Research Protocol (Version 1.4, 21/03/2024)

Study Title: A cross-sectional study assessing the agreement between sonographer based assessment of the fatty liver using conventional ultrasound and attenuation imaging scoring.

Acronym/Short Title: Ultrasound and Attenuation Imaging

Study ID (IRAS No.): 329847

REC Reference:23/WA/0332

Protocol Version No. & date: (Version 1.4, 21/03/2024)

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Study Summary

Study Outline	Non-alcoholic fatty liver disease (NAFLD) affects almost a 3rd of the population of the UK and current best practice is to evaluate this using Magnetic Resonance Imaging proton density fat fraction (MRI PDFF), however, this is inaccessible to many patients due to limited availability, cost and a large exclusion criteria. Ultrasound offers an affordable, faster and more inclusive method of liver evaluation but only subjective assessment of fatty liver disease until a recent development- Attenuation Imaging. Attenuation imaging gives a numerical score for fatty liver disease. Attenuation imaging has previously only been compared to MRI PDFF, however, when many patients do not have MRI PDFF it is essential to compare it to common practice, conventional ultrasound. This study aims to assess the agreement between conventional ultrasound assessment of the liver and attenuation imaging using a cross-sectional method. Convenience sampling will be used to select 95 participants who will have their attenuation imaging score carried out alongside their routine ultrasound scan with the sonographer blinded to the attenuation imaging results. The inter-rater agreement will be determined using Kappa statistics. The results will demonstrate the strength of relationship between the two methods. A strong agreement between the two may facilitate further investigation into the uses of attenuation imaging, such as use as a screening tool, in teaching trainee ultrasound operators or in aiding decisions in cases that Sonographers find more difficult to assess such as those patients with a high BMI.
Lay Summary	*Fatty liver disease affects almost a 3rd of the UK population. Currently, this is being investigated using a type of Magnetic Resonance Imaging (MRI) scan that reports how fatty or not a person's liver is, with a liver fat score, but many patients cannot have this type of scan due to time, cost or because they have a condition which makes MRI an unsafe scan for them to have. An ultrasound scan is cheaper, faster and safer for a wider variety of patients. New developments in ultrasound technology mean that instead of a Sonographer, or ultrasound operator, deciding whether your liver is fatty or not based on what they see on the scan, the ultrasound machine gives a liver fat score. This study will look at the relationship between the Sonographers' view on how fatty the liver is, compared with the liver fat score given by the new development in ultrasound technology.*
Key Words	*'Ultrasound' 'Non-alcoholic Fatty Liver Disease' 'Metabolic Liver Disease' 'Attenuation Imaging'*
Objectives	To assess the agreement between Sonographer based ultrasound assessment of fatty liver disease and attenuation imaging scoring.
Sample Size	*95*
Duration	1 year

Glossary / Definitions / Acronyms

EASL European Association for the Study of the Liver

GDPR	General Data Protection Regulation
HDUHB	Hywel Dda University Health Board
IRAS	Integrated Research Application System
MRI	Magnetic Resonance Imaging
MRI-PDFF	Magnetic Resonance Imaging- Proton Density Fat Fraction
NAFLD	Non-alcoholic Fatty Liver Disease
NHS	National Health Service
NICE	National Institute for Health and Care Excellence
PIS	Participant Information Sheet
R&D	Research and Development
REC	Research Ethics Committee

Statement of Compliance

The study as detailed within this Protocol (Version 1.4, 21/03/2024) or any subsequent amendments will be conducted in accordance with the International Conference for Harmonisation of Good Clinical Practice (ICH-GCP, E6), and the UK Policy Framework for Health and Social Care Research (2017), the World Medical Association Declaration of Helsinki (1996) and the current applicable regulatory requirements and any subsequent amendments of the appropriate Regulations.

Signature Page

The signature below constitutes the approval of this Protocol and the attachments and provides the necessary assurances that this research study will be conducted according to all stipulations of the Protocol, including all statements regarding confidentiality, and according to local legal and regulatory requirements.

Chief / Principal Investigator:

Signed: _____ Date (dd/mm/yyyy): **21/03/2024**

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Contents

1. Introduction

Non-alcoholic fatty liver disease (NAFLD) has a prevalence of 20-30% in the UK population (National Institute for Health and Care Excellence, 2016) 80% of these patients will have normal results from routine liver tests (NICE, 2016), meaning that diagnosis often requires several further tests. The term NAFLD represents a scale of fatty liver disease incorporating non-alcoholic steatohepatitis (NASH) and cirrhosis (British Liver Trust, 2022). However, in the earlier stages, the liver can, to an extent, repair itself without expensive drugs or procedures, as treatment at this stage is predominantly a combination of diet and exercise, meaning that an early diagnosis can easily prevent the progression to cirrhosis (British Liver Trust, 2022).

1.1. Background

Magnetic Resonance Imaging Proton Density Fat Fraction (MRI PDFF) is recommended by the European Association for the Study of the Liver as the gold standard for assessing fatty liver disease (EASL et al., 2016). MRI PDFF gives a complete evaluation of the liver enabling assessment for other pathology and quantification of the fatty infiltration for segments of the liver. MRI is non-invasive but expensive, with multiple exclusion criteria, long waiting times and limited availability (Gatos et al., 2022). Most MRI scanners are unsuitable for patients with a larger body habitus (Reynolds, 2011), who would naturally make up a significant proportion of those with NAFLD due to its causative factors- most commonly poor diet and lack of exercise. They are also poorly tolerated by patients due to noise and claustrophobia. In addition, it excludes patients with artificial heart valves, recent surgery or dental work, and internal electronic devices such as pacemakers or insulin pumps (Medicines and Healthcare Products Regulatory Agency, 2021). Insulin pumps are a particular issue for this population as there is a 53% prevalence of NAFLD within the type 2 diabetic population (NICE, 2016).

Ultrasound is recommended as a first-line test for NAFLD (EASL et al., 2016). It is easily accessible, well tolerated by most patients, more cost-effective than MRI, gives a complete overview to assess for other liver pathology and is non-invasive (Ballestri et al., 2021). However, conventional ultrasound relies on a subjective liver assessment by the operator, which research shows is open to inter-observer variation (Straus et al., 2007) and image quality can also be limited by patient obesity (Reynolds, 2011). It also has a low detection rate of mild steatosis, or steatosis involving less than 30% of the liver parenchyma (Ballestri et al., 2021). In current practice, sonographers grade the fatty appearance of the liver subjectively as normal, mild, moderate or severe through assessment of the echogenicity of the liver, hepato-renal contrast, visualisation of the intra-hepatic veins and visualisation of the liver parenchyma (Hernaez et al., 2011, Ballestri et al. 2021). Ultrasound is also recommended for monitoring those with advanced fatty liver disease, where there are often fibrotic changes with progression to cirrhosis and an increased risk of hepatocellular carcinoma (EASL et al., 2016).

A new advance in ultrasound technology, attenuation imaging, permits quantitative measurement of liver fat, which poses no additional risk to the patient than regular ultrasound and can be carried out as a part of a routine ultrasound scan (Bae et al., 2019). As attenuation imaging is not hindered by the subjectivity of conventional ultrasound assessment, it has potential as a more specific way to monitor the progress of fatty liver disease and to aid more inexperienced sonographers as an adjunct to their subjective assessment. Most of the literature compares attenuation

imaging to MRI-PDFF as the gold standard, and multiple studies suggest that attenuation imaging has reasonable specificity and sensitivity (Ferraioli et al., 2021, Jeon et al., 2019). However, as previously stated, MRI is not suitable for an extensive range of patients and long waits for MRI scans and reports make it unfeasible as a method of choice for assessing and monitoring the fatty liver locally, especially in the early stages when the risk of hepatocellular carcinoma is much lower. Consequently, whilst the literature compares attenuation imaging to MRI PDFF, as the gold standard, it is essential to evaluate the use of attenuation imaging against current ultrasound practice, which at this location is a more common method of liver evaluation than MRI PDFF. Furthermore, this study will provide a base of evidence to allow further research in the future to find answers to questions such as 'How does knowing these scores affect patients attitudes to treatment?' or 'At which stage is treatment most effective?'.

1.2. Research Question

What is the level of agreement between sonographer based assessment of the fatty liver using conventional ultrasound and attenuation imaging scoring?

2. Study Outline

2.1. Aims and Objectives

Evaluate the agreement between a sonographer-based assessment of the fatty liver using conventional ultrasound and attenuation imaging scoring.
Describe any disagreement between sonographer-based assessment of the fatty liver and attenuation imaging scoring.
Assess if there is any variation in agreement at different grades of fatty liver disease.

2.2. Method

2.2.1. Study Type

This study will be carried out using a cross-sectional quantitative methodology.

2.2.2. Study Overview

A cross-sectional design will be used for this study. The Sonographer appraisal and attenuation imaging score will be collected from observations made at a single point in time during the ultrasound scan to look at the agreement between the two factors. These features, data collected through the sample being observed at a single point in time to assess agreement, make this an appropriate design for this study (Ellis, 2019). Evidence of agreement may point towards further areas for research such as use as a screening tool or point of care ultrasound. However, as an inexpensive method of collecting and comparing a large quantity of data, a cross-sectional study is a pragmatic choice (McClean, 2020).
The data will be obtained from a population of patients having abdominal or liver scans in Bronglais Hospital, Aberystwyth, until sufficient data has been collected in line with calculated sample size. Establishing criteria for inclusion and exclusion allows exclusion of patients who may be clinically unsuitable or unable to consent. The inclusion and exclusion criteria with justification for these decisions are set out in table 1. Identifying patients eligible for inclusion in the study should be achievable from the assessment of patient referral forms. Most exclusion criteria should also be

detected from the referral form; however, patients with unknown large or multiple liver masses may be identified during the scan. Patients will be informed via the PIS that if it is found for any reason that they do not meet the criteria that they will be informed that this is the case, and we will collect no further data from them. Their care will continue as normal. Patients identified in this way will be excluded from the results.
There will be no randomisation all participants will undergo the same study procedure, which will be carried out during a single, routine hospital visit, avoiding the need for participants to attend additional appointments. The assessment will be carried out by two experienced sonographers with a minimum of 10years of abdominal scanning experience. Sonographer 1 will scan each participant, with Sonographer 2 reviewing the images later in the same conditions to avoid variation caused by lighting conditions. Both sonographers will be blind to the participant's history before completing the liver assessment to avoid any bias from past medical history. They will assess the liver using routine ultrasound, making their decision based on hepato-renal contrast, visualisation of the walls of the intra-hepatic veins and visualisation of the liver parenchyma (Hernaez et al., 2011, Ballestri et al. 2021). The sonographers will individually grade the liver as normal, mild, moderate or severely fatty, recording this on a case report form. The attenuation imaging function will then be switched on and the ultrasound machine will calculate the attenuation imaging scores, according to manufacturer guidance, which will be recorded on the case report form along with the participant's age, gender, and diagnosis. The BMI measurement will also be taken in the time around the participant's appointment and recorded on the case report form as BMI has an impact on image quality (Reynolds, 2011).

2.2.3. Study Populations, Subject Selection, Recruitment and Study Schedule

Convenience sampling permits all patients scanned in the time frame who meet the inclusion criteria to be included in a study reducing time and cost (Walliman, 2011) making this a realistic choice for this study. However, this type of sampling is not representative of the population, which limits the ability to generalise the findings (Walliman, 2011). This method is widely used in clinical research and convenience sampling at a single site is common in healthcare as data protection issues limit data transport across multiple sites (Kahn et al. 2012).
Eligible patients will be identified in line with the eligibility criteria described below. Informed consent will be obtained from all participants prior to any study procedures. A study schedule and participant flow chart are attached in Appendix 1.

2.2.4. Eligibility Criteria

Hepatic steatosis appears in different sexes at different ages and is linked to obesity and metabolic disease, such as diabetes mellitus (EASL et al., 2016) and so it is important to include this in the study. Large liver masses impede both sonographic assessment and attenuation imaging and so will be excluded. Inpatients will also be excluded as these are often difficult to scan due to poor mobility but also are often too unwell to be in the department for any length of time. Patients with complex anatomy due to congenital or surgical reasons or who due to body type are not suitable for conventional ultrasound will also be excluded. Fatty livers are unusual in the younger population unless drug induced and participants need to be able to

consent so only an adult population will be included. Patients with normal livers will be included as livers can be graded as normal, mild, moderate or severely fatty.
Table 1

Variable	Measure
Age	Inclusion:18< years Exclusion: <18 years
Patient group	Inclusion: GP and OP referrals. Exclusion: Inpatients
Clinical history	Inclusion: NAFLD, Unknown, Diabetes, Other metabolic disease Exclusion: Known large liver mass. Poor visualisation of the liver due to body type or unusual anatomy.

2.2.5. Power Calculation

The statistical test to determine inter-rater agreement when data are at the ordinal level is kappa (McHugh, 2012). The degree of agreement ranges between -1 and 1.0; 1.0 infers complete agreement, and 0 less agreement than random chance, with negative values indicating disagreement. Assessment of the strength of agreement will be based on the limits described by Landis and Koch (1977) where ≤0=poor, 0.01–0.20=slight, 0.21–0.40=fair, 0.41–0.60=moderate, 0.61–0.80=substantial, and 0.81–1=almost perfect agreement.
The sample size for kappa is calculated based on the need to detect a difference between levels of agreement. McHugh (2005) acknowledges that an agreement of 0.80 or above is more widely accepted in healthcare as the minimum interrater agreement, and a kappa of 0.59 and below an inadequate agreement. Using these values with a power of 90% and alpha set at 0.05, the sample size will be 95.

2.2.6. Statistical Analysis Plan

Initially, descriptive statistics will be used to analyse the data collected. The categorical data, gender and diagnosis, will be described using a frequency distribution able. Distribution of ratio data will be assessed using the Shapiro-Wilk test. Normally distributed ratio data will be described using mean and standard deviation, whereas non-normally distributed data will be described using median and interquartile range. Finally, the ordinal data, attenuation imaging score and sonographer appraisal will be described using a frequency distribution table with numbers and percentages, with the mode used to describe the central tendency. Inferential statistics will determine the agreement between the sonographer appraisal and attenuation imaging score, with the manufacturer cut-off values being used to create ordinal-level data. The statistical test to determine inter-rater agreement with ordinal data is kappa (McHugh, 2012). Weighted kappa will be used as this takes

into account the level of inter-rater disagreement (Sim and Wright, 2005), which in this study could be a minor inter-rater disagreement such as mild steatosis versus moderate steatosis rating as opposed to normal versus severe steatosis rating which would be a more significant inter-rater disagreement.
The previously stated values recommended by Landis and Koch (1977) will be used to evaluate the level of agreement. The magnitude of kappa can be affected by the weighting scheme used (Sim and Wright, 2005); linear weighting will be used as quadratic weighting attaches too much importance to near agreements.

2.3. Study Outcomes

The value of Kappa will be used to assess the agreement. An interrater agreement of 0.80, a value widely accepted in healthcare as the minimum interrater agreement (McHugh, 2005) so this value will be used to confirm or reject the hypothesis.

2.4. Timescale

Please see attached Gantt chart in Appendix 1.

2.5. Publication Policy

A copy will be made available for all participants, sponsors, collaborators, and research and development department.
The study will also be submitted for inclusion in the academic journal Ultrasound and results may be shared for learning within and outside the health board at conferences and events.
Data will be anonymised on collection so no individual will be able to be identified at publication. The study will form part of an MSc thesis submission.

3. Screening, Consent and Withdrawal

3.1. Screening Duties

Laura Mundy, as the researcher and a member of the clinical team, will be responsible for screening potential research participants. All ultrasound requests are vetted for suitability by a Sonographer as part of their clinical role. The researcher will review requests for abdominal scanning during the normal vetting procedure.

3.2. Informed Consent Procedures and withdrawal

Any patient identified who meets the criteria will be sent a participant information leaflet with the appointment letter. The study will be discussed with patient during their appointment visit and written consent can be obtained, if the patient agrees to take part. Any patients given short notice appointments will be given a patient information leaflet on attendance at the department to read whilst waiting to be called in for their examination. They will then be asked to sign an informed consent form if they're willing to take part. The sonographer undertaking the scan, who will have undertaken training in informed consent, will receive consent from the patient rather than the researcher to avoid coercion.

If the participant wishes to be withdrawn, then they can do so at any time up until the data is pseudonymised for analysis.

If for whatever reason the measurements cannot be taken (due to body habitus, liver lesions, etc) then the reason will be recorded, and from this point, no further data will be collected. The other data will be retained to look for patterns in patient demographics in reject analysis.

4. Risk, Ethical Considerations and Confidentiality

4.1. Risk and Benefits

Risks to patients:

Attenuation imaging uses the same principles as conventional ultrasound. Ultrasound is considered a generally safe imaging modality and details of the British Medical Ultrasound Society 'Statement for the General Public on the Safety of Ultrasound' (2017) will be made available in the information leaflet. Standard ultrasound safety practice will be adhered to as per the British Medical Ultrasound guidelines (2009). Bae et al. (2019) found that the attenuation imaging scoring increased the scan time by approximately two minutes, so the scan time should remain within the safe level and minimally impact the patient's time.

The only further impact on the patient's time will be in measuring the patients BMI which is not a time-consuming process.

The ultrasound scan will be reported in the usual manner using the sonographer's initial assessments. So, the attenuation imaging scoring will have no impact on the report produced for the referring clinician and, consequently, no impact on the patient's treatment or pathway.

Risks to staff:

Increased scan times, high patient BMI and repetitive exam types in a single session can also impact sonographers, causing work-related musculoskeletal disorders (Harrison and Harris, 2015). These factors are accounted for in site risk

assessments based on advice from the Society & College of Radiographers (2019) and in the project risk assessment (Appendix 1.); these will be followed to minimise risk to the operators.

4.2. Ethical Considerations

NHS REC approval will be sought for this study and confidentiality, anonymity and informed consent will be ensured throughout.

4.3. Patient & Public Involvement

Patients will not be involved in the development and dissemination of this study but will contribute to its conduct as participants and will be informed of the potential for dissemination of results via non identifiable reports and publications.

4.4. Confidentiality

Participants' signed informed consent forms and research data will be securely stored at all times. Research data will be pseudo-anonymised. GDPR regulations will be adhered to throughout and information governance approval will be sought prior to study commencement

4.5. Premature Termination or Suspension of Study

If premature study termination is required (eg due to insufficient protocol adherence or inability to recruit participants and collect study data), HDUHB R&D (as sponsor), RECx, and academic supervisors will be notified in writing.

4.6. Record Retention and Archiving

In line with health board policy for sponsored studies, study records will be archived for five years at the designated archiving facility.

4.7. Study Oversight

Laura Mundy, as CI will be responsible for study oversight and will report any issues to HDUHB R&D (as sponsor), Wales REC 6 and academic supervisor.

4.8. Study Reporting

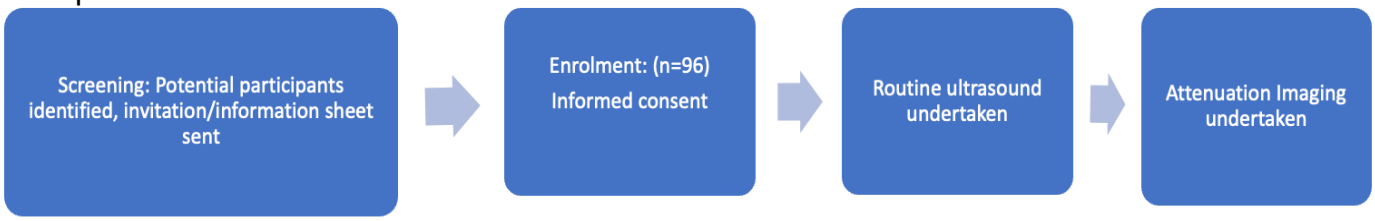
The CI will provide regular updates to the academic supervisor and HDUHB R&D team and will submit an end of study report to Wales REC 6

4.9. Safety Reporting

Any adverse events or serious adverse events occurring during the study visit will be recorded and reported to HDUHB R&D in line with standard procedures.

5. Appendix 1.

Participant flow chart.



Project Timeline	Apr-23				May-23					Jun-23				Jul-23					Aug-23				Sep-23				Oct-23					Nov-23				Dec-23			
	3	10	17	24	1	8	15	22	29	5	12	19	26	3	10	17	24	31	7	14	21	28	4	11	18	25	2	9	16	23	30	6	13	20	27	4	11	18	25
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Ethics UWE														
Introduction														
Literature review-Research														
Literature review-Write up														
Data collection														
Data Analysis														
Results-Conclusion														
Draft 1														
Condense to article														
Submission														
Deadlines														

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