The Effect of Multi-Parametric Magnetic Resonance Imaging in Standard of Care for Nonalcoholic Fatty Liver Disease: Protocol for a Randomized Control Trial

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Abstract

Background: The rising prevalence of non-alcoholic fatty liver disease (NAFLD) and the more aggressive subtype, non-alcoholic steatohepatitis (NASH), is a global public health concern. Left untreated, NAFLD/NASH can lead to cirrhosis, liver failure and death. The current standard for diagnosing and staging liver disease is a liver biopsy which is costly, invasive, and carries risk for the patient. Therefore, there is a growing need for a reliable, feasible, and cost-effective non-invasive diagnostic tool for these conditions. LiverMultiScan is one such promising tool that uses multiparametric MRI (mpMRI) to characterise liver tissue and to aid in the diagnosis and monitoring of liver diseases of various aetiologies.

Objective: The primary objective of this trial (RADIcAL1) is to evaluate the cost-effectiveness of the use of mpMRI in tertiary-referral hepatology centres as a standardised diagnostic test for NAFLD.

Methods: RADIcAL1 is a multi-centre randomised control trial with two arms conducted in four European territories (13 sites, from across Germany, Netherlands, Portugal and the United Kingdom). In total, 1072 adult patients with suspected fatty liver disease will be randomised to be treated according to the result of the mpMRI, so that further diagnostic evaluation is recommended only when values for metrics of liver fat or fibro-inflammation are elevated. Patients in the control arm will be treated as per centre guidelines for standard of care. The primary outcome for this trial is to evaluate the utility of mpMRI in reducing the burden of patients with suspected fatty liver disease that incur unnecessary additional liver-related hospital consultations and/or liver biopsies. Secondary outcomes include patient feedback from a patient satisfaction questionnaire, at baseline and all follow-up visits to the end of the study, and time from randomisation to diagnosis by the physician, as recorded at final follow-up visit.

Results: This trial is currently open for recruitment. The anticipated completion date for the study is December 2020.

Conclusions: This randomized controlled trial will provide the evidence to accelerate decision making regarding the inclusion of mpMRI-based tools in existing NAFLD/NASH clinical care. RADIcAL1 is among the first and largest European health economic studies of imaging technologies for fatty liver disease. Strengths of the trial include the high-quality research design and in-depth assessment of the implementation of the cost-effectiveness of the mpMRI diagnostic. If effective the trial may therefore highlight the health economic burden on tertiary-referral hepatology clinics imposed by unnecessary consultations and invasive diagnostic investigations and demonstrate that including LiverMultiScan as a NAFLD diagnostic test may be cost-

effective compared to liver-related hospital consultations and/or liver biopsies. Clinical Trial: ClinicalTrials.gov NCT03289897 https://clinicaltrials.gov/ct2/show/NCT03289897

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Dimitar Tonev[4], Elizabeth Shumbayawonda[4], Louise A Tetlow[4], Laura Herdman[4], Marika French[4], Soubera Rymell[4], Helena Thomaides-Brears[4], Miguel Castelo-Branco[2], Filipe Caseiro Alves[2], Carlos Ferreira[4], Minneke Coenraad[3], Hildo Lamb[3], Meinrad Beer[1], Matt Kelly[4], Rajarshi Banerjee[4], Matthias Dollinger[1].

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Keywords: NAFLD; NASH; multiparametric MRI; health economics; biomarker.

Abstract

Background: The rising prevalence of non-alcoholic fatty liver disease (NAFLD) and the more aggressive subtype, non-alcoholic steatohepatitis (NASH), is a global public health concern. Left untreated, NAFLD/NASH can lead to cirrhosis, liver failure and death. The current standard for diagnosing and staging liver disease is a liver biopsy which is costly, invasive, and carries risk for the patient. Therefore, there is a growing need for a reliable, feasible, and cost-effective non-invasive diagnostic tool for these conditions. Liver*MultiScan* is one such promising tool that uses multiparametric MRI (mpMRI) to characterise liver tissue and to aid in the diagnosis and monitoring of liver diseases of various aetiologies.

Objective: The primary objective of this trial (RADIcAL1) is to evaluate the cost-effectiveness of the introduction of LMS as a standardised diagnostic test for liver disease in comparison to standard care for NAFLD, in different EU territories.

Methods: RADIcAL1 is a multi-centre randomised control trial with two arms conducted in four European territories (13 sites, from across Germany, Netherlands, Portugal and the United Kingdom). In total, 1072 adult patients with suspected fatty liver disease will be randomised to be treated according to the result of the mpMRI in the intervention arm, so that further diagnostic evaluation is recommended only when values for metrics of liver fat or fibro-inflammation are elevated. Patients in the control arm will be treated as per centre guidelines for standard of care. The primary outcome for this trial is to compare between the study arms, the difference in proportion of patients with suspected NAFLD incurring liver-related hospital consultations and/or liver biopsies, from the date of randomisation to end of study follow-up. Secondary outcomes include patient feedback from a patient satisfaction questionnaire, at baseline and all follow-up visits to the end of the study, and time from randomisation to diagnosis by the physician, as recorded at final follow-up visit.

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Trial Registration: ClinicalTrials.gov NCT03289897 https://clinicaltrials.gov/ct2/show/NCT03289897

Introduction

Non-alcoholic fatty liver disease (NAFLD) is the most common cause of abnormal liver blood tests with an estimated prevalence of between 20%-30% in Europe, and higher in the United States of America (USA) [1,2]. The condition is associated with obesity, insulin resistance, and heart disease, resulting in patients with fatty liver disease being twice as likely to get early coronary artery disease compared to the healthy population [3][4]. If left untreated, NAFLD can progress to non-alcoholic steatohepatitis (NASH), characterised by tissue scarring steatosis, lobular inflammation, fibrosis, and ballooning, before ultimately cirrhosis and liver failure. Due to the steady increase of NALFD over the years, NASH has now become the leading cause of liver failure in the developed world, with reported predictions that it will become the leading cause of liver transplant over the coming decades [5]. NASH is a major public health concern and, with a global prevalence of 1.5%-6.5% [6,7] (12% in western populations [8]), poses a significant economic burden on health care institutions.

Similar to most liver diseases, the diagnostic gold standard for NAFLD/NASH is percutaneous liver biopsy [5,9,10]. However, biopsies are painful and carry risk, as 1:1000 people experience serious adverse events including bleeding, infection, and bowel perforation [11–13]. Biopsies only sample a small part of the liver (approximately 1/50000th of the liver volume) [14] and suffer from sampling location variability, thus affecting the reported stage of fibrosis in up to 50% of cases [15,16], as well as inter-reader variability which can result in biopsy finding disagreements amongst pathologists [17–19]. Thus, biopsies alone are not enough to obtain a diagnosis or monitor liver disease [20,21]. In addition, with the advance of various pathophysiological changes exhibited through liver disease aetiologies, some patients experience impaired clotting of their blood due to liver dysfunction [22], and are consequently at a higher risk of experiencing a combination of the risk factors associated with biopsy [8]. The resulting longer hospital stays and increased socio-economic burden after the procedure make biopsy an unpopular option amongst patients, clinicians and payers [9]. Although recommended by clinical guidelines as the gold standard for diagnosis and monitoring [10], in practice liver biopsies are not routinely used unless the patient presents with moderate to severe liver disease, or when there is a need to exclude other liver diseases such as autoimmune hepatitis [23]. In light of these factors, health institutions deviate from diagnostic pathways to stratify the risk of advanced liver disease and postpone, or even replace biopsy within this population which has resulted in a non-standardised care pathway. Therefore, in the absence of biopsy and a universal ground truth in routine care, there is a clear need for non-invasive, objective, discriminatory tests that can stratify normal liver, simple steatosis, steatohepatitis, and cirrhosis. These tests can then be used as a common reference point for clinical care.

Over the years various non-invasive techniques such as ultrasound, transient elastography (FibroScan), diffuse-weighted imaging, magnetic resonance elastography, T1 mapping and multi-parametric magnetic resonance imaging (mpMRI) have been developed for use as surrogate markers to both diagnose and monitor NAFLD/NASH disease alongside blood tests [24,25]. mpMRI (Liver*MultiScan*; Perspectum Ltd., Oxford, United Kingdom) is an

emerging quantitative mpMRI test; the first to combine corrected T1, PDFF, and T2*, that can identify the early stages of liver disease [26],[27], and predict clinical outcomes accurately [8]. mpMRI also has the potential to become a standardised consistent step along the NASH clinical diagnostic pathway in multiple healthcare systems (across Europe) as it is cost saving, non-invasive, fast, repeatable, reliable, and standardised across multiple MR vendors [8,9,27–30].

The cost benefits of introducing a non-invasive diagnostic test that detects earlier stage disease may be especially beneficial in the clinical care of people suspected with fatty liver disease and/or diabetes [27,31]. The absence of a clear consensus over patient clinical management for suspected fatty liver disease [9,29], necessitates assessment of mpMRI within existing healthcare systems to identify potential real-world cost-effectiveness of new imaging technologies and streamline healthcare for patients. Thus, to investigate the utility and cost benefit of adding mpMRI into the care pathway of those with suspected NAFLD in Europe (European union territories and United Kingdom [UK]), this randomised multi-centre phase IV control trial to investigate the use of mpMRI as a standardised diagnostic test for NAFLD/NASH was designed. With up to 13 sites across Europe included in this trial, the primary outcome is to compare between the study arms, the difference in proportion of patients with suspected NAFLD incurring liver-related hospital consultations and/or liver biopsies, from the date of randomisation to end of study follow-up. This will highlight the health economic burden on tertiary-referral hepatology clinics imposed by unnecessary additional consultations.

Methods

RADIcAL1 is a multicentre phase IV randomised controlled trial (NCT03289897) which aims to recruit 1072 patients from 13 sites in four different European territories, namely Ulm (Germany), Leiden (Netherlands), Coimbra (Portugal), and the UK (Liverpool, Southampton, Dundee, Glasgow, London, Manchester). The 5-year study consists of a 1-year study set-up, 3-year recruitment phase, and up to 12-months follow-up. The protocol, informed consent form, participant information sheet and any proposed advertising material was submitted to each host institution's appropriate Research Ethics Committee (REC), for written approval and received favourable response (and granted) in Ulm (198/17), Leiden (P17.076), Coimbra (CE-030/2017), and UK (18/SC/0725).

Patient randomisation and study participants

Patients will be randomised using a 1:1 allocation, without blinding, into an intervention arm (with mpMRI intervention) and a control arm (Figure 1). Randomisation is automatically calculated using a random number generator on patients that have been already stratified based on a combination of the inclusion criteria (Table 1) and the recruitment site. Patients in the control arm will be treated as per centre standard of care, with patients following local practice for NAFLD to potentially include physician consultations and anthropometric blood, imaging and histological assessments [32–34].

Those in the intervention arm will be treated according to the result of the mpMRI scan; if the liver fat is ≥10% or

the fibro-inflammation identified (cT1 ≥800 ms) then further diagnostic evaluation will be recommended (such as further monitoring of liver enzymes, repeat mpMRI assessment at 6-12 months, assessment of liver stiffness, or assessment of response to lifestyle management activities) [10,35]. Otherwise management in primary care for 12 months will be recommended. In both arms clinical choices will be patient and site-specific in adherence with NAFLD guideline recommendations [32–34].

Potential participants will be recruited from:

1) General practitioners or specialists from tertiary care hospital consultations (e.g., obesity consultation),

2) Secondary care clinics, and

3) Databases from previous ethically approved studies where patients have consented to have their contact details retained in order to be contacted if eligible to take part in other studies.

During recruitment, the inclusion and exclusion criteria highlighted in Table 2 will be used to identify potential participants.

Table 1: Inclusion and exclusion criteria used during recruitment in the RADIcAL1 trial

Inclusion Criteria	**Exclusion Criteria**
• Male and female patients aged 18-75 years, due to undergo evaluation for suspected non-alcoholic fatty liver disease • Within standard of care presence of: - elevated liver function tests (ALT, AST or GGT ≥1.5 x upper limit of normal and ALT, AST ≤5 x upper limit of normal) up to 1 year prior to patient recruitment OR - imaging suggestive of Fatty liver disease up to 3 years prior to patient recruitment. • OR Presence of ≥ 3 of the following criteria: 1) insulin resistance or type 2 diabetes mellitus 2) obesity (BMI >30 or waist-to-hip ratio > 1.00 for men / >0.85 for women) 3) hypertension (≥130/85 mmHg) 4) elevated triglycerides (≥1.7 mmol/l) 5) low HDL-cholesterol (<1.05 mmol/l for men / <1.25 mmol/l for women) • Participant is willing and able to give informed consent for participation in the study.	• The participant may not enter the study if they have any contraindication to magnetic resonance imaging (including pregnancy, extensive tattoos, pacemaker, shrapnel injury, severe claustrophobia). • Patients with proven liver disease other than NAFLD. • Liver transplantation • Patients that present with clinical signs of chronic liver failure (variceal bleeding, ascites, overt encephalopathy) • Alcohol over-use/ abuse as determined by local guidelines • Patient with known malignant liver tumours and those with any malignancy with life expectancy <36 months • Heart failure NYHA stages II-IV • Severe mental illness • Any other cause, including a significant disease or disorder which, in the opinion of the investigator, may either put the participant at risk because of participation in the study, or may influence the result of the study, or the participant's ability to participate in the study

Once a potential participant expresses interest in the study, they will be provided with a Patient Information Leaflet (PIL) for a minimum of 24 hours and an opportunity to discuss their eligibility and the details of the study. In accordance with good clinical practice (GCP), the participant is free to withdraw from the study at any time for

any reason without prejudice to current or future care. For those participants who wish to withdraw from the study the option to permit ongoing use of data and samples which have already been collected, and/or future recording and usage of routinely collected clinical data and results will be given. This will be clearly documented on the patient consent form. In addition to this, patients who are unable to undergo the MRI scan, e.g. due to claustrophobia may also be withdrawn from the study.

Study visits

Patients will be required to attend their respective clinical centres for up to 3 dedicated study visits as summarised in Figure 1. At study visit 1 informed consent, medical history, anthropometric readings and bloods will be taken. Visit 2 is for the intervention arm only; patients will be required to fast for 4-hours before the Liver*MultiScan*Ò MRI scan (standardised imaging protocol in a 1.5 or 3T MRI scanner following the Perspectum protocol), which will involve lying supine in the MRI scanner for 10-15 mins. At this visit optional blood sample for further tests may be taken. Visit 3 is for the intervention arm only, during which clinicians will discuss the results of the MRI scan with the patients and change patient management if appropriate.

Once they have had their scan, patients will be followed up for a period between 6-12 months. In this trial, patients will also be requested to complete questionnaires at recruitment, 2, 6, and 12 months after entering the study. In this trial, patients will also be requested to complete a resource use and quality of life (EQ-5D-5L [36]) questionnaire at recruitment and months 2, 6, and 12, after entering the study. Those in the intervention arm will also be asked to complete an MRI satisfaction questionnaire after having their mpMRI.

The resource use questionnaires completed at randomisation will cover appointments that the participant has had with a healthcare professional (inpatient and outpatient), medication usage, diet and physical exercise, paid and unpaid help the participant may require and their insurance coverage. Furthermore, at the 2, 6, and 12-month follow-up visits, participants will be asked to answer additional questions regarding changes in medication and medical examinations they received as an outpatient. These examinations include blood tests, ultrasounds, other imaging (e.g. Endoscopy, CT scan and MRI) and biopsies.

The EQ-5D-5L questionnaire [36] asks participants to describe their heath on the day of questionnaire completion in order to assess impact on quality of life. Each participant must rate their mobility, self-care, usual activities, pain/discomfort and anxiety/depression. The participant has 5 options to pick from for each parameter/question: no problem; slight problem; moderate problem; severe problems and unable to carry out the task. Finally, participants are asked to indicate how they think their health is on that day on a scale of 0 to 100.

Intervention

MRI-derived biomarkers provide many opportunities for diagnostic enrichment. MRI exploits the magnetic properties of hydrogen nuclei protons within a determined magnetic field. T1 mapping measures longitudinal relaxation time, and thus is a surrogate measure of the amount of water present or the structural distribution of water molecules (i.e. T1 can be used to indicate whether tissue water is freely moving, is structured within cells or is bound to macromolecules). Therefore, as T1 relaxation time lengthens with increases in extracellular fluid it has

shown promise as an effective biomarker of inflammation and fibrosis in several organs [37,38]. The presence of iron in the liver however, which can be accurately measured from MRI-T2 star (T2*) relaxation time, shortens the T1, and thus must be accounted for [39]. An algorithm has been created by Perspectum Ltd that allows for the bias introduced by elevated iron to be removed from the T1 measurements, yielding the iron corrected T1 (cT1) [14,39]. MRI-PDFF is a ratio, expressed as a percentage, of the fraction of the MRI-visible protons attributable to fat divided by all MRI-visible protons in that region of the liver attributable to fat and water. Taking advantage of the chemical shift between fat and water, pulse sequences, including fast spin echo and gradient-recalled echo (GRE) sequences can, be used to acquire images at multiple echo times at which fat and water signals have different phases relative to each other. cT1 maps have been shown to be correlated with fibro-inflammation and predictive of clinical events [8,14]. PDFF has been shown to have excellent correlation with histologically graded steatosis across the clinical range seen in NASH and high diagnostic accuracy in stratification of all grades of liver steatosis. Hence, together, PDFF and cT1 hold promise to accurately assess all relevant aspects of liver disease: fat, inflammation and fibrosis [25][40]. The sample reports shown in Figure 2 demonstrate the information that can be derived from the use of mpMRI to aid as a diagnostic tool for clinicians, highlighting the differences between a healthy patient, with low cT1, and a patient with suspected NAFLD and high cT1. The high repeatability and reproducibility of mpMRI (both CoV 3.3% for cT1 [25,28,41]) and predefined diagnostic thresholds for mpMRI recommendation make clinical misinterpretation of the mpMRI unlikely.

Objectives and outcomes

All primary and secondary objectives and outcome measures are outlined in Table 2. The primary objective of the study is to compare the cost effectiveness of the standard of care received by patients with suspected NAFLD in these EU territories compared to the care such patients will receive when Liver*MultiScan* is introduced as a standardised diagnostic test. The primary endpoint of the study utilises health care resource use data to compare the difference in proportion of patients incurring liver-related hospital consultations and/or liver biopsies, from the date of randomisation to end of study follow-up, with cost effectiveness dependent on local jurisdiction. One secondary objective will be based on data from patient satisfaction questionnaires to explore implementation of the intervention. Another secondary objective investigating the certainty and frequency of diagnosis is based on clinician response to a specific question (“Using all the information obtained to date, how certain are you to make a diagnosis of NAFLD today?”) posed at each diagnostic visit in the patient’s journey. The 4 possible pre-defined responses are further sub-grouped into binary categories, one sub-group for certainty and another for frequency of diagnosis. Other secondary objectives include a comparison of the time to diagnosis, which utilises data based on any liver-related diagnosis [from 7 options primary non-alcoholic fatty liver (NAFL), secondary NAFL, primary NASH, secondary NASH, mixed aetiology NAFL, mixed aetiology NASH, other aetiology]. Additionally, use of resources, actual costs over a 12-month period and level of skill or clinical specialisation required within each study arm will be investigated as secondary objectives based on the resource use questionnaires and study case report forms. Exploratory objectives include a model looking at long-term cost-effectiveness based on quality of

life over a lifetime horizon, using the EQ-5D-5L data, and analysis of the diagnostic accuracy of mpMRI and other study biomarkers.

Table 2: RADIcAL1 primary and secondary objectives

Primary Objective	**Primary Outcome Measures/Endpoints**
To investigate whether the introduction of mpMRI as a standardised diagnostic test for liver disease can prove a cost-effective method in different European territories.	Primary outcome – proportion of patients with suspected NAFLD incurring liver-related hospital consultations and/or liver biopsies, from the date of randomisation to end of study follow-up.
Secondary Objective	**Secondary Outcome Measures/Endpoints**
To investigate patient satisfaction with mpMRI instead of existing care (with other liver investigations).	Patient feedback from patient satisfaction questionnaire, at baseline, and all follow-up visits to the end of the study.
To investigate certainty and frequency of diagnosis at points of time in the patient pathway.	Certainty of diagnosis is defined as a binary (yes/no as opposed to unlikely/probable) and frequency as (yes/probable as opposed to no/unlikely), at baseline and all follow-up visits to the end of the study.
To investigate which pathway was quicker to get to the diagnosis as recorded at final follow-up visit (including all corrections and additional investigations).	Time from randomisation to diagnosis by the physician, as recorded at final follow-up visit.
To measure what healthcare resources and costs were required in the two diagnostic pathways.	Rates of liver-related outpatient investigations/ consultations/hospital admissions per 400 patients during the study.
To investigate the cost-effectiveness of mpMRI against standard of care.	Cost of mpMRI based on randomised comparison.
To investigate skills/specialisation required.	Personnel required to perform procedures and tasks from the date of randomisation to end of study follow-up.

Sample size calculation

In a study by Blake et al. 2015 it was identified that the use of Liver*MultiScan* can result in a decrease in biopsy of 18% [9]. Adopting a conservative target of identifying a 14% decrease across different regions, to maintain statistical significance (with more than 80% power (alpha=0.05) to show a difference in proportion of patients having consultations between the two pathways) each randomisation arm is required to have n=402 patients. Moreover, due to the size of the trial, the final recruitment target was powered to include a 25% dropout rate (including those lost to follow-up during the completion of the study). Thus, a total cohort of 1072 patients with suspected fatty liver disease will need to be recruited into the trial.

Statistical methods and data management plan

Statistical support for all primary and secondary analyses will be provided by Perspectum Ltd. Detailed health economic and statistical analysis plans ([42], Multimedia Appendix 1) describe the required analyses to investigate the study objectives. These include details of standard statistical analyses (t-test, ANOVA, area under the receiver

operating curve (AUROC)) and data analysis packages (such as R (R Foundation for Statistical Computing, Vienna, Austria), MATLAB (MathWorks, USA) and Python (Python Software Foundation, USA)) which will be used to report summary statistics for patients in both arms of the study. Moreover, summary statistics will be reported (number of observations, mean, standard deviation or percentages as relevant) for the demographic variables, clinical variables, and outcomes for the total group, and comparison with any non-invasive tests offered in their care.

The health economic analysis will evaluate changes in resource use/costs for which data collected from randomisation to end of study. Within this evaluation, determination of the cost-effectiveness of mpMRI from the perspective of each healthcare system following the intention-to-treat principle will be derived. Healthcare resource use (including diagnostic procedures, healthcare consultations and hospital admissions) will be obtained from medical records as well as via patient self-reported data during follow-up visits. A detailed health economic analysis plan detailing the methods used, and models developed using study data will also be agreed and developed prior to the end of the study [42].

Additional exploratory analysis will evaluate the diagnostic performance of cT1 and PDFF using AUROC, and assess concurrence of mpMRI metrics with other surrogate biomarkers associated with NAFLD/NASH used more regularly in clinical practice such as: glucose and haemoglobin A1C (HBA1C; a measure of glycated haemoglobin and contribute to diabetes diagnosis), enhanced liver fibrosis (ELF) tests (used to test for advanced liver fibrosis in NALFD patients), and cholesterol utilising correlation analyses (Pearson's correlation for normally distributed data and Spearman's Rho for non-normally distributed data). The concordance of mpMRI metrics and biopsy data will be assessed using Cohen's kappa (K) statistic, Bland-Altman analysis (bias, limits of agreement (LoA), and the corresponding 95% confidence interval (CI)), Pearson's correlation and mean coefficient of variation (CoV) will be estimated.

In this trial, all data collected will be documented in electronic Case Report Forms (eCRFs). In addition to this, all patient related data will be handled and stored according to the European and national data protection laws [43]. All outcome data will be analysed using an intention to treat principle where data from participants shall be analysed according to the group in which they were randomised even if they did not receive the allocated intervention.

Results

RADIcAI1 is funded from May 2016 and ethics approval was granted in April 2017 (Portugal), July 2017 (Germany, Netherlands) and June 2018 (UK). Data collection began in September 2017 and is estimated to be complete by the end of December 2020. As of April 2020, 726 total patients with suspected NAFLD or metabolic syndrome or both have been enrolled. Results will be analysed by the end of the study and publication of these is expected by March 2021.

Discussion

Non-alcoholic fatty liver disease (NAFLD) and its more progressive form, non-alcoholic steatohepatitis (NASH), are

emerging as the most important cause of liver disease worldwide, and are thought to potentially become the number one cause of end-stage liver disease [5]. Their increasing prevalence also share demographic and epidemiological parallels with the worldwide epidemic of obesity and type 2 diabetes mellitus [8,44,45] and the presence of these co-morbidities are thought to further increase the risk of cardiovascular disease [44,46]. Due to the increased numbers of patients now requiring both diagnosis and regular monitoring for NAFLD/NASH, great economic and time related burdens are now being placed upon already strained healthcare systems [5,45]. Current clinical guidelines and care pathways require patients to undergo liver biopsy for the diagnosis and monitoring of NAFLD/NASH which is risky, painful, and costly, leading to a reluctance from both patients and clinicians to engage in such procedures with regularity [9], thus highlighting an increasingly urgent requirement for a cost effective, repeatable, reproducible, and non-invasive tool to aid the diagnostic pathway [41].

To the best of our knowledge this will be the first large-scale, multi-centre study to evaluate the cost-effectiveness of mpMRI within the diagnostic pathway for NAFLD/NASH patients across multiple European territories. The primary objective of the RADIcAL1 trial is to evaluate the cost-effectiveness of mpMRI within tertiary care units within the Europe, assessing the impact of its utility upon the number of unnecessary consultations and biopsies that patients must attend, and the economic burden faced by healthcare systems. From these findings, RADIcAL1 has the potential to produce concordance and optimisation of the diagnosis and monitoring pathways for patients whom, with better knowledge of their NAFLD/NASH status, may be able to undertake informed lifestyle changes and prevent further progression of comorbidities, potentially producing further health-economic savings [5,9]. Qualitative data in RADIcAL1, such as the patient satisfaction survey, will provide patient experience insights directly from a population the mpMRI technology is designed to benefit. Furthermore, due to data collection throughout the clinical care pathway, RADIcAL1 also has the potential to assess both the diagnostic accuracy and speed in which care is received in both study arms, adding further evidence to the requirement for a singular, agreed upon, ideal diagnostic pathway.

mpMRI is well placed to provide accurate monitoring of individual patient responses to drugs in trials and within the care pathway, allowing researchers and clinicians to make informed decisions regarding patient care, with the potential to optimise the allocation of expensive treatments. We expect the introduction of mpMRI into the standard care pathway for patients with NAFLD/NASH to provide both health and socioeconomic benefits to patients in addition to costs-savings for healthcare providers and this will be evaluated in RADIcAL1.

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Authorship contributions:

RB, SN, HL, MD, MC, MB, MCB, FCA developed the study concept and protocols, funding and initiated the project. MK, CF assisted in further development of the protocol. MD, SR, MB, MC, HL, CF, MCB, FCA, RB drafted the clinical

study protocol, The PI at each centre (MC, MD, MCB, DT) applied for ethics application. ES, LT, LH, MF, HTB, SR drafted the manuscript. All authors contributed and approved the final manuscript.

Conflicts of interest

The members and employees of Ulm, Leiden and Coimbra Universities declare no conflict of interest with this study. Perspectum Ltd is a privately funded commercial enterprise that develops medical devices to address unmet clinical needs, including Liver*MultiScan*. Perspectum is the sponsor of this study.

Abbreviations

NAFLD – Non-alcoholic fatty liver disease
NASH – Non-alcoholic steatohepatitis
mpMRI – Multiparametric magnetic resonance imaging
PDFF – Proton density fat fraction
REC – Research ethics committee
HEAP – Health economics analysis plan
GCP – Good clinical practice
PIL – Patient information leaflet
GRE – Gradient-recalled echo
SAP – Statistical analysis plan
AUROC – Area under the receiver operative curve
CoV – Coefficient of variance
LoA – Limits of agreement
CI – Confidence interval
eCRFs – Electronic case report forms

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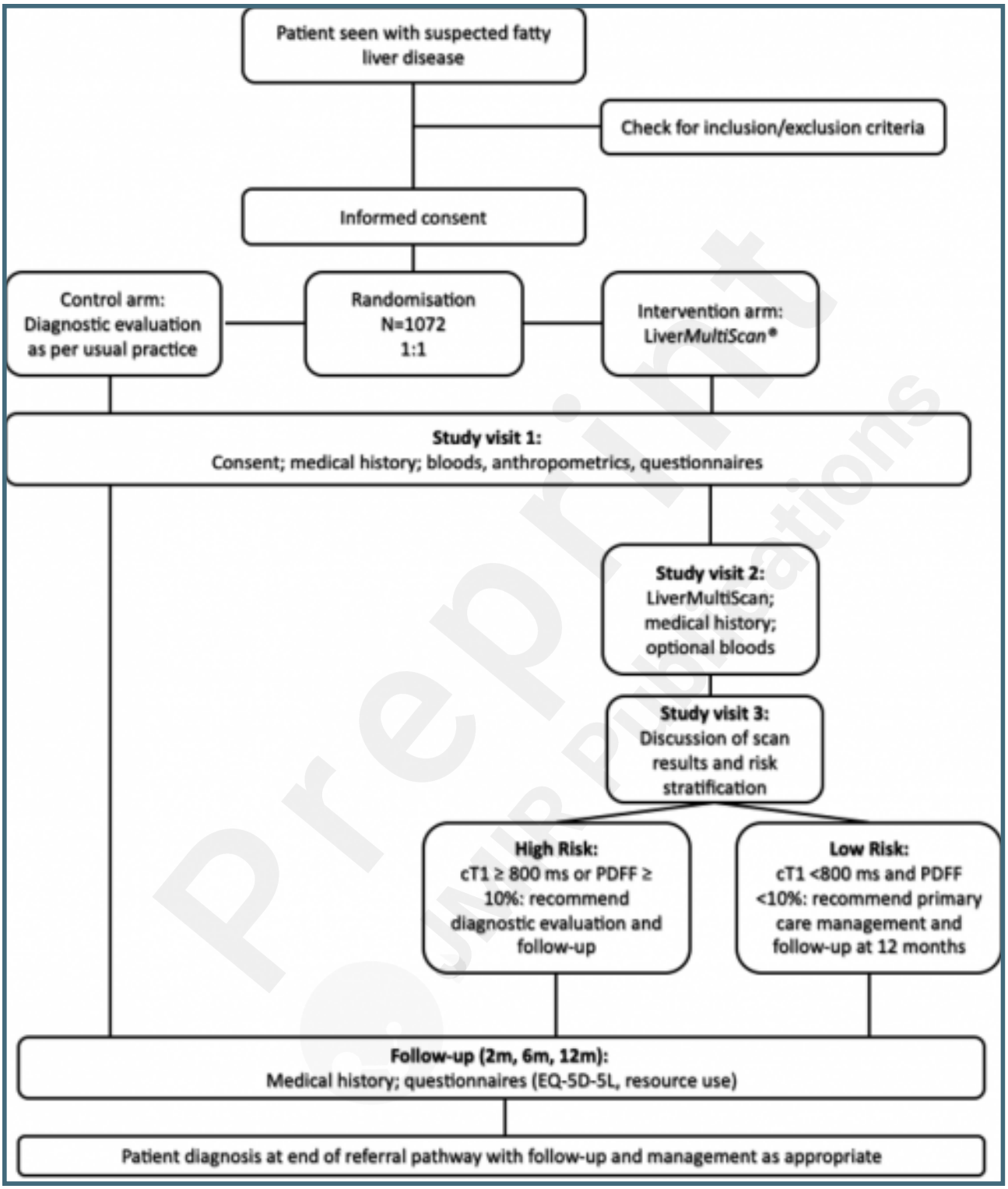
Supplementary Files

Figures

Summary of study visits for participants in the RADIcAL1 clinical trial.



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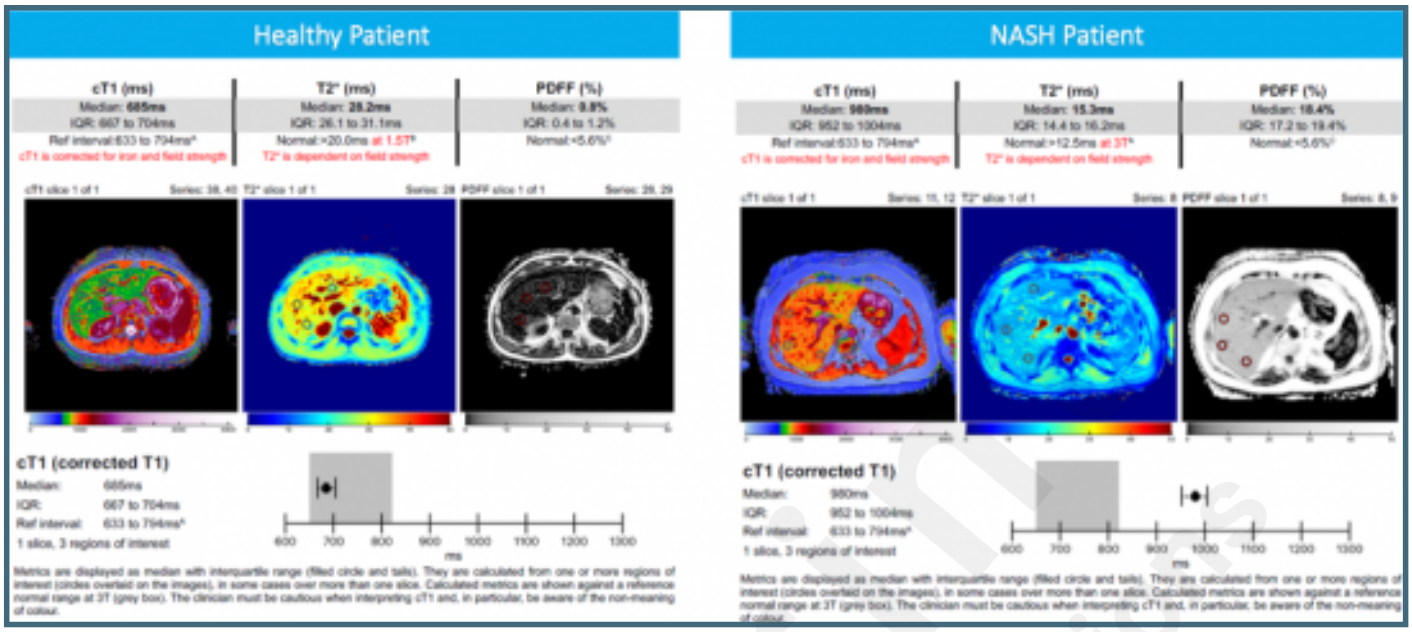

Multimedia Appendixes

Statistical Analysis Plan.
URL: https://asset.jmir.pub/assets/c53e38960bfe4393394821f9522f94f2.pdf

Grant Protocol Peer Review.
URL: https://asset.jmir.pub/assets/2970e807d46297ad294ebb23e42a3baf.pdf