Abbreviated Magnetic Resonance Imaging vs ultrasound surveillance for liver cancer detection in people at high risk of developing liver cancer

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Conflict of Interest: The investigators declare no conflicts of interest relevant to this study.

Confidentiality Statement: This document contains confidential information that must not be disclosed to anyone other than the Sponsor, the Investigator Team, HRA, host organisation, and members of the Research Ethics Committee, unless authorised to do so.

Trial Title: Abbreviated Magnetic Resonance Imaging vs ultrasound surveillance for liver cancer detection in people at high risk of developing liver cancer (AMULET)
Protocol Date and Version No: insert

Protocol signature page

The undersigned has read and understood the trial protocol detailed above and agrees to conduct the trial in compliance with the protocol.

Principal Investigator (Please print name)	**Signature**	**Site name or ID number**	**Date**

Following any amendments to the protocol, this page must be updated with the new protocol version number and date and re-signed by the site PI.

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1. KEY CONTACTS

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2. LAY SUMMARY

Aim: To use magnetic resonance imaging (MRI) scans without contrast to help improve diagnosis of liver cancer in people who are at increased risk of developing liver cancer.

Background: People with any condition that affects the liver over a long period of time can develop cirrhosis. Conditions and risk factors that can lead to cirrhosis include alcohol excess, liver steatosis (lipid or fat accumulation in the liver) and infection with the viruses hepatitis B and C. One of the concerns about people with cirrhosis is that they are at increased risk of developing liver cancer. People with cirrhosis are recommended to have an ultrasound scan (USS) every 6 months (surveillance for liver cancer) so that if a cancer develops, it is diagnosed at an early stage when it can be cured. However, ultrasound can miss cancers even in people having scans every 6 months. Furthermore, the risk of cancer is not alike among people with cirrhosis. For example, people with more advanced cirrhosis and those with cirrhosis from hepatitis B are at higher risk. It is therefore possible that better tests than ultrasound are needed for people with cirrhosis who are at particularly high risk of developing cancer.

Computed tomography (CT) and Magnetic Resonance Imaging (MRI) scans with dye injection (contrast) are used for liver cancer diagnosis. However, they cannot be done every 6 months because of costs, capacity and toxicity from high CT radiation doses, and MRI contrast build-up in the brain with repeated MRI contrast injections. MRI scans without contrast are not toxic, could be done in 20 minutes and are cheaper, so could be done every 6 months. In our experience, MRI without contrast may raise suspicion of liver cancer in cases missed by ultrasound, so it could be used for surveillance instead of ultrasound. In this study we want to find out if it is feasible to use a quick MRI (20 minutes) without contrast as surveillance for liver cancer in people at high risk of liver cancer due to liver cirrhosis and to compare this MRI with ultrasound.

Design and Methods: We will recruit 300 people at higher risk of developing liver cancer because of cirrhosis. Study participants will have an ultrasound scan every 6 months as they would in their standard clinical care and an additional 6 monthly non-contrast MRI scan for 30 months (6 visits). If the ultrasound or non-contrast MRI raises concern for a possible liver cancer, an MRI scan with contrast (with dye injection) will be done for definitive diagnosis. All participants will have an MRI with contrast at the end of 30 months to ensure that no cancers were missed. Participants will be asked to complete questionnaires to measure quality of life, anxiety, and their experience of MRI and ultrasound scans and data will be collected from their medical notes. We will compare the number of liver cancers detected by ultrasound to the number detected by the non-contrast MRI scans.

Follow up data will be collected from NHS England, the NHS Central Register for Scotland and other patient registries for up to 10 years after the last study MRI scan to determine the long-term outcomes of participants.

3. SYNOPSIS

Study Title	Abbreviated Magnetic Resonance Imaging vs ultrasound surveillance for liver cancer detection in people at high risk of developing liver cancer		
Internal ref. no. / short title	AMULET		
Study registration	NCT06658782		
Sponsor	University of Oxford Research Governance, Ethics & Assurance, Boundary Brook House, Churchill Drive, Headington, Oxford, OX3 7GB Email: rgea.sponsor@admin.ox.ac.uk		
Funder	National Institute of Health Research and Medical Research Council		
Study Design	Prospective cohort study		
Study Participants	People with cirrhosis and high risk of Hepatocellular cancer (HCC)		
Sample Size	300		
Planned Study Period	Duration of an individual participant's involvement: 30 months 1st October 2024 – 30th April 2039 (including 10 years passive follow up) No additional funding is required as we are only accessing records during the passive follow up phase.		
Planned Recruitment period	Recruitment start date: 1st November 2024 Recruitment end date: 30th April 2026		
		Outcome Measures	**Timepoint(s)**
Primary Objective To evaluate the diagnostic performance of non-contrast enhanced MRI (nceMRI) and ultrasound scans (USS) as surveillance tools for the diagnosis of hepatocellular cancer (HCC).		True positive tests for HCC per round of surveillance False positive tests for HCC per round of surveillance Positive predictive value for HCC per round of surveillance True negative tests for HCC over the 30 months of surveillance False negative tests for HCC over the 30 months of surveillance Sensitivity and specificity of nceMRI and USS for HCC over 30 months of surveillance	Per round of surveillance analysis will be done for each visit: Baseline, visits 2, 3, 4, 5 and 6 For the 30 months of surveillance, analysis will be done for the entire 30 months of surveillance
Secondary objectives			
To determine the stage and size of HCC at diagnosis and the number of indeterminate lesions detected		Numbers of HCC detected by nceMRI and USS at a very early, early, intermediate or advanced stage as defined by	At each 6 monthly surveillance round (Baseline, visits 2, 3, 4, 5 and 6

	the Barcelona Clinic Liver Cancer staging system. The number and size of HCC tumours per participant with HCC The number of new indeterminate lesions identified at each surveillance round	
To determine the proportion of patients that receive treatment with curative intent	Proportion of participants diagnosed with HCC who go on to receive treatment with curative intent	At any time point an HCC is diagnosed, the analysis will be conducted once all participants complete the study.
To evaluate the impact of the modality used for HCC surveillance on quality of life (QoL) and anxiety and depression	Results of the EQ-5D-5L questionnaire and Hospital Anxiety and Depression Scale questionnaire	At each 6 monthly surveillance round (Baseline, visits 2, 3, 4, 5 and 6
To evaluate the participants' attitude, experience, and acceptability of nceMRI and USS for HCC surveillance	Results of participant experience questionnaire	Baseline, visit 5
To evaluate the feasibility of nceMRI and USS as surveillance tools for HCC	Number of missed appointments (cancelled or missed), number of participants lost to follow-up, Number of participants where HCC surveillance is no longer indicated	At the end of the study
To evaluate whether integration of nceMRI with clinical and laboratory variables can improve performance for HCC surveillance	Sensitivity and specificity of multivariable models for the diagnosis of HCC	End of study
To perform a mechanistic study to use multiparametric quantitative MRI to assess the background liver in patients with cirrhosis.	Quantitative variables extracted from MRI data; T1 (ms), R2* (ms), PDFF (%), ADC (mm^2/s)	End of study
To determine the long-term outcomes of study participants	A composite end point including the outcomes of: all cause mortality, liver related mortality, liver decompensation (ascites, hepatic encephalopathy, variceal bleeding), hepatocellular cancer, non primary liver cancer, liver transplantation	Up to 10 years after the last study MRI scan is performed

Comparator – Reference standard	The reference standard will be diagnosis of HCC based on contrast enhanced CT/MRI or histology or by consensus in multi-disciplinary team meetings at the local liver clinic sites

4. ABBREVIATIONS

AFP	Alpha-fetoprotein
aMRI	Abbreviated MRI
ArLD	Alcohol related liver disease
ceMRI	Contrast enhanced MRI
CI	Chief Investigator
CRF	Case Report Form
CT	Computed tomography
DWI	Diffusion weighted imaging
FN	False negative
FP	False positive
GCP	Good Clinical Practice
GP	General Practitioner
HCC	Hepatocellular cancer
HRA	Health Research Authority
ICF	Informed Consent Form
MASLD	Metabolic Dysfunction-Associated Steatotic Liver Disease
MRI	Magnetic Resonance Imaging
nceMRI	Non-contrast enhanced magnetic resonance imaging
PI	Principal Investigator
PII	Participant Identifiable Information
PIS	Participant/ Patient Information Sheet
QA	Quality Assurance
R&D	NHS Trust R&D Department
REC	Research Ethics Committee
RGEA	Research Governance, Ethics & Assurance, University of Oxford
SOP	Standard Operating Procedure
TN	True negative
TP	True positive

USS	Ultrasound scan
LI-RADS	Liver Imaging Reporting and Data System

5. BACKGROUND AND RATIONALE

5.1. Hepatocellular Carcinoma

Hepatocellular carcinoma (HCC) is the most common primary liver tumour. Recent data from the Global Cancer Observatory (gco.iarc.fr/) shows that in 2020 liver cancer was the 6th most common cancer worldwide, causing the 3rd highest number of cancer-related deaths[1]. In the UK, HCC is a growing public health concern: HCC incidence tripled from 1997 to 2017[2] with predictions for a further 33% increase by 2040[3] and liver cancer mortality is predicted to increase by a further 38% by 2040[4].

HCC can be cured if diagnosed early. However, in the UK, most HCC are only detected at a stage where they are not curable[5], liver cancer 5-year survival is 13%[6] and 3-year mortality rates increased by about 50% from 2006 to 2018[7]. These were the highest increases in mortality in the 20 most common cancers, on a background of a 10% decrease in overall cancer mortality[7]. In an analysis of the epidemiology of 23 cancers over a 25-year period, liver cancer in men aged 35-69 had the highest annual increase in incidence rate from 1993-95 to 2016-18 (+4.68%). Over the same period, mortality increased only in three cancers with liver seeing the highest increase in mortality (melanoma +0.33% annual increase, oral +1.12% annual increase, liver +2.97% annual increase); mortality reduced in all other 20 cancers[8].

5.2. People at risk of hepatocellular cancer

Approximately 90% of HCCs develop in people with cirrhosis[9], most commonly caused by hepatitis B or C virus infection, alcohol related liver disease (ArLD) and metabolic dysfunction-associated steatotic liver disease (MASLD). NICE recommends that people with cirrhosis should have surveillance for HCC with 6 monthly USS[10]. However, despite surveillance, about 80% of HCC are detected at a late stage when curative treatment is not possible[5]. The poor performance of current surveillance strategies for HCC is the area of unmet need that will be addressed by this study.

Our study is relevant to people with cirrhosis who are at high risk of HCC and are undergoing surveillance for HCC. In the UK, cirrhosis is estimated to occur in at least 60,000 people and is the leading cause of death in those aged 35-49 years old[11]. A proportion of these 60,000 patients will be at high risk of HCC and would potentially benefit from more sensitive surveillance modalities. The UK incidence of cirrhosis has been rising[12] and driving considerable increases in liver mortality (+400% since 1970)[13]. Rates of cirrhosis are likely to further increase as a result of the COVID19 pandemic that has led to a surge in alcohol consumption and liver-related deaths[14].

5.3. Current practice and the scope for improvement

In current practice, and as recommended by guidelines[10, 15], HCC surveillance is recommended for people with cirrhosis. Even though surveillance for HCC appears to improve outcomes[16], the overall mortality from HCC remains high. There is therefore great need for improvement in surveillance in the following areas:

1. The sensitivity of USS for early HCC detection is low (28-47%[17, 18]). Furthermore, studies on the diagnostic accuracy of USS for HCC surveillance[18] are largely outdated and many are not directly

applicable to the UK: mainly being performed before 2010 and often conducted in East Asia in populations with higher prevalence of viral hepatitis, and included very few patients with obesity and MASLD, which now make up the majority of patients with cirrhosis in the UK. In obesity and in patients with MASLD, excess subcutaneous and hepatic fat limits liver penetration by ultrasound waves, leading to incomplete liver visualisation and compromised diagnostic accuracy in a significant proportion of patients under HCC surveillance in Western countries[14].

2. People with cirrhosis exhibit diverse risk profiles for HCC risk (risk of HCC of <0.5% to >2% per annum)[19]. This risk heterogeneity is not considered by the current surveillance approach; surveillance for HCC could be improved by using HCC risk stratification to select the most appropriate surveillance tools for each patient. Unfortunately, only one surveillance tool is presently recommended by NICE and routinely used in the NHS – i.e. liver ultrasound – which is not optimal for all patients.

3. Serological tests like alpha-fetoprotein (AFP) do not improve the performance of USS for HCC screening, and therefore these are only optional in current guidelines[10].

5.4. Study rationale

Diagnosis of HCC is made with contrast-enhanced CT or contrast-enhanced MRI. Application of these techniques for surveillance could therefore provide very high diagnostic accuracy for HCC. However, CT involves ionising radiation which precludes it from being applied every 6 months, due to the risk of cancer from accumulating doses of such radiation. Furthermore, annual CT was inferior to 6 monthly USS in the only head-to-head randomised control study[20]. Full length contrast-enhanced MRI protocols are also not practical for frequent administration due to length of scanning, costs, and concerns about accumulation of gadolinium-based contrast agent in the brain[21]. Abbreviated MRI (aMRI) protocols have therefore been developed by the investigators of this study and others[22] for possible use in HCC surveillance and will be evaluated in this study as a possible alternative to USS. Abbreviated non-contrast-enhanced MRI (nceMRI) protocols benefit from lower cost, remove the need for cannulation and risk of contrast accumulation in the brain, without significantly reduced sensitivity[23]. Abbreviated MRI protocols are derived directly from full contrast-enhanced MRI protocols, the gold standard for HCC diagnosis, and represent the most promising and mature tool for HCC surveillance instead of USS.

Our previous work showed that nceMRI can diagnose HCC that was missed by USS[24]. We have recently developed comprehensive nceMRI protocol for tumour detection and assessment of the background liver to study the “field effect” that may predispose to HCC. This comprehensive nceMRI protocol has shown 100% sensitivity for the diagnosis of HCC in a pilot study of ten patients with 13 HCC <2cm[25]. The nceMRI protocol will form the basis for the nceMRI that will be used in this study and is described in detail in the study procedures (section 9.8.2).

In addition to our pilot data, our approach is supported by the published literature where three similar studies to ours have been reported.

- The PRIUS project from Korea (NCT01446666) was a prospective study comparing the diagnostic accuracy of full-length contrast-enhanced MRI and USS[26] over 3 rounds of surveillance in patients with an annual HCC risk of ≥5%. Two post-hoc analyses of this study have been published. The first showed that the MRI sequences acquired before the administration of contrast agent (DWI (b-values: 0, 50, 500 s/mm^2) and T2WI (heavily weighted using long TE and non-fat suppressed (NFS)) had superior sensitivity (79% vs 28%) and similar specificity (98% vs 95%) to USS[17]. The second showed that a simulated abbreviated contrast-enhanced MRI protocol using subsets from the full PRIUS MRI protocol had similar sensitivity to nceMRI (90.7% vs 86.0%; p=0.56) and both were superior to the sensitivity of US (27.9%; $p < 0.001$)[23]. These findings support our choice to use a nceMRI protocol, as the addition of contrast in this setting does not appear to improve performance. The MRI protocol in this study is similar to the one we will be using for our study.

- A prospective study in Australia, examined only DWI MRI (b-values: 100, 400, 800 s/mm^2) against USS[27] in 192 patients and found higher sensitivity for USS (100% vs 83%). The MRI protocol used in this study was limited just to DWI and that makes it less relevant to our study where we include additional sequences. Furthermore, this study was limited by high attrition rate.
- The MAGNUS-HCC project from Korea compared annual non-contrast enhanced MRI to 6 monthly USS as surveillance in people with cirrhosis and an annual risk of HCC of at least 5%. The study reported no difference in the sensitivity of the two approaches (annual nceMRI (71%) vs 6 monthly USS (45%); p=0.077). However, a simulated approach where annual nceMRI was added to the 6 monthly USS improved sensitivity to 84% which was significantly better than then sensitivity of 6 monthly USS.

5.5. Potential risks and benefits

If MRI is superior to USS for HCC surveillance participants may benefit from diagnosis of HCC at an earlier stage, which in turn can lead to more effective treatment and better survival.

The main risk to participants will be risks related to false positive results that may lead to unnecessary anxiety, added investigations and possible invasive procedures. The risk of suffering harm during the MRI examination is minimised through safety screening which will be repeated before each scanning session.

6. OBJECTIVES AND OUTCOME MEASURES

	Outcome Measures	Timepoint(s)
Primary Objective To evaluate the diagnostic performance of non-contrast enhanced (nceMRI) and ultrasound scans (USS) as surveillance tools for the diagnosis of hepatocellular cancer (HCC).	True positive tests for HCC per round of surveillance False positive tests for HCC per round of surveillance Positive predictive value for HCC per round of surveillance True negative tests for HCC over the 30 months of surveillance False negative tests for HCC over the 30 months of surveillance Sensitivity and specificity of nceMRI and USS for HCC over 30 months of surveillance	Per round of surveillance analysis will be done for each visit: Baseline, visits 2, 3, 4, 5 and 6 For the 30 months of surveillance, analysis will be done for the entire 30 months of surveillance
Secondary objectives		
To determine the stage and size of HCC at diagnosis and the number of indeterminate lesions detected	Numbers of HCC detected by nceMRI and USS at a very early, early, intermediate or advanced stage as defined by the Barcelona Clinic Liver Cancer staging system.	At each 6 monthly surveillance round (Baseline, visits 2, 3, 4, 5 and 6

		The number and size of HCC tumours per participant with HCC The number of new indeterminate lesions identified at each surveillance round	
To determine the proportion of patients that receive treatment with curative intent		Proportion of participants diagnosed with HCC who go on to receive treatment with curative intent	At any time point an HCC is diagnosed, the analysis will be conducted once all participants complete the study.
To evaluate the impact of the modality used for HCC surveillance on quality of life (QoL) and anxiety and depression		Results of the EQ-5D-5L questionnaire and Hospital Anxiety and Depression Scale questionnaire	At each 6 monthly surveillance round (Baseline, visits 2, 3, 4, 5 and 6
To evaluate the participants' attitude, experience, and acceptability of nceMRI and USS for HCC surveillance		Results of participant experience questionnaire	Baseline, visit 5
To evaluate the feasibility of nceMRI and USS as surveillance tools for HCC		Number of missed appointments (cancelled or missed), number of participants lost to follow-up, Number of participants where HCC surveillance is no longer indicated	At the end of the study
To evaluate whether integration of nceMRI with clinical and laboratory variables can improve performance for HCC surveillance		Sensitivity and specificity of multivariable models for the diagnosis of HCC	End of study
To perform a mechanistic study to use multiparametric quantitative MRI to assess the background liver in patients with cirrhosis.		Quantitative variables extracted from MRI data; T1 (ms), R2* (ms), PDFF (%), ADC (mm^2/s)	End of study
To determine the long-term outcomes of study participants		A composite end point including the outcomes of: all cause mortality, liver related mortality, liver decompensation (ascites, hepatic encephalopathy, variceal bleeding), hepatocellular cancer, non primary liver cancer, liver transplantation	Up to 10 years after the last study MRI scan is performed
Comparator – Reference standard	The reference standard will be diagnosis of HCC based on contrast enhanced CT/MRI or histology or by consensus in multi-disciplinary team meetings at the local liver clinic.		

7. STUDY DESIGN

This will be a single-arm, multi-centre, prospective cohort study evaluating the diagnostic accuracy of nceMRI and USS for diagnosis of HCC in people at high risk of HCC. People at high risk of HCC include those with liver cirrhosis and a high risk of HCC, or those with previous successfully treated HCC who are back in surveillance with USS. Participants will be recruited from UK hospital-based liver clinics over a period of 18 months and study procedures will take place in UK hospitals and academic centres. Participants will undergo 6 rounds of 6 monthly surveillance with nceMRI and USS over 30 months. Participants will be invited to complete questionnaires at each study visit. Relevant data will also be extracted from the participants' medical records. If at any surveillance round, a surveillance test raises a concern for the presence of HCC, participants will undergo full diagnostic contrast enhanced MRI (ceMRI) to determine whether HCC is present or not. In cases where indeterminate lesions for HCC are reported, these may require further tests including contrast CT, follow-up contrast enhanced MRI, or biopsy as directed by the clinical team. All participants will undergo diagnostic full contrast enhanced MRI at the end of their study participation. If an HCC is diagnosed at any point in the study, then participants will receive treatment according to standard clinical protocols as part of standard of care.

Long-term follow up of medical records from NHS England, the NHS Central Register for Scotland and other patient registries may be conducted for up to 10 years after the end of the active follow up phase. Data obtained from these registries will include but is not limited to liver disease, decompensation episodes, HCC diagnosis, liver transplantation and death. There will be no additional involvement from study sites or participants, as the long-term follow up only involves accessing centrally held medical data.

The overall study design and participant flow is summarised in Figure 1.

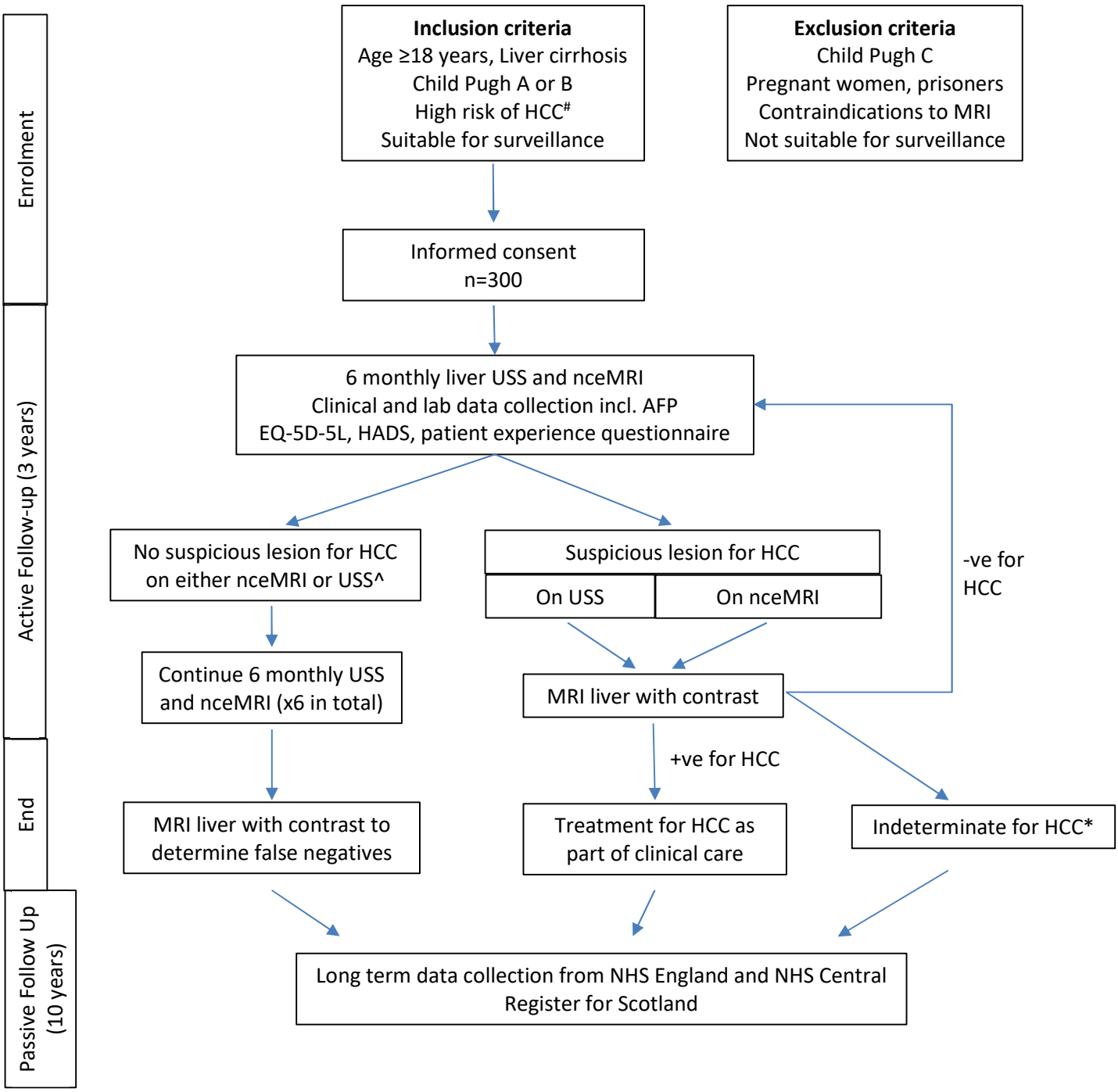

Figure 1: AMULET study design and patient flow

Abbreviations: HCC: hepatocellular cancer; USS: ultrasound scan; nceMRI: non-contrast enhanced MRI; AFP: alpha-fetoprotein; HADS: hospital anxiety and depression scale; +ve: positive; -ve: negative

see section 9.4 for the description of the procedure for HCC risk estimation

^A contrast enhanced MRI scan may be needed depending on AFP levels (see section 11.2)

*Indeterminate lesions will be those that are not definitely HCC and not definitely benign (LI-RADS 3 or LI-RADS 4). The local HCC multidisciplinary team will determine how these are followed up (assessment with alternative imaging modality, interval contrast enhanced scan, biopsy or another follow-up strategy). For the analysis of sensitivity and specificity that will be conducted over the 30 months of follow-up, cases where surveillance tests identified indeterminate lesions, will be counted as true

positives if the lesion progresses to HCC by the end of follow-up and as false positive if they remain indeterminate or are subsequently classed as definitely benign. For the analysis that will be conducted for each surveillance round, the number of indeterminate lesions identified by nceMRI and / or USS will be recorded.

8. PARTICIPANT IDENTIFICATION

8.1. Study Participants

Participants with a high risk of HCC will be included. Participants will have liver cirrhosis from ArLD, MASLD, chronic hepatitis C, chronic hepatitis B or genetic haemochromatosis, or with chronic liver disease and prior successful treatment for HCC without recurrence and who are back in surveillance with USS.

8.2. Inclusion Criteria

- Participant is willing and able to give informed consent for participation in the study AND
- All genders, aged 18 years or above AND
- Eligible for HCC US surveillance in the opinion of the local investigators AND
- Child Pugh score A or B AND
- Diagnosed with liver cirrhosis due to ArLD, MASLD, chronic hepatitis C, chronic hepatitis B, genetic haemochromatosis AND
- Have an annual risk of HCC of at least 3% as determined by the aMAP score (see 9.4 for details) OR
- Participants with chronic liver disease (with or without cirrhosis) who had successful treatment for HCC, have not had a recurrence and have returned to 6 monthly surveillance with USS

8.3. Exclusion Criteria

The participant may not enter the study if ANY of the following apply:

- Contraindication to MRI
- Known allergy / reaction to intravenous gadolinium contrast
- Prisoners
- Pregnancy or breast feeding
- Previous liver transplant
- Participants who are known to have indeterminate liver nodules on prior imaging requiring ongoing follow-up with MRI or CT
- Previous HCC treated with curative intent and still being followed up with CT or MRI with contrast for possible recurrence
- Estimated glomerular filtration rate of <30 ml/min/1.73m^2

- Participant is on haemodialysis
- Participants who are unlikely to comply with the study procedures in the opinion of the local investigator
- In the view of the clinician, if the participant has a co-morbidity likely to lead to death within the following 12 months

9. PROTOCOL PROCEDURES

9.1. Recruitment

Recruitment centres will be secondary and tertiary care hospitals. Clinical and research teams within NHS Trusts will identify and approach potential participants and may send out the Participant Invitation Letter and Participant Information Sheet ahead of the research visit. A reply slip is included in the Participant Invitation Letter which potential participants can return to the recruiting site to express their interest in the study and be invited for a visit. Participants will be recruited if they fulfil the inclusion / exclusion criteria.

To facilitate recruitment to the study eligible participants may be identified from other cohorts of participants at risk of HCC, such as the Pearl study (IRAS 285362).

9.2. Participant identification from the Pearl study

The Pearl study is a prospective cohort study of people with cirrhosis in the UK, conducted by the same investigators as AMULET. The Pearl study investigators will identify, from the database, those participants who have indicated that they are happy to be approached to take part in future studies, their eligibility will be checked and those eligible will receive an Invitation Letter and Participant Information Sheet ahead of the research visit. If they are happy to take part they will ask to indicate it on the reply slip and return it back to the study team. The research team will contact and arrange a visit.

We will ask permission of Pearl study patients who are eligible and are recruited into AMULET to store their Pearl study number for the purposes of data linkage.

9.3. Screening and Eligibility Assessment

This section refers to the screening and eligibility checks for inclusion in the study (checking inclusion / exclusion criteria and determining the annual risk of HCC) and not to the screening / surveillance for HCC that may be happening as part of routine practice. The maximum duration allowed between screening and enrolment to the study will be 12 months. There will be no exceptions made regarding eligibility, i.e., that each participant must satisfy all the approved inclusion and exclusion criteria of the protocol. Screening will be done via review of the medical record and / or screening of the Pearl cohort as described above. During screening, available data in the medical record or in the Pearl and other databases will be used to check eligibility.

9.4. Determining the annual risk of HCC

Part of the screening procedures for eligibility will be the determination of the annual risk of HCC for each participant. A number of HCC risk scores have been described[28-34] but most of them lack sufficient validation or are designed specifically for people with liver disease from a specific aetiology. The score that has been most extensively validated and the one that we will use to determine the risk of HCC or participants in our study is the "age, male, albumin-bilirubin, platelet count (aMAP)" score[35, 36]. The score ranges from 0-100, where a score of <50 is associated with a low risk of HCC, a score of 50-60 is associated with an intermediate risk of HCC and a score >60 is associated with a high risk of HCC[35]. Furthermore, the aMAP score can provide further information on the risk as a percentage risk of developing HCC over the next 3 years. For the purpose of our study high risk will be defined as an annual risk of HCC of at least 3% (or 3-year risk of HCC of at least 9%).

Our risk prediction strategy may be revised in the face of any future developments that refine and improve the aMAP score or its derivatives.

9.5. Informed Consent

The participant must personally sign and date the latest approved version of the Informed Consent form before any study specific procedures are performed.

Written and verbal versions of the Participant Information Sheet (PIS) and Informed Consent Form (ICF) will be presented to the participants detailing no less than: the exact nature of the study; what it will involve for the participant; the implications and constraints of the protocol; the known side effects and any risks involved in taking part. It will be clearly stated that the participant is free to withdraw from the study at any time for any reason without prejudice to future care, without affecting their legal rights, and with no obligation to give the reason for withdrawal.

The participant will be allowed as much time as wished to consider the information, and the opportunity to question the Investigator, their GP or other independent parties to decide whether they will participate in the study. Written Informed Consent will then be obtained by means of participant-dated signature and dated signature of the person who presented and obtained the Informed Consent. The person who obtained the consent must be suitably qualified and experienced and have been authorised to do so by the Chief/Principal Investigator. One copy of the signed Informed Consent will be given to the participant and another kept in their medical notes. The original signed form will be retained at the study site.

Continuous consent will be confirmed at subsequent visits.

9.6. Registration

This is a non-randomised study. Once participants sign the ICF they will be assigned a unique study identifier and will be registered on web-based registration systems (REDCap and XNAT).

9.7. Blinding and code-breaking

This is a single arm study evaluating nceMRI and USS as tests for HCC surveillance. The blinding procedures in the study will therefore focus on ensuring the acquisition and reporting of USS and nceMRI are blinded from each other.

Timing of USS and nceMRI acquisition and reporting

USS are usually performed and reported by the same operator. It is therefore usual practice for USS to be reported immediately after the acquisition of the data. On the other hand, nceMRI scans are usually acquired by MR radiographers and an MR radiologist reports on the data subsequently. There may therefore be an interval between acquisition and reporting of nceMRI data. For the purposes of this study, surveillance USS and nceMRI should preferably be acquired on the same day. Reports for both tests should be available to the clinical team within 4 weeks of the first scan being acquired. Therefore, the second scan can be acquired up to 4 weeks after the first scan, but in this case, the second scan must be reported on the same day it is acquired.

Blinding procedure

In any surveillance round, the surveillance test that is acquired first, will be labelled with and reported under the AMULET study identifier. This will ensure that the report and images for the first surveillance test are kept separate from the electronic patient record and the radiology department PACS systems and will not be available to the radiologist reporting the scan being performed second at each 6 monthly surveillance episode. Once the second scan is reported then the images and report of the first test will be un-blinded and uploaded to the electronic patient record and PACS system.

1. First scan is performed – either USS or nceMRI
    a. Scan is labelled and reported using AMULET study ID only – no personal identifiers should be included
    b. Report proforma is completed and entered into study database
    c. **The report and images should not be uploaded to the electronic patient record or radiology department PACS system at this point**

2. Second scan is performed within 28 days – either USS or nceMRI (whichever was not performed as the first scan)
    a. Patient identifiers may be used and report/images uploaded as normal

3. After reporting of the second scan is complete, the report/images from the first scan should be un-blinded and uploaded to the electronic patient record and PACS system.

If sites are not able to implement any of the above blinding procedures due to logistical reasons, then investigators reporting USS and nceMRI will have to confirm in their report that they did not access the reports or images of contemporaneous scans.

9.8. Description of study intervention(s), comparators and study procedures (clinical)

This a non-interventional study.

9.8.1. Description of comparator(s)

The comparator will be the diagnosis of hepatocellular carcinoma based on the typical features on contrast enhanced MRI or CT or histological diagnosis (biopsy or resection) or a consensus diagnosis of HCC as determined by the local MDT will be accepted as a diagnosis of HCC.

On study contrast enhanced MRI scans

For cases where a contrast enhanced MR is done following a positive surveillance test (on study ceMRI), lesions classified as LI-RADS 1 or 2 will be regarded as negative for HCC and lesions classified as LI-RADS 5 will be regarded as positive for HCC. Lesions classified as LI-RADS 3 or 4 will be regarded as indeterminate and will be followed up according to the local clinical routine. If LI-RADS 3 or 4 are designated as HCC by the local MDT, or they are proven to be HCC on biopsy, or they progress to LI-RADS 5 within the 30 months of follow-up then they will be defined as HCC for the analysis relating to the whole 30 month period of surveillance. In cases where LI-RADS 3 or 4 lesions remain under follow-up at the end of the 30 months follow-up without a clear classification as HCC or benign, or where they have been histologically proven to be benign, then they will be classified as negative for HCC for the purposes of the analysis. The classification of lesions at on-study ceMRI scans is shown below in Figure 2. The follow-up of LI-RADS 3 and 4 lesions in this situation will finish at the timepoint that visit 6 was due or at an earlier time point if a definitive classification is reached before then.

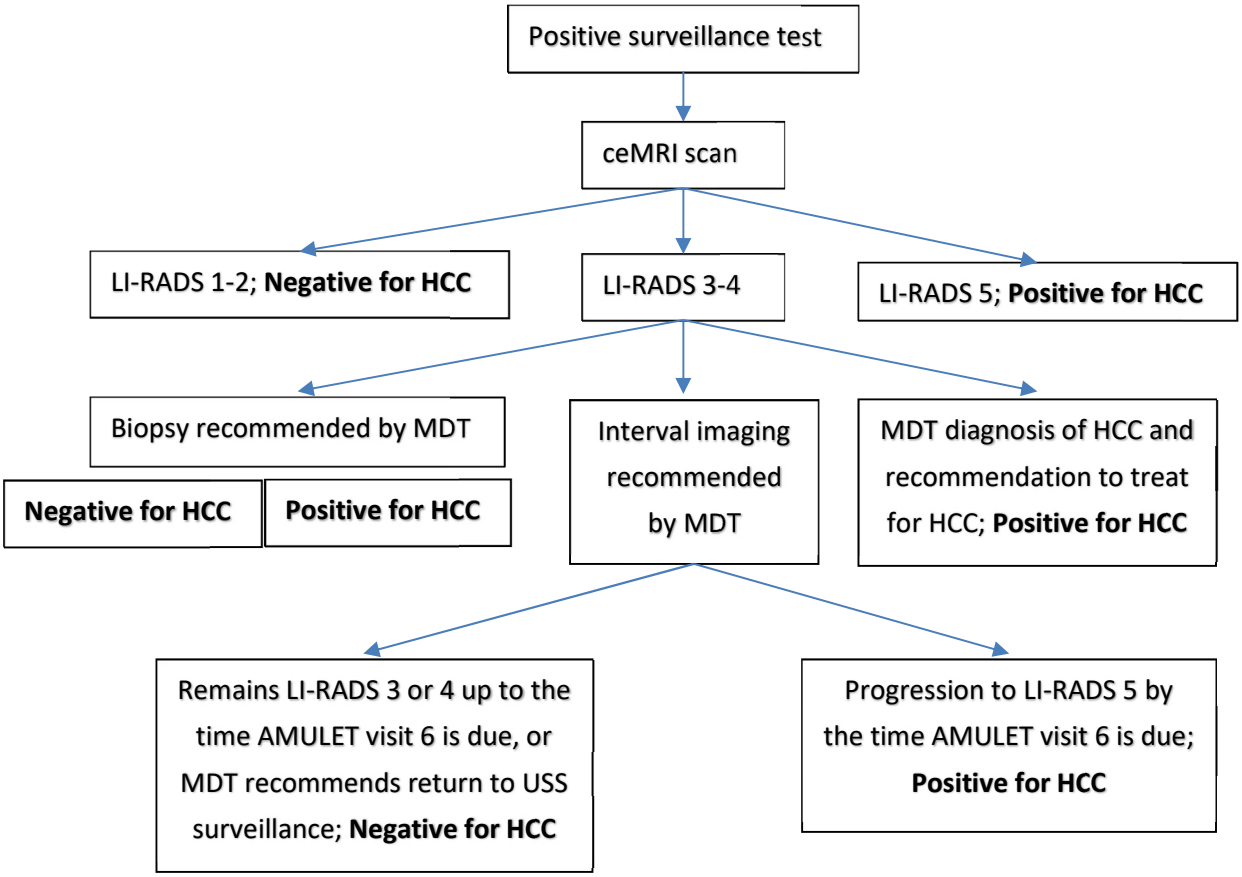

Figure 2: Flowchart for the classification of lesions detected on contrast enhanced MRI performed during the study following a positive surveillance test. In cases where lesions are determined as negative within the 30-month surveillance period, participants will re-enter the AMULET surveillance schedule until they complete the study. Where a positive for HCC diagnosis is made, participants will end their participation, will undergo no further surveillance and will be managed according to the recommendations of the local MDT. Participants with LI-RADS 3 or 4 lesions who are undergoing interval contrast enhanced imaging as recommended by the local MDT will be suspended from participation in AMULET.

End of Study contrast enhanced MRI scan

Participants that complete all 6 rounds of surveillance without a positive surveillance test and without HCC will undergo a contrast enhanced MRI at the end of the study (end of study ceMRI). The diagnostic allocation schedule will be modified for these scans as there will be no opportunity to follow-up LI-RADS 3 and 4 lesions. In these scans LI-RADS 1, 2 and 3 will be classed as not HCC and LI-RADS 4 and 5 lesions will be classed as HCC.

Follow-up for indeterminate lesions beyond 30 months

To enable potential future research, participant consent will be sought to allow follow-up through medical records or through data provided from NHS England, the NHS Central Register for Scotland and other patient registries for up to 10 years after their study participation is completed. This is to allow for collection of data relating to lesions that are still indeterminate at the end of 30 months surveillance period and to evaluate if those without HCC at the end of the study still go on to develop HCC. To facilitate this follow-up, personal identifiable information will be collected and stored centrally with participants' permissions.

9.8.2. Description of study procedure(s)

Collection of Demographics and Medical History

A member of the study team will access the medical notes of the participant to obtain information about the individual's demographics, medical history, anthropological measurements (height, weight and resulting BMI) and previous clinical imaging data.

Participant questionnaires

Participants will be asked to complete paper copies of the EQ-5D-5L questionnaire and Hospital Anxiety and Depression Scale (HADS) at each research visit, and a study specific participant experience questionnaire relating to USS and nceMRI at the baseline visit and visit 5. Data will be transferred from the completed paper copies to the study electronic case record form by the site study investigators.

Ultrasound scan

USS reporting for the imaging findings

Ultrasound scans are performed as part of the participant's routine clinical care. Surveillance USS findings will be interpreted and reported by appropriately trained and experienced sonographers or radiologists at each site, who will receive training in study specific assessments and documentation, including the blinding process. Each USS episode will have a findings category score assigned using the US LI-RADS[37] reporting system (US1-negative; US2 subthreshold; US3 positive)."US1- negative" examinations will be those where no suspicious observations are noted, or where there are only definite benign observations. "US3 -positive" examinations will be those with an observation ≥10mm in diameter

that is not definitely benign, including areas of parenchymal distortion or new thrombus in the portal vein or hepatic vein. “US2 subthreshold” examinations will be those with observations <10mm in diameter that are not definitely benign.

“US1- negative” will be designated as negative examinations for the purposes of our study. Participants will return for 6 monthly surveillance after an “US1-negative” examination.

“US3 positive” will be designated as positive examinations for the purposes of our study and will be followed up by a full contrast enhanced MRI scan.

“US2 subthreshold” will be classed as negative in our study and handled in the same way as “US1-negative”. The LI-RADS recommendation is that these cases can be followed up with repeat ultrasound in 3-6 months and since our study protocol will include 6 monthly scans, our scanning schedule is within this recommendation. Furthermore, data suggests that sub-threshold lesions are unlikely to progress to HCC[38]. Discretion will be allowed if the clinical teams decide to follow a more frequent scanning schedule (e.g. after 3 or 4 months).

USS reporting for the imaging quality

The US LI-RADS visualisation score will be used to describe the quality of the USS examination as:

VIS A: no or minimal limitations

VIS B: moderate limitations

VIS C: severe limitations

Non-contrast enhanced Magnetic Resonance Imaging

Safety screening and participant safety during the scanning sessions

Contraindications to magnetic resonance imaging will be excluded by use of the radiology departments screening forms. For this, trained radiology department staff will go through a safety questionnaire with the participant before scanning as per standard clinical practice. The MRI scanner consists of a large powerful magnet. Magnetic resonance imaging uses no ionising radiation. There are, however, potential hazards associated with MRI and the scanning of participants including the presence of surgical implants, participants’ clothing, jewellery (such as body piercings), bodily habitus, or medical conditions. A comprehensive list of potential risks has been compiled, and the participant should be checked against this by the operator, prior to entering the controlled areas of the MRI scanners, according to local SOPs. During the actual scanning procedure, the scanner produces loud noises and facility procedures will be followed regarding hearing protection including the use of earplugs. Small mirrors that will allow participants to see out of the scanner and relieve feeling of claustrophobia may be used. During the scan, the participant will be able to communicate with the operator in the control room. In addition, they will be given a call button, which allows them to alert the operator at any time. People with a history of claustrophobia may be excluded from participation in the study if they are unable to tolerate MRI. All participants will still be introduced carefully to the scanner and allowed to leave at any stage, should they wish to do so. Once in the scanner, participants will be able to indicate immediately if they wish the scanning to cease by pressing a call button in their hands.

nceMRI: image acquisition

The nceMRI protocol includes three “core” nceMRI sequences (Table 1) to address the primary aim of assessing diagnostic accuracy of lesion recognition. These can be acquired within a 15-minute scan slot. Four additional nceMRI sequences (adding ~10 minutes of scan time) will be acquired with patient consent for the purpose of the mechanistic sub-study. To ensure widespread NHS utility, our protocol is scanner/vendor/field strength (1.5/3T) agnostic and has sufficient spatial resolution (~2-3 mm in-plane, 3-5 mm axial slices) to detect small HCCs (<2 cm) across the whole liver.

All recruiting sites will need to acquire and report on the core sequences for the presence or absence of a suspicious nodule. MRI scans will be performed with participants fasted for at least 4 hours. The quantitative mechanistic sequences will be acquired by centres with appropriate MR capabilities and will not require radiological reporting.

Table 1: nceMRI protocol comprising core sequences for lesion recognition and mechanistic sequences to study the background "field effect".

	MRI sequence	Scan Duration	Suspicious Lesion Recognition	Mechanistic Study
Core Sequences:				
1	**T_2-weighted (T2WI)** A) Turbo-spin echo (TSE) echo time (TE) ~90 ms, fat suppressed (FS). B) FSE with no FS and long TE >120ms.	**3 min** (6 x 15 s breath hold (BH))	Mild-moderately hyperintense. High T_2 weighting to distinguish between cystic and solid lesions. *Fat containing HCC*: Isointense on T2WI FS. *Iron containing HCC:* Hypointense on T2WI.	Radiomics features of background liver for study of "field effects".
2	**T_1-weighted (T1WI)** A) Dual gradient in-phase (IP)/out phase (OP) recalled echo (GRE). B) 3D Thrive with FS.	**1 min** (2 x 15 s BH)	Hypointense in OP compared to IP due to fat sparing. Hypointense in IP due to iron deposition. Thrive hypointense in fat sparing. Nodule-in-nodule/mosaic architecture.	Radiomics features of background liver for study of "field effects".
3	**Diffusion weighted (DWI)** DWI with 4 b-values from 0-800 s/mm^2. (Spans range in MAGNUS-HCC and MIRACLE-HCC trials.)	**4 min** (Free breathing)	Hyperintense on high b-value. ADC of lesion similar or hypointense due to diffusion restriction. *Fat containing HCC*: Isointense on DWI FS.	"Field effects" in ADC.
Quantitative Mechanistic Sequences:				
4	**Diffusion weighted (DWI)** Protocols as collected in 3 above but with additional DWI b-values for IVIM	**4 min** (Free breathing)	Hyperintense on high b-value. ADC of lesion similar or hypointense due to diffusion restriction. *Fat containing HCC*: Isointense on DWI FS.	"Field effects" in IVIM maps of restricted diffusion and vascularity.
6	**3D multi-echo DIXON** Quantitative 6 echo DIXON with short echo times (1–6 ms).	**30 s** (1 x 16 s BH)	IP and OP as for 2, as well as fat (F) and water (W) images. Fat fraction (PDFF) and R_2* maps to detect fat sparing lesions.	"Field effects" in PDFF and R_2* maps.
7	**3D R_2* mapping** High resolution R_2* mapping with 12 echoes with longer echo times (1–18 ms).	**1 min** (2 x 16 s BH)	R_2* hyperintense for iron sparing lesions.	"Field effects" in R_2* map.
8	**3D T_1 mapping** Variable flip angle T_1, plus B_1 and B_0 mapping.	**4 min** (6 x 15 s BH)	T_1 mild-moderately hyperintense.	"Field effects" in T_1 map.

nceMRI: reporting for the imaging findings

nceMRI will be evaluated by board-certified abdominal radiologists at each site using a standardised proforma. On nceMRI, a suspicious nodule is defined as a solid newly appearing nodule ≥ 1 cm that is not definitely benign. Diffuse infiltrative lesions with or without suspected tumour in vein are also considered suspicious. Simple cysts, haemangiomas, and lesions previously diagnosed as benign lesions are not considered suspicious, irrespective of the size.

nceMRI: reporting for the quality of the scans

Automated quantitative quality assurance (QA) of nceMRI in terms of image signal-to-noise ratio (SNR) measures will be performed and these results will be stored on the XNAT platform that will be used for imaging data management. Furthermore, nceMRI scans will be reported locally using a standardised proforma that will be developed based on other multicentre studies that have investigated implementation of MRI (e.g. STREAMLINE-C[39] and STREAMLINE-L[40]).

Contrast enhanced magnetic resonance imaging

In addition to the checks for the safety of having an MRI scan (which will be the same as for the nceMRI scan) there will be added check for the safety of receiving intravenous gadolinium contrast. Gadolinium contrast is contraindicated in people with eGFR <30 ml/min/1.73m^2. Estimated GFR will therefore be checked prior to inclusion in the study (see exclusion criteria) and before each ceMRI procedure. For the ceMRI an intravenous cannula will be inserted into the participants arm by a radiographer or other appropriately trained person. Scans will be acquired before and after the administration of an intravenous contrast agent. Scans will be reported by study radiologists at each site using a standardised proforma including LI-RADS classification.

9.9. Baseline Assessments

The baseline visit (visit 1) will last around 120 minutes and will take place at NHS Hospital Trusts and academic centres. This visit will ideally take place on a single day but may take place on two separate days, with the first imaging scan and data collection taking place up to 28 days prior to the second imaging scan (see also section 9.7).

A member of the study team will check eligibility of the participant and will answer any further questions a participant might have. The participant is fully enrolled into the study if eligibility criteria are met and written informed consent has been obtained. On enrolment into AMULET, each patient will be assigned a unique study number. All clinical and imaging data will be recorded against that number. Once written informed consent has been obtained, participants will receive the following assessments/procedures (details can be found above):

- Collection of Demographics and Medical History (duration 10 minutes)
- Physical Examination (recording of height and weight) (duration 5 minutes)
- Completion of MRI safety check (5 minutes)
- Clinical care USS (20 minutes)
- NceMRI (20 minutes)
- Completion of EQ-5D-5L and HADS questionnaires at the beginning of the study visit (30 minutes)
- Acceptability of MRI and USS as surveillance test questionnaire (to be completed immediately after the relevant scan; 30 minutes)

9.10. Subsequent Study Visits

At each subsequent visit, the patient's eligibility to the study will be checked and patients will undergo another formal safety assessment before undergoing MR examinations. Patients will have to attend their MRI having fasted for at least 4 hours.

Each follow up visit will ideally take place on a single day but may take place on two separate days, with the first imaging scan and data collection taking place up to 28 days prior to the second imaging scan (see also section 9.7).

Participants will attend follow-up every 180 days for five visits after baseline (total of six visits including baseline). At each subsequent visit, confirmation of continuous consent will be obtained from the participant and an eligibility check will be carried out to ensure that participants still fulfil the inclusion and exclusion criteria.

Study visits will last for 120 minutes and assessments/procedures are as follows:

- Collection of Demographics and Medical History (duration 10 minutes)
- Physical Examination (recording of height and weight) (duration 5 minutes)
- Completion of MRI safety check (5 minutes)
- Clinical care USS (20 Mins)
- nceMRI (20 minutes)
- Completion of EQ-5D-5L and HADS questionnaires at the beginning of each study visit (30 minutes)
- Acceptability of MRI and USS as surveillance test questionnaire (to be completed immediately after the relevant scan on visit 5 only, 30 minutes)

Visit 6, final study visit (120 minutes)

At visit 6, in addition to the other study procedures listed above, a contrast enhanced MRI will be performed on all participants.

Contrast enhanced MRI will also be performed at any visit if the surveillance USS or nceMRI show a suspicious nodule for HCC.

Timing between visits

The baseline visit (visit 1) will be designated as D0. If the study procedures take place on different days for the baseline visit then D0 will be the first day on which study procedures were carried out. Once the baseline visit is completed, dates will be assigned for subsequent visits (visit 2: D180, visit 3: D360; visit 4: D540 etc).

A study visit that takes place within 30 days of the designated visit date will be regarded as a visit that took place on time. Accepting that there will be instances where there are last minute cancellations due to unforeseen circumstances and to allow flexibility in these situations, out of schedule visits will be permitted. Visits taking place between +30 and +90 days of the scheduled visit will be counted as a delayed visit. If the visit cannot be organised within the 90-day window then the visit will be regarded as missed and any procedures taking place more than 90 days after the scheduled visit time, will be assigned as subsequent visit procedures. This schedule will ensure that all study visits are completed within the 30-month window of follow-up.

If only one scanning procedure is performed within the designated visit window, this will be classed as a missed visit.

Examples of study visit timings are set out in Figure 3 below.

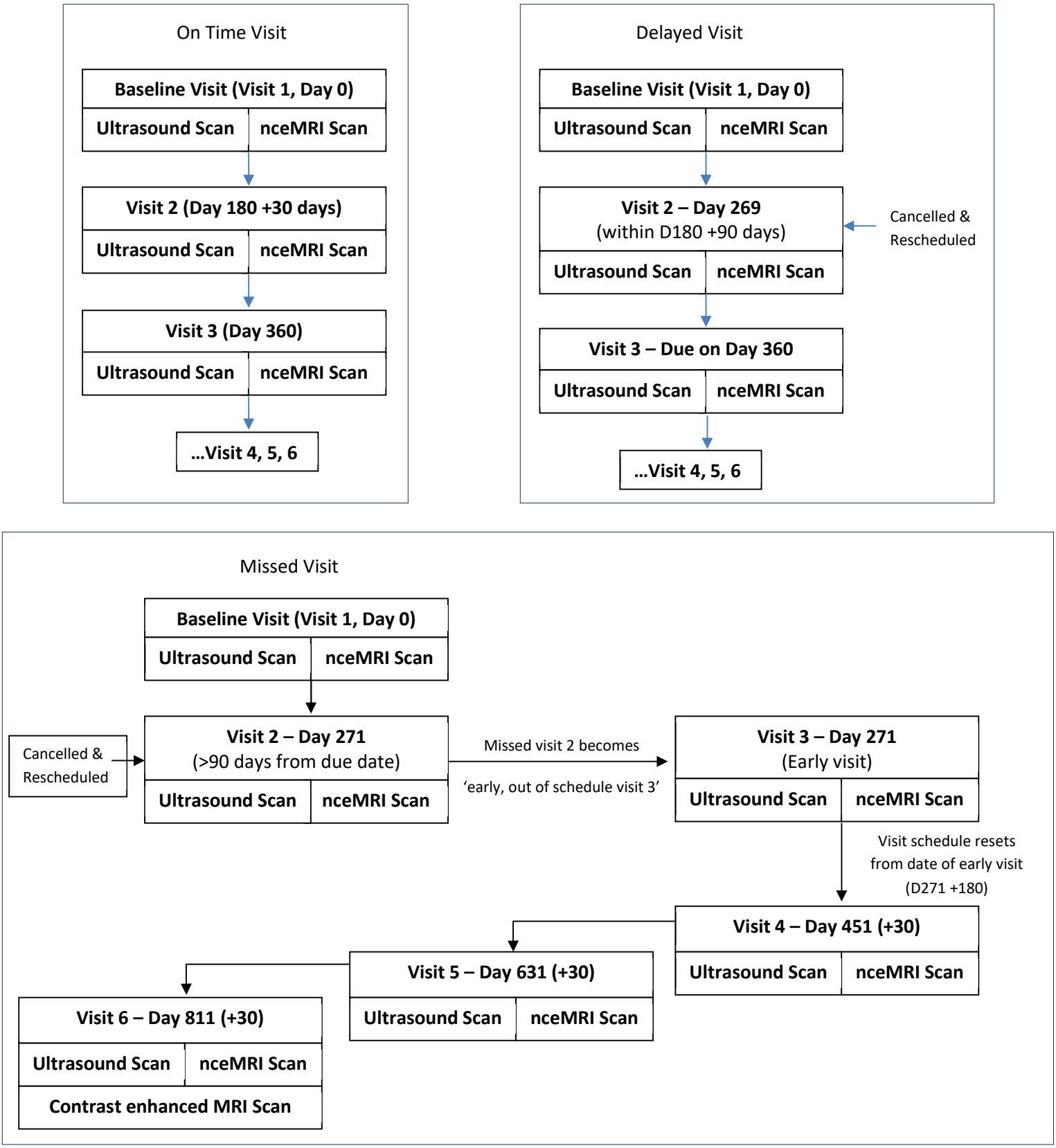

Figure 3. Examples of interval allowed between each study visit

9.11. Follow Up

Follow up visits/procedures after specific clinical outcomes (HCC diagnosis/liver transplant and death)

HCC Diagnosis

If a diagnosis of HCC is made during the study, no further in person follow up visits or nceMRI scans will take place. Follow up data will continue to be collected at 6 monthly intervals from hospital records.

Liver Transplant

If a participant receives a liver transplant during the study, no further in person follow up visits or nceMRI scans will take place. Follow up data will continue to be collected at 6 monthly intervals from hospital records.

Death

If a participant dies, the date and cause of death should be clearly documented using the 'Mortality' form within REDCap. In the event that a participant's death certificate is not available on hospital records, the local study team may be asked to contact the relevant GP to obtain date/cause of death data.

Long-Term Follow-up

The study teams will obtain data from NHS England, the NHS Central Register for Scotland and other patient registries on participants for up to 10 years after the last follow-up visit, phone call or email. This will be a passive follow-up with no participant involvement.

9.12. Sample Handling

Blood or other biological samples will not be collected from participants.

9.13. Early Discontinuation/Withdrawal of Participants

During the course of the study a participant may choose to withdraw early from the study at any time. This may happen for several reasons, including but not limited to:

- The occurrence of what the participant perceives as an intolerable AE.
- Inability to comply with study procedures
- Participant decision

Participants may choose to stop study assessments but may remain on study follow-up.

Participants may also withdraw their consent, meaning that they wish to withdraw from the study completely. In the case of withdrawal before completing the 30 months of study participation and without completing the 6 research visits, the following options for a tiered withdrawal from the study will be available to participants:

1) Participants may withdraw from further research visits, and further communication but allow the study team to continue to access their medical records and any relevant hospital data that is recorded as part of routine standard of care; e.g., scans, blood results and disease progression data etc.

2) Participants can withdraw from the study but permit data obtained up until the point of withdrawal to be retained for use in the study analysis. No further data would be collected after withdrawal.

3) Participants can withdraw completely from the study and withdraw the data collected up until the point of withdrawal. The data already collected would not be used in the final study analysis.

In addition, the Investigator may discontinue a participant from the study MRI procedures at any time if the Investigator considers it necessary for any reason including, but not limited to:

- Pregnancy
- Ineligibility (either arising during the study or retrospectively having been overlooked at screening)
- Significant protocol deviation
- Significant non-compliance with the study requirements
  Clinical decision (e.g. patient no longer suitable for ongoing surveillance)

Participants who withdraw will not be replaced as the sample calculation already allows for attrition.

The type of withdrawal and reason for withdrawal will be recorded in the CRF.

If the participant is withdrawn due to disease progression or an adverse event, the Investigator will arrange for follow-up visits or telephone calls until the adverse event has resolved or the participants condition optimised.

Procedures to minimise attrition

Attrition may result due to patients not returning for follow-up visits, or progression of liver disease to Child Pugh stage C or other comorbidities such that surveillance is no longer indicated. To avoid attrition from missed scans, we plan to call participants within two weeks prior to their appointment to remind them of their upcoming visit and participants will be reimbursed for travel and food. To avoid attrition from liver disease decompensation, sites will be asked to manage patients according to National guidelines[10].

9.14. Definition of End of Study

The end of the study from a participant perspective will be month 30 (visit 6). The end of study will be the date of the final analysis of the data of the last participant.

10. SAFETY REPORTING

This is not an interventional study, but MRI scanning can have potential side effects.For this reason, data on serious adverse events (SAE) relating to the MRI procedures (ceMRI and nceMRI) will be collected in the SAE report form.

10.1. Definition of Serious Adverse Events

A serious adverse event is any untoward medical occurrence that:

- results in death
- is life-threatening
- requires inpatient hospitalisation or prolongation of existing hospitalisation
- results in persistent or significant disability/incapacity
- consists of a congenital anomaly or birth defect.

Other 'important medical events' may also be considered a serious adverse event when, based upon appropriate medical judgement, the event may jeopardise the participant and may require medical or surgical intervention to prevent one of the outcomes listed above.

NOTE: The term "life-threatening" in the definition of "serious" refers to an event in which the participant was at risk of death at the time of the event; it does not refer to an event which hypothetically might have caused death if it were more severe.

10.2. Follow-up of Serious Adverse Events

Any serious adverse event will be followed up until resolution or stabilisation.

10.3. Reporting Procedures for Serious Adverse Events

A serious adverse event (SAE) occurring to a participant should be reported to the REC that gave a favourable opinion of the study where in the opinion of the Chief Investigator the event was 'related' (resulted from administration of any of the research procedures) and 'unexpected' in relation to those procedures. Reports of related and unexpected SAEs should be submitted within 15 working days of the Chief Investigator becoming aware of the event, using the HRA report of serious adverse event form (see HRA website).

11. STATISTICS AND ANALYSIS

11.1. Statistical Analysis Plan (SAP)

The statistical aspects of the study are summarised here with details fully described in a statistical analysis plan that will be available from the time that the first participant is recruited. The SAP will be finalised before any analysis takes place.

11.2. Description of the Statistical Methods

Statistical analysis for Primary outcome measure

Measures of diagnostic performance will be determined per round of surveillance and over the 30 months of study participation.

Diagnostic performance per round of surveillance

At each round of surveillance, the following data will be calculated and compared between USS and nceMRI.

1. Number and proportions of positive surveillance USS and nceMRI – see section 9 for definitions of positive tests
2. Number and proportions of true positive (TP) and false positive (FP) USS and nceMRI.
   As each positive test will be followed by a full contrast enhanced MRI, TP and FP tests per round of surveillance will be calculated
3. Positive predictive value (PPV) of USS and nceMRI

Diagnostic performance for the overall study period of 30 months

For the purpose of this analysis, each USS and nceMRI scan for each participant completing the study will be assigned only one of the 4 possible diagnostic categories of: true positive (TP) or false positive (FP), true negative (TN) and false negative (FN). The sum of TP, FP, TN and FN in this analysis will therefore be equal to the total number of participants completing the study. TP and FP will be determined at each visit as described above. TN and FN will be determined at the end of the study when participants undergo the reference standard ceMRI as part of the study protocol. FN results will also include those cases that present with HCC during the study without a prior positive test (interval cancers) or cases where both USS and nceMRI are negative tests but a ceMRI scan is triggered by an AFP>20. Cases that are initially FP may subsequently change diagnostic category. For this analysis, the diagnostic category which is applicable at the end of the study will be used. For example, if a finding initially classed as an FP develops into an HCC that was correctly identified by the surveillance tests, then the diagnostic test will be counted as a TP for this analysis.

Sensitivity and specificity estimates will be calculated separately for nceMRI and USS and compared. Statistical significance of the observed differences in sensitivity/specificity will be evaluated using the McNemar's test of paired proportions, with a two-tailed P-value <0.05 used as the significance criteria.

Further, we will assess if specific individual-level factors are associated with the diagnostic performance of nceMRI and USS. These will include BMI, gender, age and underlying disease aetiology. For sensitivity, we will assess this by fitting a logistic regression model including all patients with HCC. The dependent variable will be detection via USS/nceMRI, whereas age/BMI and gender will be included as independent variables. Equivalent models will be fitted to determine factors associated with specificity, but this time confined to patients without HCC instead of patients with HCC. A further sensitivity analysis will be conducted in order to compare the sensitivity of nceMRI with USS depending on the USS visualisation scores.

Other considerations relevant to measuring the primary outcome

Alpha-fetoprotein

Alpha-fetoprotein will be measured as part of clinical care at each study visit. In the situation where both USS and nceMRI do not report suspicious lesions (test negative), a contrast enhanced MRI scan will still be needed if:

AFP ≥ 20 ng/mL OR doubling of AFP (or more) OR increasing on two consecutive tests.

If an HCC is diagnosed on a ceMRI that was triggered by AFP thresholds rather than by USS / nceMRI, then both USS and nceMRI will be regarded as false negatives

Incidental findings:

Focal hepatic lesions: If an incidental finding is noted in the liver but no further imaging recommended (e.g. simple cysts), scans will be classed as test negative. Lesions in the liver, which are not thought to be HCC, but are considered to require imaging clarification with e.g. contrast-enhanced imaging, will be classed as test positive in the main study endpoint, but will be subject to a planned sensitivity analysis.

Cirrhosis-related complications: If a new ascites is identified on USS or MRI, this will be recorded (small, moderate and large volume). Other non-cancer complications of cirrhosis, such as development of features of portal hypertension, or venous thrombosis will be recorded for both tests.

Extrahepatic: Extrahepatic incidental findings will be documented on the study proforma and assessed for likely significance. If a significant incidental finding is noted outside the liver this will be documented. Subsequent follow-up investigations will be recorded, as well as any significant diagnoses. Incidental findings in organs outside the liver will be managed according to local clinical routine, and not be counted as TP or FP when calculating sensitivity and specificity of nceMRI/USS.

Statistical analyses for secondary outcome measures

1. At each surveillance round, graphical methods will be used to analyse data for the numbers of:
    a. very early, early, intermediate and advanced stage HCC as defined by the Barcelona Clinic Liver Cancer Staging system
    b. the size and number of HCC, in TP cases
    c. The number of new indeterminate lesions
2. Graphical methods will be used to analyse data on the number and proportions of participants with HCC who receive treatment with curative intent.
3. Quality of life and anxiety and depression: QoL will be assessed using the EQ-5D-5L questionnaire and anxiety and depression using the Hospital Anxiety and Depression Scale (HADS). Patients will be asked to complete the questionnaires at 6 monthly intervals to coincide with their visits for MRI / USS. Associations of the results from these questionnaires with other variables will be explored, particularly with HCC diagnosis and FP surveillance tests.
4. Acceptability of MRI and USS as surveillance tests: Patients will be asked to complete questionnaires documenting their experience of USS and MRI at the baseline visit and visit 5. These questionnaires have already been developed based on the questionnaires used in the METRIC study[41], which assessed the acceptability of USS and MRI in patients with Crohn's disease. Scores derived from these questionnaires will constitute the outcome measure and they will be compared between nceMRI and USS.
5. Feasibility of nceMRI and USS as surveillance tools: To measure feasibility of nceMRI and USS as a surveillance tool, data will be collected on the number and reasons for missed scans. In particular we will determine if scans were cancelled by the hospital due to capacity issues, if the patient was lost to follow-up, or surveillance for HCC is no longer indicated. This data will be analysed using graphical methods.
6. Multivariable algorithms: Demographic, laboratory and clinical data will be collected every 6 months including Child Pugh and Model for End-Stage Liver Disease (MELD) scores. Multivariate analysis will be used to assess if inclusion of nceMRI sequences and routinely available data or other biomarkers

improves diagnostic performance compared to USS. The multivariate models will be developed and reported according to the updated TRIPOD (Transparent Reporting of a multivariable prediction model for Individual Prognosis Or Diagnosis) statement[42].

7. Mechanistic sub-study outcomes: Image processing of quantitative nceMRI and radiomics will be performed using semi-automated pipelines to study the "field effect". This will include:
    a. automated liver segmentation using a convolution neural network, and manual definition of HCC;
    b. creation of quantitative parameter maps from physical signal-models. We will perform model driven registration of DWI data to compute ADC and IVIM (D, D*, F) maps, quantify T1, R2*, and PDFF maps;
    c. extraction of summary quantitative parameters and radiomics features in background liver parenchyma using a region growing algorithm progressively away from the defined HCC lesions
    d. reporting the results in a standardised format and returning a table of imaging biomarkers for upload into the electronic data capture system.

11.3. Sample Size Determination

Sample size calculations were performed to estimate a) the minimum number of HCCs and b) patients with cirrhosis and number of HCC needed to detect a difference in sensitivity and specificity between nceMRI and USS. Calculations used McNemar's test for paired proportions (power 90%, type 1 error at 5%). Based on literature, we assumed nceMRI and USS sensitivity of 70-90%[43] and 30-50%[18] respectively, and nceMRI and USS specificity of 80%[43] and 90%[18] respectively. The calculations suggest that in most scenarios, 50 HCCs and 200 controls would be sufficient to identify a difference in sensitivity/specificity.

Table 2. Minimum number of participants required to demonstrate a statistically significant difference in sensitivity/specificity

Sensitivity		Ultrasound		
		se=30%	se=40%	se=50%
nceMRI	se=70%	31	54	116
	se=80%	21	30	50
	se=90%	14	19	27

Specificity		sp=90%	sp=95%	sp=98%
nceMRI	sp=80%	244	96	61
	sp=90%	NA	530	173
	sp=98%	173	2	NA

To observe at least 50 HCCs, the cohort will be enriched with people with a risk of HCC of at least 3% per year (see section 9.4 also). This 3% per year threshold is derived from risk distribution observed among the first 1500 patients recruited to the Pearl cohort. Assuming there will be 2150 participants in Pearl at the time of AMULET inception, and assuming we will continue to see the same risk distribution in the

latter recruited patients as for the first 1500 patients, we determined that selecting patients with a 3-year risk of >9% would give rise to 50 HCCs plus ~250-300 controls with liver cirrhosis and no HCC.

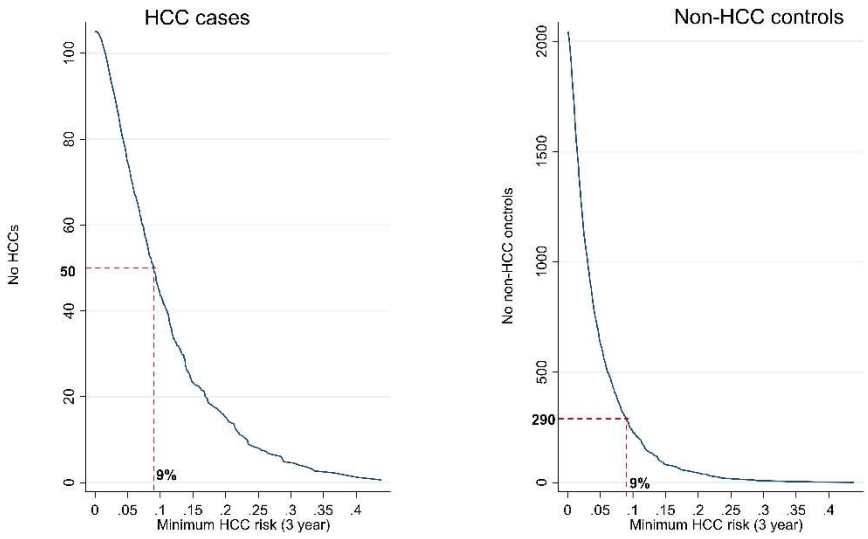

Figure 4. HCC risk distribution in Pearl – expected number of HCCs and non HCCs at a >3% annual HCC risk threshold

11.4. Analysis populations

All participants registered will be included in the analysis.

11.5. Decision points

A decision point is planned at the end of July 2025 to assess the study feasibility. Stop / go criteria based on recruitment will be assessed at this point. By the end of July 2025, it is anticipated that 90 participants would be recruited and if this is achieved the study will continue. If fewer than 90 participants are recruited by end of July 2025 then the Steering Committee will decide on whether to continue the study considering the following numbers as a guide:

If at least 80 participants are recruited, consider continuing the study;

If fewer than 80 participants are recruited, consider stopping the study.

11.6. Stopping rules

The final decision to terminate the study at any point will rest with the Study Steering Committee.

11.7. The Level of Statistical Significance

Statistical significance will be set at $p<0.05$.

11.8. Procedure for Accounting for Missing, Unused, and Spurious Data.

Participants must attend the baseline and last visit (v6) and have at least one ceMRI (after a positive surveillance test, or as per protocol at the end of the study period) in order to be included in the final analysis. Participants who do not meet this will be removed and replaced for the purposes of the statistical analysis. All data from participants that fulfil this criterion will be used and analysed using intention to diagnose methods. This is to ensure that cases where a participant completes one surveillance test but not the other at a particular visit are still included. The diagnostic category of the missed test will be determined according to the diagnosis on that visit and the final diagnosis at the end of the study. In cases of HCC diagnosis, the missed test will be assigned as FN. In cases of FP results on the surveillance test performed at that visit, the missed test will also be assigned as FP.

11.9. Procedures for Reporting any Deviation(s) from the Original Statistical Plan

Any deviations from the statistical analysis plan will be described and justified in the final report.

11.10. Health Economics Analysis

No health economic analysis is planned. However, the data we collect on health-related quality of life will provide the building blocks for future health economic analyses.

12. DATA MANAGEMENT

The data management aspects of the study are summarised here with details fully described in the Data Management Plan.

12.1. Source Data

Source documents are where data are first recorded, and from which participants' CRF data are obtained. These include, but are not limited to, hospital records (from which medical history and previous and concurrent medication may be summarised into the CRF), clinical and office charts, laboratory and pharmacy records, diaries, microfiches, radiographs, and correspondence.

CRF entries will be considered source data if the CRF is the site of the original recording (e.g. there is no other written or electronic record of data). All documents will be stored safely in confidential conditions. On all study-specific documents, other than the signed consent, the participant will be referred to by the study participant number/code, not by name.

12.2. Access to Data

Direct access will be granted to authorised representatives from the Sponsor and host institution for monitoring and/or audit of the study to ensure compliance with regulations.

12.3. Data Recording and Record Keeping

Imaging data

Imaging data will be managed on the XNAT (www.xnat.org) imaging informatics platform, which is designed and set up specifically for studies of this kind. The central XNAT instance will be hosted by the University of Oxford. XNAT provides a web-based interface for uploading and sharing imaging data in a user-friendly and interactive manner. Recruiting sites will be able to use the web-based interface to upload their data. All images will be uploaded in DICOM format from MRI (nceMRI and contrast-enhanced MRI collected at end of follow-up or earlier if HCC detected) and USS scanners.

Imaging data anonymisation

Imaging data will be pseudonymised and labelled with the study ID at the site before being uploaded to the study XNAT.

If MRI data containing participant identifiable information (PII) are uploaded to the study XNAT, the XNAT allows for these PII to be stripped and the files to be labelled with the study ID in an automatic process.

USS data may contain PIIs in the images themselves although these will be acquired under study ID, so should be pseudonymised at the point of acquisition. In such instances a semi-automated process will be employed to remove / mask the PII before the files are stored.

This anonymisation process ensures that every effort will be made to ensure only pseudonymised data will be uploaded by the sites, and only imaging data labelled with the study ID are kept centrally for long term storage.

Data from questionnaires

Participants will complete paper versions of the EQ-5D-5L, HADS and patient experience questionnaires. Questionnaires will be labelled only with the study ID. Site personnel will then enter data from the questionnaires directly into the study REDCap CRF. The completed paper questionnaires will be stored securely at the sites.

Data from clinical notes

Data from clinical notes will be entered directly into the study REDCap CRF. The data extracted includes but is not limited to:

1. Basic demographics
2. Social history
3. Laboratory blood results
4. Liver disease aetiology
5. Cirrhosis diagnosis and severity
6. Medical history and medications
7. Imaging data
8. Feasibility end-points

12.4. Imaging data quality assurance process

All data stored in XNAT are associated with a user-defined project with users given access to data on a project-by-project basis, ensuring well-controlled data protection and security. XNAT enables quality control procedures and image analysis pipelines to be integrated and automated according to image type. QA of the nceMRI images will be performed on data upload, to provide feedback to the sites and resolve any significant issues before the next patient is scanned. QA will partly be based on automated analysis verifying compliance of acquisition parameters with prescribed protocol, and other meta-data in the DICOM header. In addition, simple quality metrics will be automatically extracted from the data (such as signal-to-noise ratio) and compared against benchmarks. If a problem is detected, the local physics contact and the central image acquisition lead will be alerted, and further analyses performed if needed to identify the source of the problem and implement a solution. A visual assessment by a trained image analyst will be performed to check for unexpected artefacts. For each participant, a report will be compiled summarising the results of the QA and returned to the recruiting site. We will implement a similar QA procedure for USS data.

12.5. Personal data

Participants' personal data will be collected and stored securely on the study REDCap database. If personal data are uploaded together with imaging data to the study online portals then these will be removed as soon as possible as described above. Electronic and physical documents containing personal identifiable information of participants such as the code-breaking file linking the study specific number with the study participant's identity/contact details will be produced and stored securely, centrally and at the recruiting sites. Informed consent forms and MRI safety screening forms containing participant's names will be stored securely in locked cupboards at study sites and access is only given to authorised study members and authorised personnel.

Personal data (such as contact details and information which could identify a participant) will be destroyed as soon as it is practical to do so and no later than 12 months after the end of the study. The personal identifiers contained in consent forms and MRI safety forms will be stored or accessed for up to 20 years after study end by the study sites, after which time the custodian will agree a date for destruction and it will be destroyed confidentially.

In order to facilitate long-term data collection of mortality and cancer related endpoints, study investigators may request patient information from NHS England, the NHS Central Register for Scotland and/or other patient registries. The minimum personally identifiable information will be recorded in REDCap for the purpose of linkage with patient registries. These may include NHS or CHI number, initials and date of birth of participants. Data returned to the research team will only contain the unique study specific number.

As part of our commitment to maximise patient/service user involvement in research, participants will give consent (optional) for their contact details to be retained to hear about future research projects. This will be kept securely and independently of the study records on the High Compliance Server, Oncology Department, University of Oxford and a copy of their consent will be filed with retained contact information in this case. This will allow investigators to contact participants about future ethically approved research.

12.6. Data storage and data sharing

Participant identifiable data will be held on the study REDCap database on University of Oxford secure servers. Participant identifiable data will not be shared with co-investigators outside Oxford.

Data labelled with the study ID (pseudonymised data) will be shared with co-investigators at the University of Nottingham, Bournemouth University, Glasgow Caledonian University, and Nottingham University Hospital NHS Foundation Trust, during the study.

Anonymised data may be shared with global academic, commercial or other collaborators after analysis and publication of results, which is expected to be after the end of the study.

Essential documents will be stored securely for 20 years and thereafter the custodian of the data will agree a date for destruction. During the retention period, essential electronic data will be archived on a secure server at the University of Oxford and essential paper documents will be stored in adequate, secure archiving facilities (please refer to section archiving)

13. QUALITY ASSURANCE PROCEDURES

The study may be monitored, or audited in accordance with the current approved protocol, GCP, relevant regulations and standard operating procedures.

13.1. Risk assessment

A risk assessment and monitoring plan will be prepared before the study opens and will be reviewed as necessary over the course of the study to reflect significant changes to the protocol or outcomes of monitoring activities.

13.2. Study monitoring

Regular monitoring will be performed according to the study specific Monitoring Plan. Data will be evaluated for compliance with the protocol and accuracy in relation to source documents as these are defined in the study specific Monitoring Plan. Following written standard operating procedures, the monitors will verify that the clinical study is conducted, and data are generated, documented and reported in compliance with the protocol, GCP and the applicable regulatory requirements.

13.3. Study Committees

Study Management Group

A Study Management Group (SMG) will provide day-to-day management of the study. The SMG group will include the study investigators, PPI representatives and the study project managers. The SMG will convene at least monthly during the first 2.5 years of the project (either face-to-face or via teleconference), then 2-3 monthly thereafter. Extended SMG meetings to include investigators from each of the recruiting sites will be convened as required within this schedule. The SMG will be further structured in the following themes to have oversight of different aspects of the study:

1. Study Governance, Recruitment and PPI
2. Radiology and USS

3. MRI set-up and mechanistic sub study
4. Data and analytics

Project Steering Committee

A Project Steering Committee (PSC) will be established and will have overall responsibility for the conduct of the study. The PSC will consist of 8 members (6 independent, 2 study investigators). The 6 independent members will include an independent chair, a PPI representative and 4 members with expertise relevant to the trial (hepatology, radiology, MRI physics, epidemiology / statistics). The PSC will meet at least annually. Additional meetings will be organised as needed at the request of the chair or the CI. Observers from relevant stakeholders including the investigators, sponsor, study funder and patient support organisations will be invited to attend PSC meeting.

Data Monitoring and Ethics Committee

A Data Monitoring and Ethics Committee (DMEC) will be established and will have oversight of primary data collected from participants and to uphold the safety, rights and well-being of the participants. The DMEC will consist of 3-4 members all of whom will be independent with expertise relevant to the trial (hepatology, radiology, MRI physics, epidemiology / statistics). The DMEC will meet at least annually. Additional meetings will be organised as needed at the request of the chair or the CI. The primary DMEC reporting line is via the Chair to the Steering Committee.

PPI Advisory Group

A PPI advisory group that includes the PPI co-applicant, PPI coordinator, and PPI representatives from the Hepatitis C Trust, Haemochromatosis UK, British Liver Trust has been established. This group will act as a conduit between the SMG, PSC and the wider PPI membership.
The PPI advisory group will provide insight and advice on:

- study design
- review of patient facing materials e.g. ICF, PIS
- issues that might arise in recruitment and retention of study participants
- dissemination of results.

14. PROTOCOL DEVIATIONS

A study related deviation is a departure from the ethically approved study protocol or other study document or process (e.g. consent process or administration of study intervention) or from Good Clinical Practice (GCP) or any applicable regulatory requirements. Any deviations from the protocol will be documented in a protocol deviation form and filed in the study master file.

15. SERIOUS BREACHES

A “serious breach” is a breach of the protocol or of the conditions or principles of Good Clinical Practice which is likely to affect to a significant degree –

(a) the safety or physical or mental integrity of the trial subjects; or

(b) the scientific value of the research.

In the event that a serious breach is suspected the Sponsor must be contacted within 1 working day. In collaboration with the C.I., the serious breach will be reviewed by the Sponsor and, if appropriate, the Sponsor will report it to the approving REC committee and the relevant NHS host organisation within seven calendar days.

16. ETHICAL AND REGULATORY CONSIDERATIONS

16.1. Declaration of Helsinki

The Investigator will ensure that this study is conducted in accordance with the principles of the Declaration of Helsinki.

16.2. Guidelines for Good Clinical Practice

The Investigator will ensure that this study is conducted in accordance with relevant regulations and with Good Clinical Practice.

16.3. Approvals

Following Sponsor approval, the protocol, informed consent form, participant information sheet and any proposed advertising material will be submitted to an appropriate Research Ethics Committee (REC), and HRA (where required) and host institutions for written approval.

The Investigator will submit and, where necessary, obtain approval from the above parties for all substantial amendments to the original approved documents.

16.4. Other Ethical Considerations

16.4.1. Incidental findings

The imaging procedures in this study are being carried out as surveillance tests for HCC in the liver. Other abdominal organs will also be imaged in the process, and it is therefore possible that incidental findings that may be clinically relevant are discovered in these other organs. Therefore, an incidental finding is an image feature of potential pathological nature that is discovered unintentionally in addition to the study protocol required imaging endpoints. The incidental finding can additionally not directly be discarded as caused by an imaging artefact.

Participants will be informed of incidental findings on their scans if, as part of the assessment procedure described below, the local reporting of research scans identifies findings that are considered to have clear implications for the participant's current or future health. It is important to note that scans are carried out for surveillance purposes, so the scanning protocols do not include full diagnostic evaluations.

Ultrasound incidental findings

The ultrasound scans in the study will be conducted as part of participants routine care, so each site will follow local procedures for managing incidental findings and the local referring physician or local PI will be responsible for organising appropriate follow-up scans or procedures and further clinical follow up as needed.

Magnetic Resonance Imaging incidental findings

All nceMRI will be read by a radiologist at the site for the purposes of suspicious liver lesion for HCC. The presence of a suspicious lesion in the liver is a study outcome. However, other potentially clinically relevant findings may be noted in the liver or other organs during this central reading process. Such findings that, in the judgment of the local radiologist, require further investigation will be flagged and a second opinion from an expert radiologist will be obtained. If an incidental finding is identified, the referrer or a delegated individual will be responsible for informing the participant. The patient's clinician will be responsible for organising any additional clinical follow up or scans that may be required, in discussion with the reporting radiologist and local PI, as required.

16.5. Reporting

The CI shall submit once a year throughout the study, or on request, an Annual Progress report to the host organisation, Sponsor and funder (where required). In addition, an End of Study notification and final report will be submitted to the REC, HRA host organisation, Sponsor and funder (where required).

16.6. Transparency in Research

Prior to the recruitment of the first participant, the trial will have been registered on a publicly accessible database.

Where the trial has been registered on multiple public platforms, the trial information will be kept up to date during the trial, and the CI or their delegate will upload results to all those public registries within 12 months of the end of the trial declaration.

16.7. Participant Confidentiality

The study will comply with the UK General Data Protection Regulation (GDPR) and Data Protection Act 2018, which require data to be de-identified as soon as it is practical to do so. The processing of the personal data of participants will be minimised by making use of a unique participant study number only on all study documents and any electronic database(s), with the exception of USS DICOM data. All documents will be stored securely and only accessible by study staff and authorised personnel. The study staff will safeguard the privacy of participants' personal data.

Process for managing USS DICOM data

USS Images usually have participant identifiable information (PII) embedded into the DICOM files. The USS data will therefore be uploaded to the study XNAT platform with the PII included. The central data management team will erase the PII from the USS data at the earliest opportunity and label the scans with the appropriate study identifier. Therefore, USS data will be pseudonymised soon after the initial upload and will be kept on the study databases labelled only with a study identifier.

16.8. Expenses and Benefits

Participants will be reimbursed £30 per study visit to cover travel and meal / snack expenses for attending the nceMRI scans. Payment should be made to the participant by the local study team who can then invoice the central study team for reimbursement.

17. FINANCE AND INSURANCE

17.1. Funding

The study is funded by the Efficacy and Mechanism Evaluation (EME) Programme, a partnership between the National Institute for Health and Care Research and the Medical Research Council.

17.2. Insurance

The University has a specialist insurance policy in place which would operate in the event of any participant suffering harm as a result of their involvement in the research (Newline Underwriting Management Ltd, at Lloyd's of London). NHS indemnity operates in respect of the clinical treatment that is provided.

17.3. Contractual arrangements

Appropriate contractual arrangements will be put in place with all third parties.

18. PUBLICATION POLICY

The Investigators will be involved in reviewing drafts of the manuscripts, abstracts, press releases and any other publications arising from the study. Authors will acknowledge that the study was funded by the Efficacy and Mechanism Evaluation (EME) Programme, a partnership between the National Institute for Health and Care Research and the Medical Research Council. Authorship will be determined in accordance with the ICMJE guidelines and other contributors will be acknowledged.

19. DEVELOPMENT OF A NEW PRODUCT/ PROCESS OR THE GENERATION OF INTELLECTUAL PROPERTY

Ownership of IP generated by employees of the University vests in the University. The University will ensure appropriate arrangements are in place as regards any new IP arising from the trial.

20. ARCHIVING

Study data will be stored securely in commercial archiving facilities sub-contracted by University of Oxford to provide an archiving service. The data will be stored according to University policy and then securely destroyed. Local site files will be archived at the clinical sites according to Standard Operating Procedures.

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22. APPENDIX A: SCHEDULE OF STUDY PROCEDURES

Procedures	Visits						
	Visit timing -360 days to Day 0	**Baseline Day 0 (+28)**	**Day 180 ±30 days**	**Day 360 ±30 days**	**Day 540 ± 28 days**	**Day 720 ± 30 days**	**Day 900 ±30 days**
	Screening	**Visit 1**	**Visit 2**	**Visit 3**	**Visit 4**	**Visit 5**	**Visit 6**
Informed consent/continuous consent		x	x	x	x	x	x
Demographics		x					
Medical history		x	x	x	x	x	x
Physical examination		x	x	x	x	x	x
MRI Safety Checks		x	x	x	x	x	x
Case notes review	x	x	x	x	x	x	x
Eligibility assessment Inclusion / exclusion criteria aMAP score calculation	x						
Standard of care liver USS		x	x	x	x	x	x
Liver nceMRI		x	x	x	x	x	x
Contrast enhanced liver MRI		*	*	*	*	*	x
HADS		x	x	x	x	x	x
EQ-5D-5L		x	x	x	x	x	x
Patient experience questionnaires		x				x	
Adverse event assessments		x	x	x	x	x	x
* A contrast enhanced liver MRI scan is mandatory at visit 6 and must be performed at any of the study visits if standard of care ultrasound scan or non-contrast enhanced MRI scan show possible hepatocellular cancer							

23. APPENDIX C: AMENDMENT HISTORY

Amendment No.	Protocol Version No.	Date issued	Author(s) of changes	Details of Changes made
1	2.0	02/12/2024	Michael Pavlides	1. Added Ethics Reference Number 2. Added Study Registration Number 3. Addition of details for Data Monitoring and Ethics Committee