are common findings in the available economic evidence – firstly, that projected costs associated with NAFLD are set to increase, with one study reporting that per capita costs would rise from 2% to 11% in five decades (18) and another noting that hepatology clinic costs are already large and are projected to rise (19). Secondly, an evidence gap clearly exists in relation to rigorous examination of the economic burden associated with NAFLD, particularly in Australia.

1.4 Model of care for hepatitis C virus infection

This study will build on the partnership formed during the study of a new model of care for another chronic liver condition, hepatitis C virus (HCV) infection. That study (title: "Regional Hepatology Partnership") conducted in 2018/2019 included Chief Investigators (CIs) O'Beirne and Brain and was funded by Queensland Health's *Integrated Care Innovation Fund*. The objective of the study was to increase access to a revolutionary Hepatitis C cure as part of the national drive to eradicate Hepatitis C.

The HCV study concerned hepatology service delivery in the Sunshine Coast and Wide Bay Hospital and Health Services (HHSs), Queensland. That hepatology partnership is a nurse led fibrosis assessment service (using a mobile Fibroscan™) that operates in eight regional settings using a hub and spoke model. It has been successful in engaging patients with HCV who live in regional areas and/or patients from marginalised groups, such as prisoners at Maryborough correctional centre.

The partnership model of care has gained traction and support with GPs and other primary care service providers. It has reduced the number of people in the community with HCV, reduced hospital utilisation, and is cost-saving, with CIs Brain and O'Beirne conducting a formal cost-effectiveness analysis. The partnership model of care has facilitated community treatment to the extent that more than 80% of HCV treatment now takes place in primary care compared. More than 600 patients have been assessed and treated in the primary care setting with a cure rate of over 95% (20). Seventy patients have been diagnosed with cirrhosis and entered surveillance programs for HCV and gastroesophageal varices, and over 1,500 appointments in secondary care have been avoided.

The HCV study included outcomes such as patient access, treatment outcomes, and value for money. An implementation evaluation framework was used and was a significant component of the evaluation of the existing service, which examined workforce satisfaction, barriers and facilitators to implementation, and factors required for scale-up. This study of NAFLD will learn from the barriers and facilitators identified by the HCV study.

2. STUDY AIMS

Aim 1: Produce evidence about the effectiveness of the model of care

The current model of care for NAFLD patients is burdensome on the health system in two ways:

1. Patients with low-risk disease are referred to hospital for specialist appointments that are conducted via outpatient clinics.
2. There is no coordinated approach for managing complications related to high-risk disease.

Better and faster assessment and stratification of patients in the community should significantly reduce referrals for hospital-based appointments. Improving surveillance of high-risk disease should result in enhanced management of complications that result in avoidable, high cost admissions such as variceal bleeding, hepatocellular carcinoma treatment, and liver transplantation.

Aim 2: Produce evidence about the long-term economic benefits for payers of services

Shifting care from the hospital to primary care will likely have a sizeable, long-term economic benefit. Decreased emergency presentations and a reduction in avoidable admissions associated with NAFLD will free capacity in an already congested public hospital system. We hypothesise that long-term, sustained economic improvements are achievable by:

- increasing detection and referral of patients with advanced liver disease and cirrhosis to hospital gastroenterology departments
- reducing the number of unnecessary referrals to these specialty outpatient clinics.

For patients and carers, the economic benefit of receiving care close to home is well established for other conditions (21). This is particularly important for Australians living outside of the major cities, where high travel costs and lost productivity are incurred both by patients and carers who need to access services far from their home.

Aim 3: Evaluate the model of care for NAFLD in the Sunshine Coast and Metro South HHSs, using implementation science methods.

We will evaluate the pathway for diagnosis and assessment of NAFLD by using the partnership model that has been successful for HCV, and applying it to patients with this complex, chronic condition. We will use a process evaluation guided by the Reach, Effectiveness, Adoption, Implementation, Maintenance (RE-AIM) framework, to identify factors that support and barriers that impede the reach, effectiveness, adoption and implementation of the service model (22). Factors that may be important for sustainability, scale-up and fidelity will also be identified.

3. OBJECTIVES

3.1 Primary objective

Our primary objective is to reduce NAFLD-associated hospital outpatient clinic utilisation.

3.2 Secondary objectives

Our secondary objectives are to:

- Build on the health services research into HCV that has shown effectiveness at a local level.
- Underpin the study with implementation science.
- Create sizeable and long-term economic improvements.
- Maintain strong partnerships between clinicians, researchers, service providers and healthcare decision-makers.

4. HYPOTHESIS

The new model of care for NALFD patients will improve patient outcomes and be cost-effective, by more appropriately triaging NALFD patients, reducing time to appropriate care, and avoiding unnecessary appointments.

5. STUDY DESIGN

5.1 Parallel randomised trial

We will conduct a 1:1 parallel randomised trial to compare two alternative models of care for NAFLD: usual care versus LOCal Assessment and Triage Evaluation (LOCATE) care. Participants will be randomised to usual care or the LOCATE model of care, and then followed for a year to monitor their outcomes.

5.2 Reasoning

A parallel randomised trial is an excellent study design for estimating the benefits of a new model of care compared with a usual model of care (which could be called a "control" group, although we will use "usual care"). By randomising participants to the LOCATE model of care, it almost certainly rules out confounding as the two groups will be comparable in their characteristics and disease severity. Randomising groups in parallel means that variables that change over time (e.g. state-wide policy changes in liver disease) cannot confound the comparison of interest, because any changes are equally experienced by both groups.

5.3 Limitations

Randomised trials sometimes do not reflect real world settings because of their inclusion and exclusion criteria (23). We aim to use as similar patient group in the trial as would be eligible for the service in real life. We do make exclusions to reduce loss to follow up in order to maximise the value of the trial.

Allocation concealment is not possible because the model of care cannot be blinded, hence participants and staff will be aware of the randomised group.

5.4 Stakeholder and consumer involvement in design

A stakeholder reference group will be established for the study in February 2020. This group will include GPs, consumer, and patient representatives, who will be invited to review the study design, communication materials and education materials.

Consumer/patient representatives will also be invited to provide input on their perception of the burden and benefits of the study, to identify any things missing from the study that are important to them and to check that participant information sheets are understandable.

6. STUDY SETTING/LOCATIONS

We will recruit patients from the Sunshine Coast and Metro South HHSs. These are non-neighbouring HHSs located in the south-east of Queensland.

6.1 Metro South HHS

The Metro South HHS covers the south side of Brisbane, and the regions of Logan, Redlands and Scenic Rim. The catchment area is 3,860 square kilometres. It provides healthcare to more than one million people, which is 23% of Queensland's population. The key health facilities are Beaudesert

Hospital, Logan Hospital, Princess Alexandra Hospital, Queen Elizabeth II Jubilee Hospital, and Redlands Hospital.

6.2 Sunshine Coast HHS

The Sunshine Coast HHS contains the three local government areas of Sunshine Coast, Gympie and Noosa. The catchment area is 10,020 square kilometres. The resident population is 407,600, which is 8% of Queensland's population. The key health facilities are Sunshine Coast University Hospital (tertiary hospital), Nambour General Hospital, Gympie hospital, Glenbrook Residential Aged Care Facility, Caloundra Health Service, and Maleny Soldiers Memorial Hospital.

7. STUDY DURATION

The study will take three years. A timeline is shown in Figure 1 below. The study will commence once all ethical and governance approvals are in place.

We anticipate 7 months for recruitment, which is 22 participants per month (see Section 12.1 for sample size). Participants will be followed-up for one year. The data analysis can start before the final follow-up is complete. The "Publish main results" in the figure means sharing the results as a preprint (e.g., Open Science Framework, https://osf.io), as publication in a journal will almost certainly go beyond the three year study duration.

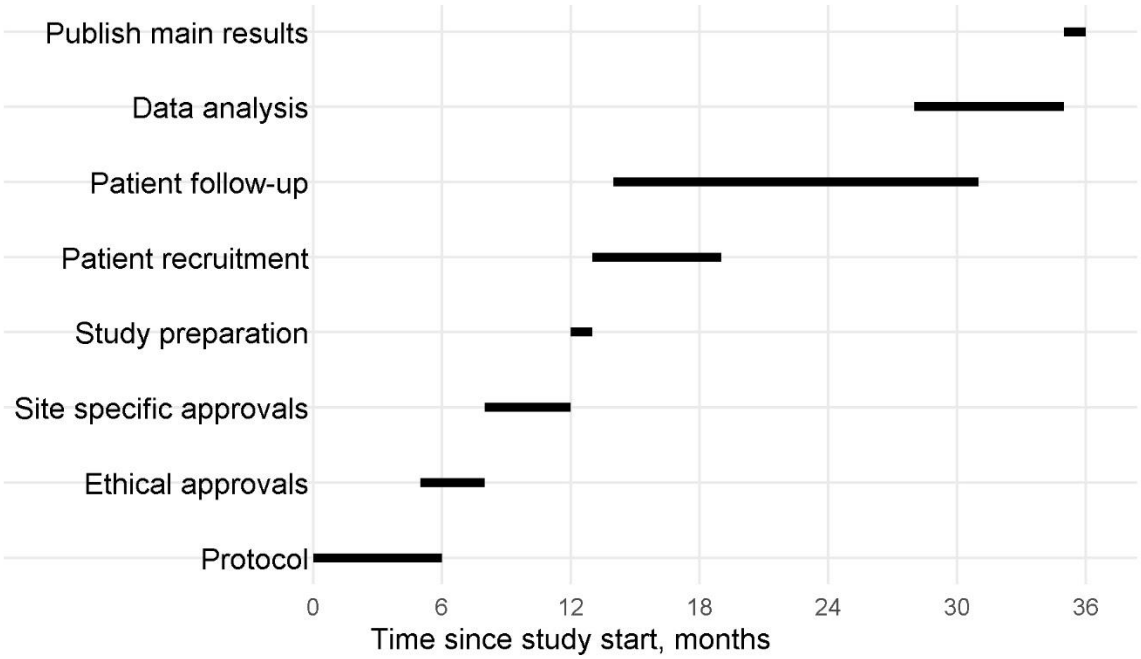

Figure 1: Planned study timeline over three years

7.1 Milestones

These milestones are designed to keep the study on track. All milestones are references to the time since receiving funding from the NHMRC.

Protocol

- Publish the protocol in an open access repository (e.g., Open Science Framework) and submit to a journal within four months. The trial will also be registered by this time with the ANZCTR.
- Create a publication plan that details the likely papers and conferences and assigns key authors within five months.

Ethical and governance approvals

- Receive ethical approval to conduct the trial from QUT and Queensland Health within eight months. Administrative ethical approval from UQ and QIMR should quickly follow these approvals.
- Complete site-specific approvals within 12 months.

Patient recruitment

- Recruit the first participant within 13 months.
- Recruit fifty percent of the target sample size (78 patients) within 16 months.
- Recruit our target sample size (156 patients) within 19 months.

Data analysis

- Complete the quantitative data analysis on effectiveness and cost-effectiveness within 35 months.

Publish main results

- Upload the key results to ANZCTR one-month after the analysis is complete.
- Report the results to Queensland Health one month after the analysis is complete.
- Submit the main paper to a journal six months after the analysis is complete.
- Share the anonymised patient-level data when the paper is published in a journal.

The project's official time is 1 June 2019 to 31 May 2022, however QUT did not receive the first payment from the National Health and Medical Research Council until September 2019.

8. STUDY POPULATION

8.1 Patient inclusion criteria

Patients will be included if they:

- Have had NAFLD diagnosed or suspected by their GP (from a GP referral letter) or suspicion of NAFLD by triaging hepatologist.
- Are aged ≥ 18 years
- Understand the consent procedures and give their full consent (See Section 13.1.2).

8.2 Patient exclusion criteria

Patients will be excluded if they:

- Are pregnant.
- Have advanced cardiac disease or another terminal illness.
- Have high current alcohol consumption, defined as two or more standard drinks per day.
- Have Hepatitis B or C (extracted from the GP referral letter).
- Require priority review at the Hepatology Clinic
- Have been evaluated in a specialist hepatology clinic in the previous 12 months.
- Have plans to leave the area within the next 12 months.

The exclusion criteria are designed to exclude patients who would be ineligible for a wider roll out of the service, who require priority care and review, and to reduce loss to follow-up. We will record the number of patients excluded and the primary reason.

8.2.1 Potential for risk, burdens and benefits to participants

There is little risk for participants as the study involves either current usual care or a modification to model of care that uses an established modality and treatment pathways.

The study will require the participants' time in order to: understand the study and consent forms, complete the study questionnaires, and (for the LOCATE model of care group) attend a Fibroscan appointment in a local clinic. The study makes extensive use of routinely collected data, which reduces the burden on participants.

Participants in the LOCATE model of care group may benefit from a faster diagnosis, as per our key study hypothesis. Participants in either group may benefit from participation because of an increased monitoring of their condition (24).

8.3 Discontinuation of whole study

The study will only be discontinued if a regulatory body, funding body, or Human Research Ethics Committee (HREC) judges it necessary for medical, safety, regulatory, or other reasons consistent with applicable laws, regulations and good clinical practice.

If the study is discontinued before the expected date of completion, we will write to each chief investigator's host institution, the NHMRC, and the HREC to inform them of the expected date of completion and the reason for the discontinuation. We will not write to participants.

9. INTERVENTION

Participant progress through the study is shown in Figure 2 (page 14).

The starting event is a patient visiting their GP. If the GP has enough concerns about the patient's liver health, they will write a referral letter requesting a specialist hepatology clinic review/appointment. They may also request blood tests or have already performed those tests.

Referral letters will be screened by a hepatologist at the Sunshine Coast University Hospital and Logan Hospital hepatology clinics to identify patients eligible for the study (Section 8.1). The details of potential patients will be recorded for potential recruitment into the study (Section 11.1.1).

Randomised to LOCATE

Study participants randomised to the new model of care will be invited to attend a local clinic to have their suspected NAFLD assessed using mobile TE, using the Fibroscan machine (Section 9.1). The invitation and assessment will be made by a specialist study nurse.

At the Fibroscan assessment the nurse will remind participants that:

- the scan does not replace their existing appointment at the specialist hospital hepatology clinic, and
- depending on the outcomes of the scan, they may still attend their scheduled or yet to-be scheduled appointment at the hospital hepatology clinic, as per their original GP referral for review, and
- depending on the outcomes of the scan, they may have an earlier appointment at the hospital hepatology clinic or have a GP appointment/s before their hospital appointment

The study nurse will write a report on the results and send it to the hepatologist for triage. The patient will be triaged to low or high risk by the Hepatologist depending on the assessment of liver scarring.

LOW RISK: Participants with low Fibroscan scores (TE under 8.0 kiloPascal (kPa)) will be classified as 'Low Risk'. A letter will be sent to participants with a summary of their results and instructions on scheduling a GP appointment for review. A letter will be sent to the referring GP informing them of the results and with advice on multidisciplinary NAFLD management and guidelines for follow up (15).

Patient experience: Participants will be followed up by their GP for management of low-risk NAFLD prior to their hospital scheduled hepatology clinic appointment.

HIGH RISK: Participants with clinically significant fibrosis (TE over 8.0 kPa) will be classified as 'High Risk'. Participants will be sent a letter summarising their test results and asking them to call the hospital hepatology clinic to arrange an appointment. GPs will be sent a letter informing them of the results and proposed management.

Patient experience: Participants are offered an appointment based on their high-risk NAFLD profile and offered follow up as indicated in secondary care hepatology clinics and enrolled in Hepato Cellular Carcinoma (HCC) and variceal surveillance programs.

Randomised to usual care

For those participants randomised to usual care, their referral letters will be dealt with in the usual way, and the patients will wait to see a hepatologist at the hospital clinic as originally intended.

9.1 Fibroscan service

The Fibroscan service will enable participants to undergo reliable assessment of the degree of liver fibrosis (scarring) and to identify those with advanced fibrosis and cirrhosis who need both secondary care input and surveillance for liver cancer. The mobile fibroscan clinics will occur on a rotational basis in the two regions using the GP clinics and primary care facilities. This will make it easier for participants to keep their appointments, particularly those in rural areas.

The Fibroscan will give the following test results:

- Liver stiffness measurement (LSM), which is marker of advanced fibrosis and cirrhosis on a scale of kilopascals (kPa).
- Controlled attenuation parameter (CAP), which detects and quantifies steatosis on a scale of decibel-milliwatts (dB/m) (25).

The study nurses will be trained in the safe and reliable performance of the Fibroscan.

A scan can take between 2 to 20 minutes to perform. Scans will be scheduled in 30-minute time slots to allow for discussion time with the patient. As an example, a hospital in the Metro South Hospital and Health Service schedules 18 visits per day between 8am and 4pm. Participants who did not attend an arranged appointment will be phoned to see if they want to reschedule.

Around 7% of Fibroscans cannot be performed because a patient's BMI or weight prevents an accurate assessment. Should this occur, these participants will be scheduled for a hepatology clinic visit as per the usual model of care.

We will record the number of times the scan could not be performed and the reason why. We will also record whether the patient adhered to the 2-hour fasting rule or not and will still attempt to perform the scan on patients who did not adequately fast. We will also record where the scan was performed and how long it took.

9.1.1 Other diagnostic information

Some additional information may be collected from GP referral letters if it is available. This information, including blood tests, may be used to help in the triage and diagnosis and may include:

- Fibrosis-4 (FIB-4) score – this score uses age, aspartate aminotransferase (AST), alanine transaminase (ALT) and platelet count, and can be used for any liver disease.
- NAFLD fibrosis score which estimates amount of scarring in the liver based on several blood tests (16). It uses age, BMI, impaired fasting glucose/diabetes, AST, ALT, platelet count and albumin levels. This test is aimed at people already diagnosed with NAFLD.

Other information that may be collected from GP referral letters is: Enhanced Liver Fibrosis (ELF) test, which is a blood test examining markers of fibrosis.

If collected, this information will only be used for post-hoc analysis and it is only completed at additional cost with a private pathology service and is not currently available through Pathology Queensland or refundable on the MBS and so not be widely used.

10. TRIAL PARTICIPANT OUTCOMES

As well as the outcomes listed in this section, there will be an economic analysis (Section 11) and implementation analysis (Section 12) with additional outcomes.

10.1 Primary outcome: Time to diagnosis of high-risk NAFLD

This will be calculated based on the number of participants in each arm who receive a diagnosis of significant fibrosis (TE over 8.0 kPa), with the time measured from date of referral by a GP to a confirmed diagnosis. In the intervention arm, this diagnosis would be expected to be made following participants' Fibroscan and review by a hepatologist. In the usual care arm, it is expected this would occur after completion of the planned scan and specialist appointment, which we will follow up. It is expected that participants in the intervention arm would receive a diagnosis much faster, therefore decreasing the time between their initial referral and accessing specials care and management for their NAFLD.

10.2 Secondary outcomes

10.2.1 Referral to a specialist (other than a hepatologist)

A potential positive consequence of the intervention is that patients manage their disease better, through a more holistic, multidisciplinary care plan. A sign of this would be a referral to a specialist other than a hepatologist, for example a dietician or psychologist. We will examine this using self-report data from the patient questionnaire at 12 months.

10.2.2 Validation of results in intervention arm

Participants in the intervention arm will receive additional screening for their NAFLD in the form of the earlier Fibroscan. These participants will also attend their planned hospital hepatology appointment after the scan. The results of this planned appointment will provide an opportunity to review the assessment based on the earlier Fibroscan. We will examine the agreement of the assessments of the Fibroscan and later appointment using a categorial triage variable.

10.2.3 Time to first successful fibrosis assessment with Fibroscan

This will be measured from the date of the participant's referral letter until the date of their successful scan. If the participant does not attend or have a scan within their 12-month follow-up, then they will be censored at 12 months.

This outcome will include scans that could not be performed, e.g. because the participant's weight prevented an accurate reading. It will not include scans where the participant did not attend as scheduled.

10.2.4 Admissions to hospital

Improvements to the triaging process for NAFLD patients would be expected to result in fewer admissions to hospital. The follow-up period will be the 12 months following each participant's referral letter. For each participant we will count the number of admissions during the 12-month follow-up, being careful to avoid double counting the same admission for patients who are transferred during their stay. We will include elective and emergent admissions. This outcome will come from a review of the participants' individual medical record by the study nurse.

Reasons for admissions could include NAFLD-related illnesses such as hepatic encephalopathy, bleeding requiring emergency endoscopy, drainage of ascites, acute chronic liver failure and management of fluid retention. However, given that NAFLD patients generally have other comorbidities, we may also see admissions for related conditions like cardiovascular disease.

10.2.5 Presentations to an emergency department

Improvements to the triaging process for NAFLD patients could be expected to result in fewer presentations to emergency departments. This outcome will be created based on routinely collected data from the participants' records in Queensland Health administrative databases. For each participant we will count the number of presentations during the 12-month follow-up period.

10.2.6 Health-related quality of life

Quality of life data will be collected directly from participants at baseline and 12 months using the validated EQ-5D-3L tool (26). The baseline version will be the self-completed version and the 12-month follow-up will use the telephone version. This difference in administration mode is not a big concern because any change in response should be the same in the usual care and intervention groups. Hence this change will not bias the key comparison of the difference between the usual care and LOCATE intervention groups.

Patients in the new model of care could have a better quality of life by 12 months because their disease is being managed better. However, we acknowledge that it is difficult to improve overall quality of life.

10.2.7 Hepatocellular carcinoma (HCC) detected outside specific surveillance

This is the most common type of primary liver cancer. This data will come from chart review at 12 months. Participants identified as cirrhotic by the study will be enrolled into a HCC surveillance program. Participants with undiagnosed cirrhosis or advanced fibrosis that are identified by the program that have an HCC diagnosed on initial ultrasound, would be classed as out of program.

10.2.8 Variceal bleeding occurring without variceal surveillance.

We anticipate this outcome will be rare. These data will come from chart review at 12 months.

10.2.9 Statin use

Better management of a patient's liver disease may create time for GPs to examine important cardiovascular comorbidities. Hence, we will compare prescriptions for statins between the two groups, accounting for those who had a prescription in the year prior to follow-up. This will come from self-report data from the patient questionnaire at 12 months.

10.2.10 Death

We will examine the participant's date and cause of death. We plan to use all causes but may exclude accidental causes if they are relatively common. These data will come from the National Death Index (27). We anticipate this outcome will be rare, and that any difference between groups would have a relatively large statistical uncertainty. However, knowing the death date will also improve our accuracy of other secondary outcomes (e.g., time to scan), because participants who died can be censored.

10.2.11 Long-term follow-up

We plan to follow-up patients after 10 years in order to examine whether there was a long-term benefit to the LOCATE model of care. Further funding will be necessary to resource this data collection and analyses.

11. ECONOMIC EVALUATION OUTCOMES

11.1 Aim

To produce evidence about the economic benefit of the new model of care. The evaluation will follow the guidelines in the Consolidated Health Economic Evaluation Reporting Standards (CHEERS) checklist (28).

11.2 Primary Economic Outcome

To evaluate the cost-effectiveness of the new model of care, we will conduct a within-trial cost-effectiveness analysis, where the costs and health outcomes associated with the LOCATE model of care are compared to those experienced under usual care.

11.3 Secondary Economic Outcome

We will conduct a modelling study, projecting the potential for longer term cost-savings due to improved identification and stratification of high-risk NAFLD patients in the community and the reduction in high cost, hospital-based complications.

12. IMPLEMENTATION PROCESS AND IMPACT

12.1 Aim

The purpose of the implementation evaluation is to identify the uptake, reach and effectiveness of the LOCATE model of care as used by the research study, and determine the impact on specialist hospital outpatient referrals for assessment of liver disease. It is useful to examine the reach and utility of the model of care, as well as capture knowledge, attitude and practice changes and patient satisfaction and acceptability. The evaluation will also be used to inform current and prospective funding bodies and stakeholders about the return on investment and future planning of resources.

12.2 Evaluation model

The RE-AIM model will guide the evaluation of the community model of care for liver assessment and referral, by:

- Assessing the **Reach** of the initiative across metro and regional locations including number of GP practices and referring GPs
- Assessing the **Effectiveness** of the model at triaging appropriate referral pathways for low and high risk patients and the engagement of GPs managing low risk NAFLD in the community
- Assessing the fidelity of the **Implementation** of the model across two sites

In addition, we will assess the **Scalability** of the intervention, including Structure, Practice and Culture

*Note that evaluation of the **Adoption** and **Maintenance** domains in the RE-AIM framework is outside of the current scope of this project.*

12.3 Objectives

1. Map the reach of the model of care by location of GP practice, number of GP practices and GPs exposed to the model of care.
2. Determine the impact of the model of care on the proportion of low risk and higher risk NAFLD being seen in specialist clinics.
3. To determine if patients with low risk and high risk NAFLD received appropriate care for their condition.
4. To determine the factors associated with implementation of the model of care including: a) individual factors (awareness, knowledge, skills, acceptance), b) institutional factors (Practice management barriers and enablers) and c) systemic factors (communication processes, referral processes, triage workflow, waiting lists etc)
5. To explore the GP and patient experience with the LOCATE model of care including acceptability of community based non-specialist screening and community-based care for lower risk conditions
6. Determine whether LOCATE is a sustainable and scalable model of care in the community beyond the current research funding.

13. STUDY PROCEDURES

13.1 Recruitment and consent

13.1.1 Recruitment

Potential participants will be identified based on the referral letter sent from their GP to the hepatology clinic. Potentially eligible participants will be sent a letter containing an invitation to participate and details of who to contact should they be interested in participation.

NEGATIVE OR NO RESPONSE: Should no response to the initial letter be received after two weeks, a study nurse will contact the patient by phone to enquire if they are interested. Should the potential participant not answer the phone, a voicemail will not be left. Instead, an SMS will be sent from a study phone to their mobile, informing them that it was a study nurse who called, and providing a brief explanation of the study and contact information for participation. It will then be up to the participant to call back if they are interested in trial participation. If at any stage of this process they state they are not interested, they will not be contacted again.

POSITVE RESPONSE: Those who are interested in participating will be able to call a study nurse (the phone number will be provided in the initial letter, as well as in the SMS if this is sent) who will provide further detail about the study, including informing the potential participant that their eligibility will be confirmed based on the responses provided in their initial questionnaires. These

potential participants will then be mailed the Participant Information and Consent Form (PICF), withdrawal form, study questionnaires, a $20 voucher and a reply-paid return envelope.

To help with recruitment, we will use a professionally produced short video that will explain the study to potential participants and their involvement. Although the evidence for the use of videos to improve recruitment is mixed (29), our experience is that they save time during recruitment and provide consistent information to prospective participants.

13.1.2 Consent

Potential participants who agree to be contacted after the recruitment process (above) will be sent the PICF in the mail. They will be asked to read, sign and return the forms in the mail. The mail-out will include a reply-paid envelope and a $20 voucher to compensate them for their time. The mail-out will also include a short eligibility questionnaire (see later Data Collection section).

The study nurses will make one follow-up call (and SMS if not answered) to potential participants who have not returned the consent and enrolment questionnaires after 2 weeks.

Participants will be asked to sign the study consent form (PICF) for participation in the trial.

We will record the number of participants declining to consent and will ask the study nurse to record why they thought the patient did not consent, as this will assist the researchers to understand how our results might be biased compared with the target population. We will also record the number of potential participants who could not be contacted.

In the event that, after return of study questionnaire, the participant is found to be unsuitable based on the answers provided in the LOCATE Questionnaire: Alcohol Use Disorders Identification Test (AUDIT) tool or single question on historic liver disease (participants will not be eligible should they have an AUDIT score of 8 or more which is defined as “risky”), they will be contacted by phone by the study nurse, who will explain that they are not considered eligible and are removed from the trial and so will progress to their hospital hepatology appointment as planned. Their consent form and questionnaires will be securely destroyed. A study ID number will be assigned to the removed participant for the purposes of record keeping, along with the reason why they were unable to be enrolled, however no identifiable or potentially re-identifiable information will be kept.

The recruitment and consent process are summarised in the study process flow chart below (Figure 2).

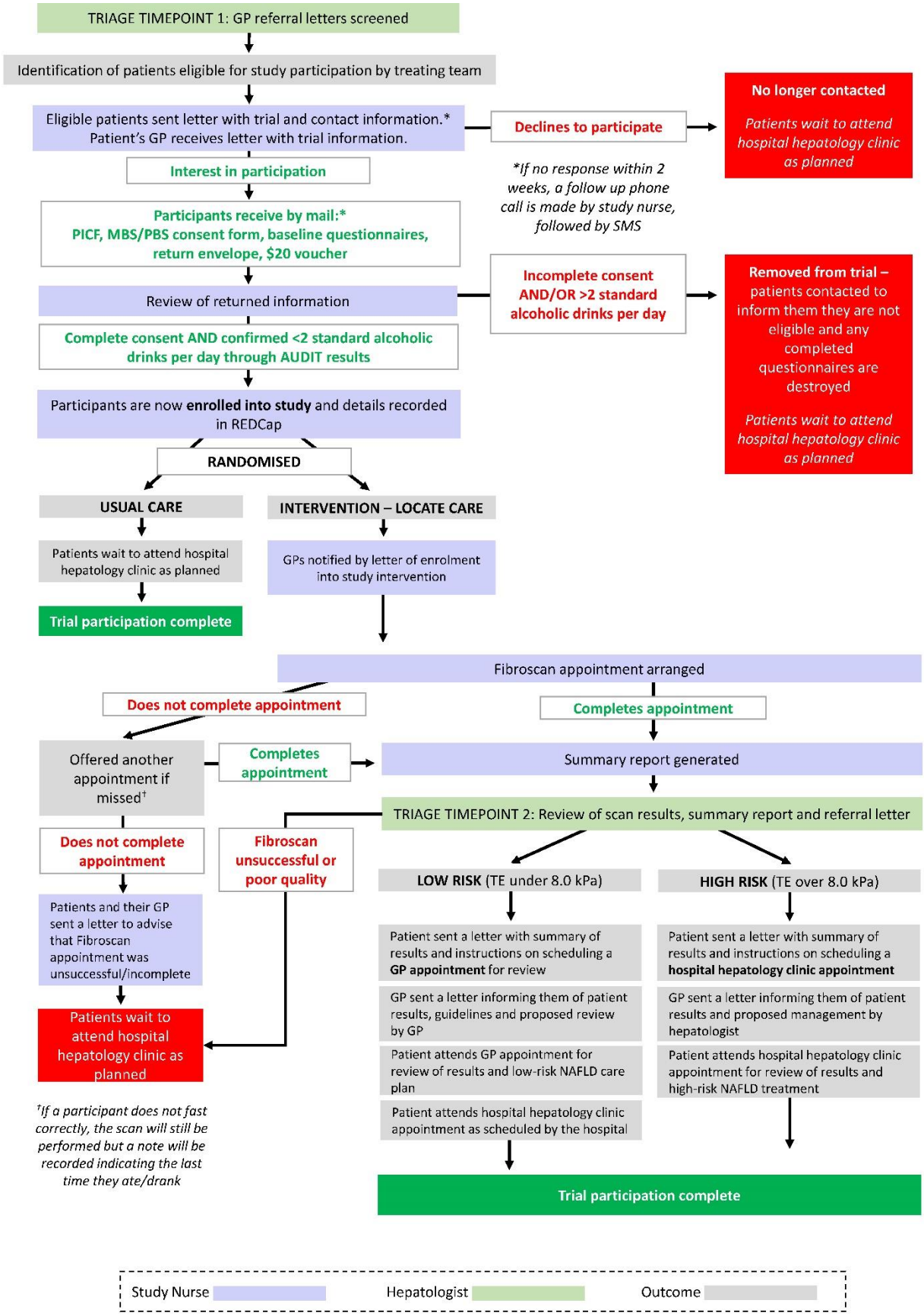

Figure 2: Recruitment and patient flow pathway for LOCATE-NAFLD Study

13.2 Withdrawal

13.2.1 Participant withdrawal

Participants will be able to withdraw from further participation at any time, either in writing using the form provided to them at recruitment, or verbally to either a study team member and/or chief investigator. We will not collect any further data from the participant but will keep the data already collected unless the participant makes it clear that they do not wish this. Should this be the case, any identifiable or potentially re-identifiable information would be destroyed, along with previously collected data such as questionnaires.

There will be no negative consequences to any participants who withdraw.

The number of participants withdrawing, and the timing during the study, will be included in our final report.

13.3 Randomisation

A 1:1 randomisation list will be created by statistician CI Barnett in the *R* software (version 3.6.1 or higher). The list will be stratified by HHS (Sunshine Coast and Metro South). The list will be in randomised blocks of size 6 and 8, as this helps create balanced groups over time and means that group sizes will be approximately equal if the trial recruitment ends early.

The list will be uploaded into the REDCap software (30). Patients will be randomised once they have returned the signed consent form and questionnaires. The study nurses will open a new form for each patient that returns the required information and randomise them (by pressing a button in REDCap) once they have entered the patient's data and their eligibility.

13.4 Blinding

It is challenging to hide the randomised group because this is an open-label study where both the participants and researchers will be aware of what group participants are in.

Baseline data will be collected blind to randomised group, as it will be done prior to randomisation.

Many of the outcomes are informed by data collected from the patients' Integrated Medical Record (IMR). The study nurses employed to collect these data will be aware of the study's aims and may also know each participant's group based on the notes in the IMR. We will reinforce with these nurses the importance of collecting the data in an unbiased manner.

13.5 Data collection

13.5.1 Referral letter

The following data will be extracted from the referral letter:

- Date of referral*
- Patient's age*
- Body Mass Index (BMI)
- Relevant blood test results:
    - AST, ALT
    - Platelet count
    - Viral (Hepatitis B Virus and Hepatitis C Virus) serology
    - Ferritin

*Age and BMI may not be available; therefore these will be included in the study recruitment questionnaire. AST and ALT are basic liver tests and should be in the referral letter.

13.5.2 Study questionnaire

The study recruitment questionnaire will contain:

- Year of birth, for calculating age
- Gender
- Self-reported height and weight, for calculating BMI
- A single question on lifetime liver problems
- Alcohol consumption in the past year using the Alcohol Use Disorders Identification Test (AUDIT) (31). This is a 10-item screening tool developed by the World Health Organization.
- Current employment status (full-time, part-time, unemployed, disability pension) for examining economic outcomes. We will not ask for job title or wage as this might be intrusive. We will use average Australian wage rates for costs.
- EQ-5D-3L five questions and visual analogue scale for quality of life.

13.5.3 Twelve-month telephone follow-up

Participants will be telephoned by study staff at 12 months post recruitment and asked:

- The number of GP visits in the last 12 months
- If they have visited a dietician in the last 12 months
- If they have been prescribed a statin in the last 12 months
- EQ-5D-3L questions and visual analogue scale for quality of life
- Current employment (full-time, part-time, unemployed, disability pension)

The wording for the health usage questions were based on the Australian Bureau of Statistics Patient Experience Survey.

We will record the number of participants that are lost to follow-up due to being unable to be contacted.

13.5.4 Twelve-month chart audit

Study nurses will audit the patients' individual medical record at 12 months post-recruitment and extract much of the data needed for the primary and secondary outcomes (see Sections 10.1 and 10.2).

13.7 Data management

13.7.1 Data sources

Summary table of data sources for the primary and secondary outcomes:

Data	Source
NAFLD-associated hospital outpatient clinic utilisation	Queensland Health administrative databases
NAFLD-associated admissions to hospital	Queensland Health administrative databases
NAFLD-associated re-presentations to hospital	Queensland Health administrative databases
NAFLD-associated hospital utilisations	Queensland Health administrative databases
Health related quality of life EQ-5D	Participants at baseline and 12 months

Data for outcomes involving contact with tertiary care will be collected from Queensland Health administrative databases and the patient consent process will include permission to access their

individual health records. Health-related quality of life will be collected directly from participants at baseline and 12 months, using the validated and highly cited EQ-5D-3L tool (26).

To achieve the implementation evaluation objectives outlined in Section 12.3, we will be auditing data collected throughout the study, as well as conducting semi-structured interviews with key stakeholders and consumers within the study. These interviews will occur within 8 weeks of the trial's conclusion.

Summary of data sources for implementation evaluation:

Data	Source
Referring GP locations/ representativeness of GP practices	Participant referrals (initial)
Addresses of participating patients	Participant referrals (initial)
Health professional and patient experiences with model of care	Semi-structured interviews with health professionals and patients

13.7.2 Use of existing data

Table of Existing dataset access

Name of data set	Data custodian	Agency type	Data collection format	Variable	Justification
Queensland Hospital Admitted Patient Data Collection (QHAPDC)	Statistical Services Branch	State	Individually identifiable	Length of stay (LOS) ICU admission Hospital re-admissions Discharge outcomes Referrals	Primary and secondary outcomes
Queensland Health clinical costing unit	Queensland Health	State	Non identifiable	Average costs for admissions and investigations related to liver disease	Economic outcomes
Hepatology department's administrative database	Queensland Health	State	Individually identifiable	Fibroscan results, specialist assessment of liver disease	Primary and secondary outcomes

Death data from National Death Index	Australian Institute of Health and Welfare	Federal	Individually identifiable	Date of death	Secondary outcome of death and long-term follow-up

13.7.3 Participant data

Following recruitment and the return of the consent forms and baseline questionnaires to the study team at QUT, a research assistant will enter the following data directly into REDCap: Full name, address, telephone number, today's date, date of birth and results of the postal baseline questionnaires. A study nurse will then log into the secure REDCap platform and determine that participants meet the eligibility requirements according to the inclusion/exclusion criteria. The study nurse will then follow up with the participants regarding their eligibility. Those who are not eligible due to the results of the AUDIT survey will have all their existing data destroyed and deleted from any electronic servers.

The 12-month telephone survey will be entered directly into REDCap by the study staff.

The participants' addresses will be used to calculate out of pocket costs and will be deleted from REDCap once their travelling distance (to clinic and hospital) have been calculated. Distances will be calculated using the Google Maps API via the ggmap package in R (32).

13.7.4 Data storage

The project manager will maintain a list of appropriately qualified persons to whom the chief Investigator has delegated study duties. The project manager, investigators and other QUT-based project staff are responsible for maintaining a comprehensive and centralised bibliographic filing system of all study-related (essential) documentation, suitable for inspection at any time by the approving HREC or applicable regulatory authorities.

A detailed data management plan will be completed, in line with QUT policy. This will direct that all document data will be stored on hard disk drives. These computers will be networked to a file storage server, where an automated batch file copy procedure will back up the entire hard disk drive of each computer daily. Data will be shared via a password protected file storage server at QUT that only members of the research team can access. All references will be stored in one bibliographic database that can be accessed by the research team.

13.7.5 Data retention

Study records will be retained as per the Queensland Government University Sector Retention and Disposal Schedule. At the end of the study, final non-identifiable data sets will be deposited in QUT's Research Data Storage System (RDSS). In line with publication embargoes and requirements, we will generate a document object identifier (DOI) for each non-identifiable data set and make this record publicly accessible.

13.7.6 Data Access

Processes for data access will be established in the data management plan. During the study, only members of the study team or the data monitoring group will access patient data.

A fully executed Collaborative Research Agreement is in place to inform data access by the study investigators.

All final non-identifiable data sets will be available from the study statistician (CIs Barnett) once the main papers have been published.

13.8 Safety Evaluations

The following will be used to evaluate the safety of staff involved in the study:

- protocol deviation and adverse events reporting
- incident and unanticipated problem monitoring.

13.8.1 Protocol deviations and adverse event reporting

The project manager is responsible for ensuring that all protocol deviations and adverse events observed by the investigator/s or project team, or reported by sites are collected, reviewed with CI Barnett, recorded in the source documents, and reported to the approving HREC and site Research Governance Officers.

A protocol deviation is any noncompliance with the study protocol or HREC requirements. The noncompliance may be either on the part of the participant, the investigator, project team or the study site staff. As a result of deviations or adverse events, corrective actions are to be implemented promptly.

13.8.2 Incident and unanticipated problem monitoring and reporting

The project manager is responsible for ensuring that all incidents and unanticipated problems observed by the investigator/s, project team or reported by sites are collected, reviewed and recorded in the source documents. Incidents could require reporting to the approving HREC and site Research Governance Officers.

13.9 Monitoring

13.9.1 Data monitoring committee

We will recruit an independent study monitoring committee of three researchers (one clinician, one statistician, and one trialist) who have not worked with any of the chief investigator team in the past five years. We will give this group access to the study's REDCap data collection site from where they will be able to view live reports on recruitment at any time (we will control their access and they will not be able to view individual-level participant data). Their REDCap access will be controlled, and they will not be able to see individual patient information. The recruitment reports will show:

- The current cumulative sample size over time compared with our cumulative target.
- Summary statistics on the sample's baseline characteristics.

We will also prompt the data monitoring committee for their feedback every six months and share a brief one-page report on our progress against the milestones (Section 7.1). Any concerns about delays or data quality raised by the committee will be dealt with initially by the project manager. If this does not resolve the concerns, then there will be a special teleconference meeting of the study committee, project manager and chief investigators.

We will share this protocol with the study monitoring committee.

14. SAMPLE SIZE AND STATISTICAL ANALYSES FOR TRIAL PARTICIPANT OUTCOMES

14.1 Sample size and statistical power

We aim to have a minimum total sample size of 156 participants for our primary outcome but will aim for a sample size of 234. This number of participants will give us a 95% power to detect a 50% reduction in the primary outcome of time to diagnosis of high-risk disease. Our minimal sample size of 156 participants gives us an 83% power. We used a two-sided 5% significance level. We assumed

an average time of 180 days in the usual care group and halving of this time in the intervention group. We assumed that 5% of participants would be censored due to death or loss to follow-up. Participants still undiagnosed at 365 days were also censored, as this is the end of follow-up. The sample size was estimated by simulating survival data using the "sim.survdata" function from the "coxed" package in *R* using 1,000 simulations (33). We assumed a log-normal hazard function with a standard deviation of 10 days. The statistical code to run the sample size is available here: https://github.com/agbarnett/LOCATE. We assume that half of all patients approached will agree to participate, hence we will need to approach 468.

14.2 Data analysis – overall considerations

We will present results as means and 95% confidence intervals. We will include p-values in our reports, but will aim not to present them in any external reports or papers given the widespread misunderstanding of their meaning (34).

An initial analysis will be created using a scrambled intervention group by randomly allocating each participant to the usual care or intervention arm. A complete statistical report will be created using this scrambled data and sent to all investigators for discussion. This allows investigators to query the methods and approaches used prior to the final report. It can also uncover errors in the code or data. Changes can be made prior to seeing the main results, which helps avoid the bias of only making changes where results are perceived as unfavourable.

We will use residual checks for all our models and will look for non-normality and outliers. These checks will be published in a supplementary to any paper and/or on *github* (https://github.com/agbarnett/LOCATE). We will consider using a log-transformation (base e) if the residuals show a strong skew.

14.3 Per protocol definition

We will use an intention-to-treat (ITT) approach meaning that participants will be analysed according to their randomised group, regardless of whether they followed that model of care (35). For example, a participant may be randomised to receive the scan but not complete their appointment and hence receive care similar to the usual care group. Using an intention-to-treat approach this participant would be included in the intervention group.

In a sensitivity analysis we will use a per protocol (PP) analysis by only including patients that attended their Fibroscan appointment and were able to be scanned. The per protocol analysis will be applied to the primary and secondary outcomes, and the economic analysis.

If five or fewer participants are excluded according to the per protocol definition, then we will not present any additional results beyond the intention-to-treat results. This is because there is unlikely to be any meaningful difference between the ITT and PP results.

An intention-to-treat approach gives an indication of the value of the model of care in practice, because it includes the missed appointments that will happen in other clinics. A per protocol approach gives an indication of the potential benefits of the model of care. If the PP results show a larger benefit than the ITT results, then it provides impetus for finding ways to help patients attend their Fibroscan appointment.

14.4 Analysis of the primary outcome

We will use survival analysis methods to examine the primary outcome of time to diagnosis of high-risk NAFLD. We will use Kaplan–Meier plots to highlight any differences between the usual care and intervention groups, using the GP referral letter date as the start time and diagnosis date as the

event time. Participants without an event will be censored using: i) their date of death, ii) 12 months from their baseline visit if there have not experienced the event. We will use parametric Weibull survival models to examine a statistical difference. We will check the parametric assumption and the model residuals.

14.5 Analyses of secondary outcomes

For the three time-to-event outcomes of NAFLD-associated admissions and re-presentations, and first fibrosis assessment, we will use Kaplan–Meier plots to highlight any differences between the usual care and intervention groups. The event time would be the time of re-admission, re-presentation, or assessment. Participants without an event will be censored using: i) their date of death, ii) 12 months from their baseline visit if there have not experienced the event. We will use parametric Weibull survival models to examine a statistical difference in all the three time-to-event outcomes. We will check the parametric assumption and the model residuals.

For health-related quality of life we will model the participants' 12-month result whilst adjusting for their baseline. This is equivalent to examining the within-participant change in quality of life and helps adjust for regression to the mean (36,37). We will use a linear regression model and check the model residuals. The two independent variables in the regression model will be baseline and intervention group.

Statin use will be compared between groups by examining the number of participants given a new statin script during the follow-up period. The denominator will be the number of patients not on statins at the time of their referral letter to the hepatology clinic. We will compare the numbers using a 2-by-2 table and Chi-squared test.

Deaths and HCC detection will be compared between groups using a 2-by-2 table. As these two outcomes are likely to be rare, we anticipate needing to use Fisher's exact test to look for statistical differences between the two groups.

14.6 Missing data

We will report the number and percent of missing data for every study variable and examine wave and item missing data. Wave missing occurs when a participant misses an entire follow-up (e.g., 12-month follow-up call) and item missing occurs when a wave is partially completed (e.g., weight missing in baseline questionnaire). We will investigate variables that have relatively high levels of missing data (over 5%) and seek to identify the cause of the missing data and the potential for bias. For variables with more than 5% missing we will use multiple imputation to fill in the missing data and then re-run the relevant analyses and compare the results from the complete case and imputed data sets. The multiple imputation will use either the multivariate normal assumption or Multivariate Imputation by Chained Equations (MICE) depending on the distribution of the variable(s) and pattern of missing data (38).

14.7 Interim analysis

There is no planned interim analysis nor any stopping rules.

14.8 Planned subgroup and adjusted analysis

There are three planned subgroup or adjusted analysis:

1. The per protocol analysis (Section 14.3).
2. A sensitivity analysis for missing data (Section 14.6).

3. Separate analyses in the younger (under 75) and older (75 and over) age cohorts. The Fibroscan results may be more uncertain in the older age groups due to measurement difficulties, which may reduce the observed benefit of the intervention.

We will adjust for baseline variables in the analyses, not because we expect any confounding but because we could increase our statistical power by explaining more variance in the outcomes. All analyses will adjust for HHS (Metro South or Sunshine Coast), age, gender and BMI. The analysis of 12 month EQ-5D will also adjust for baseline EQ-5D.

14.9 Additional information

The results will be written up using the Consolidated Standards of Reporting Trials (CONSORT) and Template for Intervention Description and Replication (TIDieR) checklists (39,40). As per the CONSORT guidelines, we will not use statistical tests to compare the two groups of patients at baseline and will instead look for differences using a table of summary statistics.

15. ANALYSIS FOR ECONOMIC EVALUATION

15.1 Decision-analytic model

15.1.1 Model

A Markov model will be developed to answer questions about the primary and secondary outcomes, taking account of patients' typical clinical pathways. The model will be state-based and able to handle recursive events, an important reality when evaluating a chronic condition such as NAFLD. A hypothetical cohort of patients, based on trial data, will move through the model's health states over time. This structure will provide the framework for the economic evaluation and will be used to estimate the costs and health outcomes associated with the differing approaches to service provision. The model will be constructed and analysed in Microsoft Excel 2010.

15.1.2 Perspectives

The baseline results will be presented from the societal perspective, and this will be the overarching perspective of the model. The costs included will be healthcare system costs, as well as participants' costs associated with accessing care such as transportation, pharmaceuticals, GP/allied health, and lost productivity.

The flexibility of the model will be used, and results will also be presented from a different costing perspective, in order to produce meaningful results for a varied stakeholder audience. Analysis from the healthcare perspective will use only the costs associated with treatment, health service utilisation, NAFLD-associated adverse events, and administration and monitoring of the intervention. These will produce results that are of use to healthcare decision-makers who are only interested in health system costs.

15.1.3 Time horizon

A lifetime horizon will be used for this analysis. It is appropriate to consider an extended time horizon due to the chronic and long-term nature of the condition. We expect that this time horizon will effectively capture outcomes associated with ongoing management.

15.1.4 Discounting

In line with other evaluations of this nature, future cost and health outcomes will be valued lower than present values. A discounting rate of 3.5% per year will be applied to all costs and health outcomes, as per published guidelines (41).

15.2 Input data for the model

15.2.1 Transition probabilities

For the analysis of the primary outcome, movement between health states is based on transition probabilities that will be estimated from the study. The rate of movement amongst the health states will differ between usual care and the intervention according to the intervention's effectiveness.

For analysis of the secondary outcome, transition probabilities will be estimated from a combination of the study and the published literature. Specifically, estimates regarding probability of longer-term negative NAFLD-related outcomes such as hepatocellular carcinoma will be derived from the published literature, as our study period is not long enough for estimation from the data collection period.

15.2.2 Costs

Costing data will be prospectively collected from multiple sources. Individual level costs associated with hospital utilisation will be collected from the Queensland Health clinical costing unit. We will prospectively measure costs associated with patient travel, lost productivity and out-of-pocket expenses using a costing survey that has been developed and used in a previous study.

15.2.3 Quality of life

To estimate health utility, quality of life data will be collected using the validated EuroQol EQ-5D-3L tool and assigned to each health state in the model. Data will be collected from participants at two time points: 1) upon enrolment into the study, and 2) at the end of the 12-month follow-up period. Comparison of health utility will be drawn between participants who are enrolled under usual conditions (Phase 2) and those who are recruited during the intervention period (Phase 4), to measure improvement or decrement.

15.3 Model outputs

The main purpose of this evaluation is to estimate the expected value for money of the new model of care, in comparison to usual practice. This will be indicated by the incremental cost-effectiveness ratio (ICER), where the mean change to costs associated with the new model of care is divided by the mean change in Quality Adjusted Life Years (QALYs) (42). The ICER will be compared against a cost-effectiveness threshold, which is assumed to be the willingness to pay for an additional QALY. Incremental cost-effectiveness ratios that fall under this threshold are deemed to be cost-effective. Cost-effectiveness will be interpreted using the recently published Australian willingness to pay (WTP) of $28,000/QALY gained (43).

15.4 Handling Uncertainty

Uncertainty related to the model's inputs will be quantified using probabilistic sensitivity analysis. The model will be evaluated 10,000 times, using Monte Carlo simulation, where each simulation will take a random draw from each parameter's assigned statistical distribution (44). Different model inputs will be assigned statistical distributions that are appropriate to that parameter – transition probabilities and health utilities will be assigned beta distributions, while costs will be assigned gamma distributions, reflecting the skew associated with this type of data (44). For each model simulation, the change to costs and the change to QALYs will be recorded, resulting in 10,000 pairs of incremental costs and effects.

Given that the ratio of two numbers has awkward statistical properties and causes practical issues for use in decision-making, we will also present results from a net monetary benefit (NMB) analysis

(45). Using the NMB framework, the ICER will be simplified to a single number through the linear rearrangement of the ICER equation:

$$\text{NMB} = (\text{WTP threshold} \times \text{Change in Effects}) - \text{Change in Costs}$$

Using the NMB makes interpreting cost-effectiveness simple; a positive NMB indicates that a strategy is cost-effective and a negative NMB indicates that a strategy is not cost-effective. Using this approach will give decision-makers a clear and easily understood framework for choosing to adopt, or not, the intervention being evaluated.

Uncertainty in other aspects of the model will be explored through one-way sensitivity analysis, where one parameter's mean value will be changed at a time, and the results recorded to examine differences. We will also conduct scenario analysis, where key parameter values will be changed to reflect plausible clinical scenarios. These processes will test the model's robustness and increase the scope of information that is available to decision-makers, making the results pragmatic and useful for decision-making.

15.5 Unnecessary tests

Some of the non-invasive testing ordered by GPs may be unnecessary and have a low pre-test probability. Some tests are costly, so this could be an important source of wasted healthcare resources. To examine this, we will collect data on selected tests mentioned in the GP referral letter. The table below shows the potential tests and flags those that are likely unnecessary for most patients (46).

Test	**Unnecessary**
Full blood count	No
Urea and electrolytes	No
Liver function tests	No
Coagulation profile	No
Hepatitis B, C	No
ANA, ASMA, AMA	No
Immunoglobins	No
Ferritin	No
Transferrin saturation	No
Copper	Yes
Caeruloplasmin	Yes
HFE mutation analysis	Yes
Alpha-1 antitrypsin	Yes
CMV and EBV serology	Yes

We do not expect this testing to change as part of the study, hence this will be a secondary analysis that looks at the overall costs of these tests and creates a separate report with the aim of starting a discussion around ways to reduce these potentially unnecessary tests.

16. ANALYSIS FOR IMPLEMENTATION EVALUATION

Interview notes and transcripts, and results of referral reviews will be subject to thematic analysis. A project team member with implementation science and qualitative research expertise will complete this process, under the guidance of CI Hickman.

Analysis will be iterative: firstly, identifying emerging themes, then comparing and refining these. Analysis will continue until no new themes emerge and agreement on themes is achieved.

17. ETHICAL CONSIDERATIONS AND REGULATORY OBLIGATIONS

17.1 Human Research Ethics Committee

Ethics approval will be sought primarily through the Royal Brisbane and Women's Hospital HREC. Additional administrative approval will then be sought through QUT's University Human Research Ethics Committee, as well as Site Specific Assessments from recruitment sites and the Department of Human Services External Request Evaluation Committee. No participants will be approached, and no data collected, prior to all approvals being received.

17.2 Informed consent

All participants will be required to sign the consent form prior to enrolment in the study. Consent forms will be mailed to eligible participants along with in-depth information about the study, and details of who to contact should they require further information.

No participant data will be recorded prior to written consent being received. Further information on the consent process is in Section 13.1.2.

17.3 Waiver of consent

A waiver of consent is not required for this study. Referral letters, which are being screened for study eligibility, are being received and screened by the patient's treating team. No additional information will be collected until written consent has been received and enrolment to the study has been completed.

17.4 Site/governance review

Site Specific Assessments will be submitted to the participating recruitment sites after receiving ethics approval. No participants will be approached, and no data collected, prior to all approvals being received

17.5 Confidentiality

Referral letters will be screened by the patient's treating team as per usual practice within the clinic, with no external study team members accessing patient information until written consent is received and participants are enrolled. In this way, patient confidentiality within the clinic will be maintained until they are fully aware of the study what information will be collected and required.

Participant data will be collected by study team members in the clinics, with participant privacy and confidentiality in full consideration. Study team members external to the clinic will not have access to identifiable or re-identifiable participant information. Participant data provided to study team members external to the clinics for the purposes of achieving study outcomes will be de-identified prior to being shared. No individual participant information will be shared with anyone outside the study team during or after the trial.

Any participant information available after the trial will be in an aggregate format to avoid individual re-identification.

17.6 Funders

The NHMRC has provided funding for this trial. This funding source had no role in the design of this study and will not have any role during its execution, analyses, interpretation of the data, or decision to submit results

18. DISSEMINATION OF RESULTS & PUBLICATIONS

18.1 Intellectual property

Intellectual property requirements will be informed by the collaborative research agreements and clinic site agreements.

18.2 Dissemination of results to clinics and participants

Results will be directly disseminated to each participating HHS using a report that will include: i) a brief lay summary of the results in their HHS, ii) the detailed overall results.

At recruitment all participants will be asked if they would like to receive a summary of the results, and those who agree will be e-mailed a lay one-page lay summary of the results once the analyses have been written up. Participants will be able to review their collected data at any time during the trial by contacting a study team member; this is outlined in the PICF.

18.3 Dissemination of results to health consumers, policy makers and other stakeholders

Results will be directly disseminated to key staff in Queensland Health for further distribution to consumers, policy- and decision-makers in the form of evidence briefs, plain language summaries and policy recommendations.

A publication plan that details the likely papers and conferences will be established within five months of funding to inform systematic publication of results through the clinical and academic communities. We aim to publish in Open Access journals to allow the widest readership of our results. We will adhere to the International Committee of Medical Journal Editors requirements for authorship and will report the contributions of each author. We will not use professional writers.

The key details of the protocol will be publicly available via ANZCTR (https://www.anzctr.org.au).

18.4 Dissemination of data and statistical code

All final non-identifiable data sets will be available from the study statistician (CI Barnett) once the main papers have been published. The complete statistical code will be published and fully accessible on *github* (https://github.com/agbarnett/LOCATE).

19. OUTCOMES AND SIGNIFICANCE

This is a nationally important health services research trial that will examine a change to the model of care for triaging patients with liver disease. A relatively simple change to care could result in faster treatments for sick patients and lower overall costs for the health system. The study uses a strong randomised design and will collect high quality data to provide clear information for decision makers. The implementation part of the study will provide valuable information for other HHSs that may want to implement the model of care based on the trial results.

20. ABBREVIATIONS

In alphabetical order.

AUDIT	Alcohol Use Disorders Identification Test
ANZCTR	Australian New Zealand Clinical Trials Registry
ALT	Alanine transaminase
AST	Aspartate aminotransferase
BMI	Body mass index
CAP	Controlled attenuation parameter
CHEERS	Consolidated Health Economic Evaluation Reporting Standards
CI	Chief investigator
CONSORT	Consolidated Standards of Reporting Trials
DOI	Document Object Identifier
ELF	Enhanced liver fibrosis
GP	General Practitioner
HCC	Hepatocellular carcinoma
HCV	Hepatitis C virus
HHS	Hospital and health service
HREC	Human research ethics committee
ICER	incremental cost-effectiveness ratio
IMR	Individual medical record
ITT	Intention-to-treat
kPa	kilopascals
LOCATE	LOCal Assessment and TriagE
LSM	Liver stiffness measurement
MBS	Medicare Benefits Schedule
MICE	Multivariate Imputation by Chained Equations
NAFLD	Non-alcoholic fatty liver disease
NHMRC	National Health and Medical Research Council
NMB	Net monetary benefit
PICF	Participant Information and Consent Form
PP	Per protocol
QALY	Quality-adjusted life year
QHAPDC	Queensland Hospital Admitted Patient Data Collection
QIMR	Queensland Institute of Medical Research
QUT	Queensland University of Technology
RE-AIM	Reach, Effectiveness, Adoption, Implementation, Maintenance
RDSS	Research Data Storage Systems
SPIRIT	Standard Protocol Items: Recommendations for Interventional Trials
TE	Transient elastography
TIDieR	Template for intervention description and replication
UQ	University of Queensland
USC	University of the Sunshine Coast
WTP	Willingness to pay

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