Perspectum

Title	Longitudinal Assessment of Multiple Organs in Patients with Type 2 Diabetes (MODIFY study)
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Sponsor	Perspectum Ltd
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Issue control

Issue	Paragraph	Details	Reason	Date/Initial
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3.0	Pages 1, 18	Changing name of NHS Trust in Liverpool	Trust merger on 1st October 2019	19NOV2019JW
4.0	Page 1 & footer all pages	Changing date and version	New version and date to reflect change outlined below	04Feb2020JW
4.0	Page 29	Changing date and version	Changing the number of years in a sentence (from 10 to 5) in section 11 which should (and now does) correspond with another in section 11 regarding enrolment log	04Feb2020JW
5.0	All relevant pages	Company name change, protocol date and version number	Changing name of company to Perspectum Ltd./Perspectum and not Perspectum Diagnostics	13Mar2020 JW
5.0	Pages 2, 4	Updated page numbers in TOC	Updated page numbers in TOC	13Mar2020 JW
5.0	Pages 15, 16	Amending Visit 2 to take place within 35 days of visit 1, and not 21. Text page 15 and Fig.4 page 16	To accommodate local availability to undertake both MRI and ECHO	13Mar2020 JW
5.0	Page 19	Addition of Diabetes UK Online Patient Forum	Addition of this organisation as an advertising platform for recruitment to the study	13Mar2020 JW
5.1	Page 19	Addition of precautionary measures for COVID-19 relating to study visits	To provide further guidance on how to reduce risk to staff and participants due to COVID-19	02Jun2020 GG

	Page 19, 22 and 27	Referral to additional imaging guidelines	To provide guidance on research imaging whilst considering COVID-19	
	Page 32-35	Addition of Appendix 1	To provide guidance on research imaging whilst considering COVID-19	
5.2	Page 14, 15, 18, 19 and 28	Addition of information regarding e-consent	To provide an alternative method for consent and how the data is managed	09Jun2020 GG
5.3	Page 7 and 29	Removal or PDPA 2012 and replace Edison with Perspectum Portal	To comply with GDPR relevant to this study and renaming of Perspectum Portal	01Jul2020 MS
5.4	All	Incorporating all feedback and adding signatories	Review	02Jul2020 GG
5.5	Page 8, 9, 13-16, 22 and 24	Update of study timepoint and analysis	To ensure timepoint is more reflective of patient follow up	07Jul2020 AR/GG
6.0	All	Final review and update of version	Finalised document	14Jul2020 GG
6.1	Page 16	Adding Perspectum as clinical site open for recruitment	To make up deficit of slow recruitment at London clinical site	23Apr2021 JW/RS
6.2	Page 18, 24 and 32 Pg 25 Pages 25 and 27	Healthy Volunteers additional information Statistical analysis plan Revised Incidental Findings process and SAE reporting	To include healthy individuals from other studies to ensure age and gender matching Clarification of wording and exploratory metrics SAE requires updating as this is an observational study. IF process has been revised within Perspectum.	18May2021 JW/RS
7.0	All	Final review and update of version	Finalised document	21May2021 JW/RS
7.1	Page 19	Addition of wording to use the ATLAS short film	To utilise the participant-interview ATLAS short film to raise awareness of MODIFY and assist recruitment	18Jun2021 JW
8.0	All	Final review and update of version	Finalised document	21Jun2021 JW
8.1	Pages 18 text, Table 1 pp22/23 and	Addition to p18 text and table 1, pp22/23 and text on pp24/25 to, include potential supplementary telephone	Review document	27Jan2022 JW

	text on pages 24/25	call to participant to clarify any data that may missing or unclear from medical record, or where medical record cannot be accessed by a approved non-NHS clinical study site such as Perspectum Ltd.		
	Page 29	Addition of text to include letter fo feedback to participant		
9.0	All	Approved update of version	Finalised document	28Jan2022 JW/HTB

ABBREVIATIONS

ALT	Alanine Transaminase
AST	Aspartate Transaminase
APR	Annual Progress Report
BMI	Body Mass Index
CI	Chief Investigator
CKD	Chronic Kidney Disease
CTRG	Clinical Trials & Research Governance, University of Oxford
CVD	Cardiovascular Disease
DPA	Data Protection Act 2018
ECG	Electrocardiogram
ECHO	Transthoracic echocardiogram
eGFR	Estimated glomerular filtration rate
GCP	Good Clinical Practice
GDPR	General Data Protection Regulation
GGT	Gamma-glutamyl transferase
HbA1c	Glycosylated haemoglobin A1c
HRA	Health Research Authority
ICF	Informed Consent Form
ISO	International Organization for Standardization
LFT	Liver Function Test
MRI	Magnetic Resonance Imaging
NAFLD	Non-alcoholic Fatty Liver Disease

NASH	Non-alcoholic Steatohepatitis
NRES	National Research Ethics Service
NT-proBNP	N-terminal pro b-type natriuretic peptide
PI	Principal Investigator
P3NP	N-terminal levels of type III procollagen (P3NP)
PIL	Participant/Patient Information Leaflet
PREMs	Patient Reported Experience Measures
PROMs	Patient Reported Outcome Measures
R&D	Research and Development (NHS)
REC	Research Ethics Committee
SAE	Serious Adverse Event
SIN	Study Identification Number
SOP	Standard Operating Procedure
T2D	Type 2 Diabetes

1. SYNOPSIS

Study Title	Longitudinal Assessment of Multiple Organs in Patients with Type 2 Diabetes (MODIFY)
Internal Ref. No.	EC-148 / CA064
Study Design	Multi-site, prospective, longitudinal, observational cohort study
Study Participants	Adult patients with type 2 diabetes recruited from community, primary care or secondary care settings
Number of Participants	150
Planned Study Period	84 months
Primary Objective	1. To determine the degree of liver fibroinflammation in a large cohort of patients with type 2 diabetes, using multi-parametric abdominal MRI.
Secondary Objectives	1. To determine the degree of other liver abnormalities (such as fat infiltration) in a large cohort of patients with type 2 diabetes, using multi-parametric abdominal MRI. 2. To determine the degree of abnormality in other organs associated with type 2 diabetes and its comorbidities (pancreas, spleen, kidneys, aorta) using multi-parametric abdominal MRI. 3. To assess whether multi-parametric abdominal MRI can quantify changes in multiple organs (liver, kidneys, pancreas, spleen and aorta) that occur over 6-9 months. 4. To assess changes in multiple organs (liver, kidneys, pancreas, spleen and aorta) that occur over 6-9 months, with conventional biochemical biomarkers utilised in the clinical pathway for T2D, chronic kidney disease (CKD) and non-alcoholic fatty liver disease (NALFD). 5. To evaluate the impact of multi-parametric abdominal MRI on type 2 diabetes management. 6. To determine the prognostic information provided by abdominal imaging for longer-term evaluation of clinical outcomes (after 1, 3 5 years).
Primary Endpoint	7. MRI metrics for liver fibroinflammation in patients with type 2 diabetes compared with the same metrics in healthy, non-diabetic individuals at baseline.

Secondary Endpoints	1. Correlations between liver MRI metrics in patients with type 2 diabetes with the same metrics in healthy, non-diabetic individuals, at baseline for: • fat infiltration • organ volume • proportion of patients with evidence of non-alcoholic fatty liver disease (based on thresholds for liver fat or fibroinflammation) 2. Correlations between MRI metrics in patients with type 2 diabetes with those in healthy, non-diabetic individuals, at baseline for: • organ volume, fat infiltration and fibroinflammation in abdominal organs affected by type 2 diabetes (spleen, pancreas, kidney) • aortic health (aortic distensibility, diameter) 3. At 6-9 months: to assess the difference, from baseline, across the cohort in the following MRI metrics: • organ volume, fat infiltration and fibroinflammation in abdominal organs affected by type 2 diabetes (liver, spleen, pancreas, kidney) • aortic health (aortic distensibility, diameter) • proportion of patients with evidence of non-alcoholic fatty liver disease (based on thresholds for liver fat or fibroinflammation) 4. At 6-9 months: to assess the difference, from baseline, across the cohort in the following metrics: • glycaemic control (HbA1c) • lipid profiles • renal health (serum creatinine, eGFR, urine albumin-creatinine ratio) • liver health (FBC, LFT) 5. To review and analyse the patient and clinician reported outcome measures collected from non-validated questionnaires. 6. At 1, 3 and 5 years: to assess the odds ratio for developing cardiovascular, liver, pancreatic and kidney related events and/or death, including hospital admissions.

2. INTRODUCTION

2.1. Background and Rationale

There has been a surge in incidence of the metabolic syndrome; a cluster of conditions which increase the risk of:

- type 2 diabetes (T2D) (90% of diabetes cases),
- non-alcoholic fatty liver disease (NAFLD),
- non-alcoholic steatohepatitis (NASH),
- cardiovascular disease (including ischaemic heart disease and heart failure),
- ischaemic or haemorrhagic stroke

This project concentrates on T2D, a disease whose multiple pathophysiological defects include:

- increased renal glucose reabsorption,
- decreased peripheral glucose utilisation,
- increased hepatic glucose production due to insulin resistance,
- increased glucagon secretion,
- reduced insulin secretion (pancreas),
- and incretin secretion (gastrointestinal tract)

Estimated UK prevalence of T2D is 5.26%. This represents 3.3 million people (1) (comparatively in the US, 9.1% or 26.44 million people (2)), which equates to £8.8bn in associated healthcare costs in UK (3).

Type 2 diabetes is associated with a heterogeneity in its aetiology – this is observed in its clinical presentation and subsequent rate of progression. Further factors associated with T2D include micro-and macrovascular complications and an observed decline in multiple organs (end-organ damage). End-organ damage contributes to the clinical picture of individuals with T2D and is demonstrated when observing the high prevalence of co-morbidities in this patient cohort. For example, the presence of NAFLD is seen in 60% of T2D patients (4, 5), along with a 34.2-50.7% presence of chronic kidney disease (CKD)(6) and a 32.2% presence of cardiovascular disease (CVD)(7).

Currently, T2D and its complications are monitored using circulating plasma and serum biomarkers (8). However, these lack sufficient sensitivity or specificity. An example of this is highlighted in one researcher's preliminary data that suggests that 85% of obese people with T2D had NAFLD, detected by MRI. However, a vast proportion of this patient cohort have recorded normal biochemical biomarkers, such as Alanine Transaminase (ALT).

Metformin is typically the initially treatment for T2D (8). However, due to its progressive nature, metformin monotherapy proves to be inadequate in maintaining long-term glycaemic control (9). Metformin has been used safely and effectively for decades, but newer drugs are becoming available. Numerous recent studies have shown that newer drug classes, including the SGLT-2 inhibitors and GLP1 receptor agonists (GLP-1RA), have substantial beneficial effects

beyond modulation of glycaemic levels, and can confer protection against CVD and CKD (10–13). It is now recommended that use of these drugs is advocated for high risk populations with evidence of CKD or CVD (14–16).

This study aims to develop an MRI-based method that is able to identify the individuals at high risk of disease complications, looking particularly at renal, hepatic and cardiovascular pathology, and further compare this to the conventional biochemical approach. This has future potential in assisting in the stratification of patients to the most appropriate tailored treatment for their disease. We will further evaluate the additional synergistic value of incorporating MRI-metrics into patient pathways.

There is a healthcare need to provide further decision-making support for clinicians in the care of patients at risk or diagnosed with T2D. This would combine multi-modality approaches, an incorporation of biochemical evaluation and imaging techniques. There is also a pressing need for treatment stratification to identify the T2D patients who would benefit from being triaged to receive the newer, more expensive drugs. This would also empower patients and aid in their engagement of the lifestyle changes often required for treatment. This should have the added benefit of reducing associated NHS costs by minimising the pool of patients with severe disease, who would be highlighted through early detection and early medical management.

To address this growing need, we propose adding a complementary imaging aspect to the currently used biomarkers. MRI, specifically, provides excellent soft-tissue contrast. Perspectum's Liver*MultiScan*™ is a quantitative multiparametric MRI method, FDA-cleared and CE-marked, that is used to detect and stage early liver disease. It is already widely used in pharmaceutical trials for NAFLD therapeutics. The MRI metrics from Liver*MultiScan*™ can quantify changes to liver tissue characteristics, like fibro-inflammation and fat, as a result of intervention (for example, bariatric surgery - see Fig. 1). The accuracy and reproducibility of Liver*MultiScan*™ has been demonstrated in studies scanning patients within different MRI scanners. It continues to be further supported by data from clinical trials in liver disease cohorts, from comparative studies that include healthy controls, as well as whole-population studies in the UK and US (17–24).

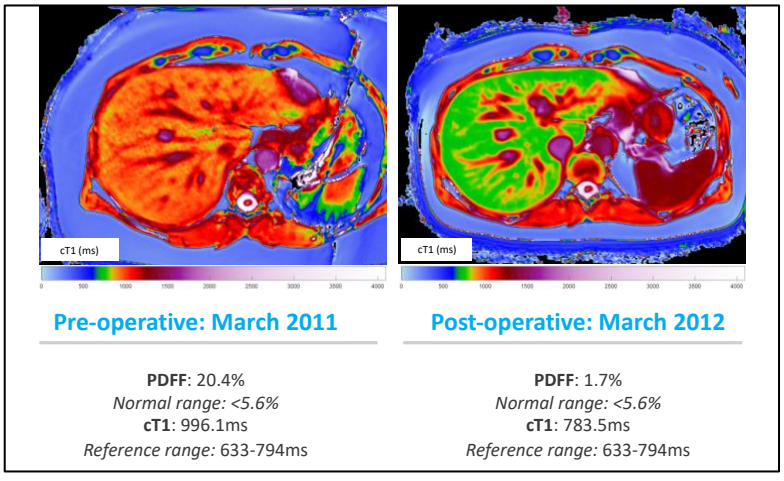

*Figure 1 - Example of MRI metrics and images from Liver*MultiScan™ *before and after bariatric surgery*

With this study we aim to develop a new MRI image analysis technique, "ATLAS", that builds on Liver*MultiScan*™ technology. We also plan to gather clinical evidence that will demonstrate the potential added value to the NHS, as well as support future regulatory clearance. The phenotypical information that ATLAS delivers, combined with information from circulating biomarkers, will form the basis of a future clinical decision support tool for T2D (Fig. 2).

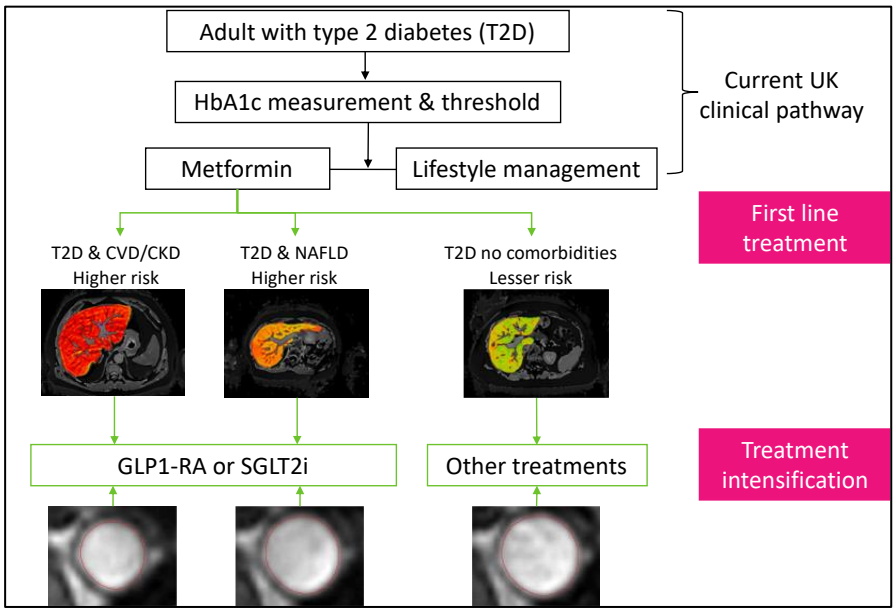

Figure 2 – An example schematic of the impact of ATLAS in the clinical pathway of T2D, based on MRI metrics of liver and cardiovascular system health

Perspectum has pilot data showing that Liver*MultiScan* can:

- estimate portal hypertension (spleen),
- detect pancreatitis,
- characterise the tissue of the kidneys

This study looks at the potential to extend Liver*MultiScan* to each of the other relevant organs – pancreas, kidneys and spleen. The technical development of "ATLAS" will be complemented by the accumulation and analysis of clinical data, circulating biomarkers and imaging. This information will be obtained from three diverse UK clinical centres (Liverpool, Oxford and London).

The innovation comes from combining a number of quantitative MRI metrics to achieve this (Fig. 3):

- volumes - for liver, spleen, kidneys, pancreas (25–27);
- fibroinflammation: cT1 and/or T1 – for liver, spleen, kidneys, pancreas (25);
- fat infiltration: PDFF – for liver, kidneys, pancreas (28);
- aortic distensibility and diameter (29).

We will also incorporate kidney diffusion and renal flow (25). There will be strong patient and clinician involvement in the collection of patient-reported experience and outcome measures throughout the study (PREMs and PROMs), both qualitative and quantitative, to reflect the patients' experience of the clinical care pathway.

The resulting MRI diagnostic solution will enable rapid and comprehensive stratification of T2D and affiliated diseases (NAFLD, CKD, CVD), allowing clinicians to facilitate personalised medicine. It is anticipated that adopting a clinical approach which utilises ATLAS will result in substantial cost savings for the NHS and will help improve patient experience by providing access to advanced treatments to those patients most at risk.

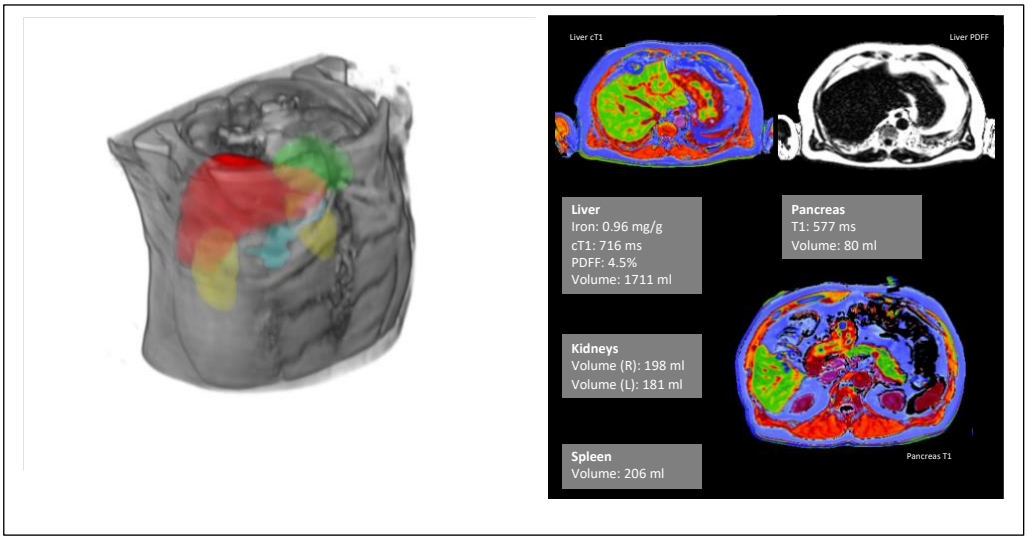

Figure 3 *– Example MRI images and metrics that are generated with ATLAS. Left panel shows liver (red), kidneys (yellow), pancreas (blue) and spleen (green) volume images within the thorax. Right panel shows single MRI slices with associated organ volume, fat infiltration or fibroinflammation metric values.*

3. STUDY OBJECTIVES

The main objective of this study is to assess the health of multiple organs over a period of 6 to 9 months, using multiparametric abdominal MRI, in patients with type 2 diabetes who have been prescribed glucose lowering therapy (as per their standard of care).

Primary Objective	Primary Outcome Measure
1. To determine the degree of liver fibroinflammation in a large cohort of patients with type 2 diabetes, using multi-parametric abdominal MRI.	MRI metrics for liver fibroinflammation in patients with type 2 diabetes *vs.* the same metrics in healthy, non-diabetic individuals at baseline.
Secondary Objectives	**Secondary Outcome Measures**
1. To determine the degree of other liver abnormalities (such as fat infiltration) in a large cohort of patients with type 2 diabetes, using multi-parametric abdominal MRI.	1. Liver MRI metrics in patients with type 2 diabetes *vs.* the same metrics in healthy, non-diabetic individuals, at baseline for: • fat infiltration • organ volume • proportion of patients with evidence of non-alcoholic fatty liver disease (based on thresholds for liver fat or fibroinflammation).
2. To determine the degree of abnormality in other organs associated with type 2 diabetes and its	2. MRI metrics in patients in patients with type 2 diabetes *vs.* those in healthy, non-diabetic individuals, at baseline for:

comorbidities (pancreas, spleen, kidneys, aorta) using multi-parametric abdominal MRI	• organ volume, fat infiltration and fibroinflammation in abdominal organs affected by type 2 diabetes (spleen, pancreas, kidney) • aortic health (aortic distensibility, diameter).
3. To assess whether multi-parametric abdominal MRI can quantify changes in multiple organs (liver, kidneys, pancreas, spleen and aorta) that occur over 6-9 months.	3. At 6-9 months: difference from baseline across the cohort in the following MRI metrics: • organ volume, fat infiltration and fibroinflammation in abdominal organs affected by type 2 diabetes (liver, spleen, pancreas, kidney) • aortic health (aortic distensibility, diameter) • proportion of patients with evidence of non-alcoholic fatty liver disease (based on thresholds for liver fat or fibroinflammation).
4. To assess changes in multiple organs (liver, kidneys, pancreas, spleen and aorta) that occur over 6-9 months, with conventional biochemical biomarkers utilised in the clinical pathway for T2D, chronic kidney disease (CKD) and non-alcoholic fatty liver disease (NALFD).	4. 6-9 months: difference from baseline across the cohort in the following metrics: • glycaemic control (HbA1c) • lipid profiles • renal health (serum creatinine, eGFR, urine albumin-creatinine ratio) • liver health (FBC, LFT).
5. To evaluate the impact of multi-parametric abdominal MRI on type 2 diabetes management.	5. Review/analysis of patient and clinician reported outcome measures collected from non-validated questionnaires.
6. To determine the prognostic information provided by abdominal imaging for longer-term evaluation of clinical outcomes (after 1, 3 5 years).	6. At 1, 3 and 5 years: odds ratio for developing cardiovascular, liver, pancreatic and kidney related events and/or death, including hospital admissions.

4. STUDY DESIGN

a. Study Description

This will be a multi-site study adopting a prospective, observational, longitudinal, cohort study design. There will be no intervention to the standard of care. Participants will be required to attend a screening visit and additional study visits on up to three time points – baseline (visit 1), a visit within 35 days of baseline (visit 2) and at 6-9 months (visit 3). The second and third visit will involve having a multiparametric MRI scan. Where possible some visits (the screening visit 1 or visit 1 /visit 2) may be on the same day or within standard of care, depending on patient and MRI scanner availability. The screening visit may be able to take place remotely over the phone, depending on the preference of the participant and the study team, facilitated by the use of an online platform to obtain Informed Consent. In consideration of the COVID-19 pandemic, prior to each study visit, participants will be asked to confirm whether they have experienced any

of the documented symptoms. Participants may also undergo a temperature measurement at the discretion of the local clinical care team.

Patients with type 2 diabetes and prescribed with glucose lowering therapy (as per standard of care) will be recruited from community settings, primary care centres and diabetes clinics within secondary care settings (see Fig. 3). We aim to recruit patients who have been newly prescribed medication; also, those patients undergoing treatment intensification (when an additional treatment is being considered due to evidence of poor glycaemic control), as per their standard of care HbA1c level results. Clinical outcome measurements, blood samples and urine samples will be collected to assess the response to standard of care treatment. There will be an optional thoracic echocardiogram (ECHO) included at visit 2. This is a non-invasive way in which we can capture data to enable us to assess cardiovascular disease.

Study participants will be enrolled in this study for a total of 5-years. During this time, consented participants will be asked to attend for up to 3 study visits: Visit 1 (baseline), Visit 2 and Visit 3.

Visit	Time	Visit Details
Screening visit	0 weeks	• Informed Consent • Medical Record Review
Visit 1 - Baseline, Day 0	0 weeks	• Medical Hx • Blood Tests • Basic measurements (incl. height, weight, BMI, hip & waist circumference) • Urine Sample • Questionnaire
Visit 2	Within 35-days of Visit 1	• MRI Scan • BP (optional) • ECHO (optional) • Questionnaire
Visit 3	6-9 months	• Medical Hx • Blood Tests • Basic measurements (incl. height, weight, BMI, BP) • Urine Sample • Questionnaire

Visit	Time	Visit Details
		• MRI • Medical Record Review

Further to this, participants will be asked to give consent to the review of their medical records at 3 time points - years 1, 3, and 5, following baseline assessment. This review will be conducted by authorised study investigators who will obtain clinical outcome measures relating to the study objectives, for example, measures of liver or kidney function.

In the majority of cases, follow-up data at years 1,3,5 will be entered from participants' medical records. However, some participants may receive a short telephone call at years 1,3,5 to clarify any data which may be unclear or, to supply data which may be missing from their medical record. All participants recruited and scanned at Perspectum Ltd. in Oxford (a non-NHS clinical study site) will complete their years 1,3,5 follow-up medical history over the telephone: although all participants have consented to a medical records review during the study, medical records are not available to staff outwith the NHS. Thus self-reported data will be collected from these participants.

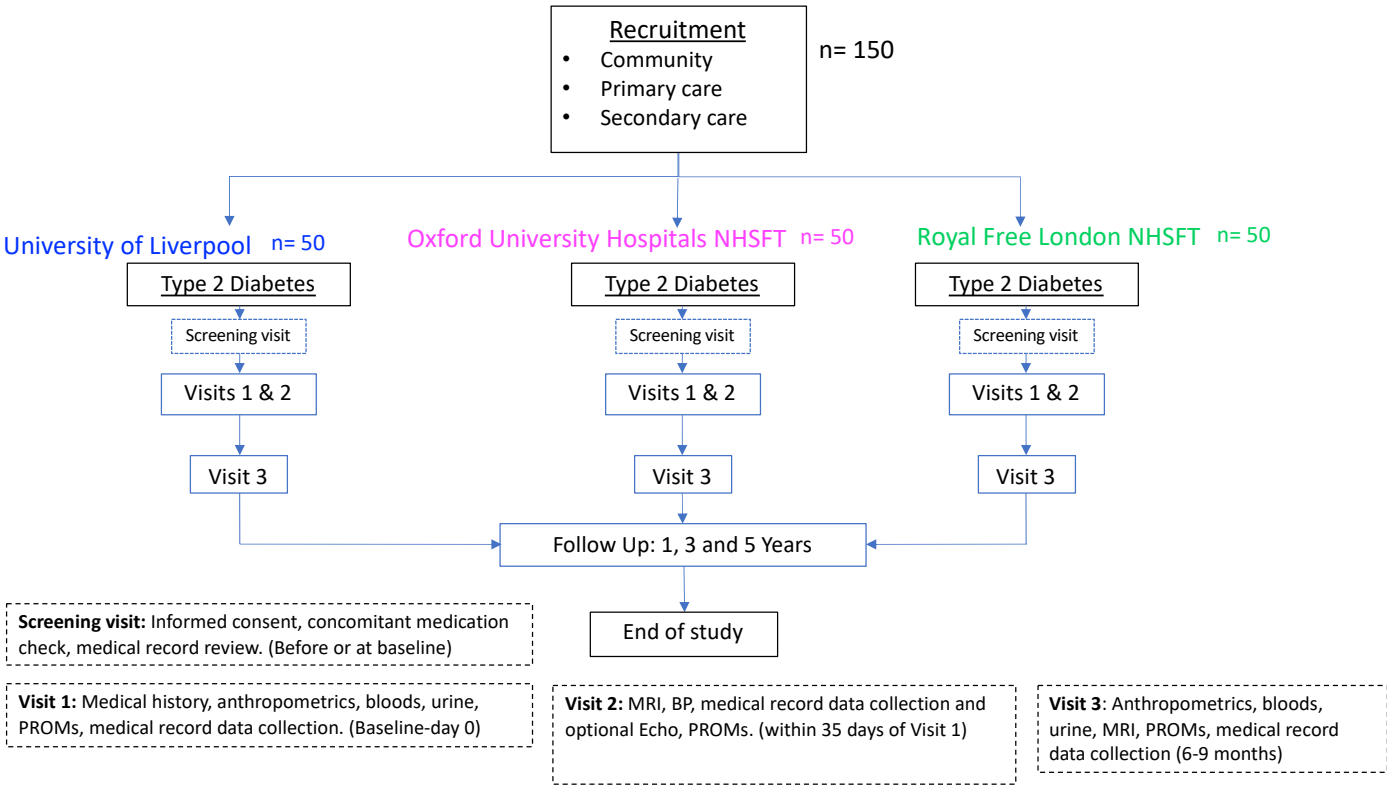

Figure 4 - Schematic of patient recruitment and study pathway (participants will be asked to confirm an absence of COVID-19 symptoms prior to each visit and may undergo a temperature measurement if necessary)

b. Study Setting

This is a multi-centre study conducted in 4 localities:

1) Liverpool
2) Oxford (Oxford University Hospitals NHS Foundation Trust - OUHNHSFT)

3) London (in the catchment of the Royal Free NHS Foundation Trust)
4) Oxford (Perspectum Ltd.)

Site 1) and 2) to recruit 50 T2D patients each, with the remaining 50 patients to be recruited between sites 3) and 4). Recruitment will be carried out from various settings to include community, primary care and secondary care diabetes clinics. Imaging will be carried out at local imaging centres for each locality.

5. Study Participants

Adult participants, aged 18 years and over, with type 2 diabetes and prescribed with glucose lowering therapy as per their standard of care.

5.1. Inclusion criteria

- Male or female over 18 years of age and diagnosed with type 2 diabetes.
- Participant currently taking glucose lowering therapy.
- Participant willing and able to give informed consent for participation in the study.

5.2. Exclusion Criteria

- The participant may not enter the study if they have any contraindication to magnetic resonance imaging (standard MR exclusion criteria including pregnancy, extensive tattoos, pacemaker, shrapnel injury, severe claustrophobia).
- Patients with known autoimmune hepatitis, viral hepatitis, Wilson's disease, haemoglobinopathies or significant structural renal tract abnormality.
- Patients with known excessive alcohol intake.
- 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 participant's ability to participate in the study.

6. Sample size

The primary endpoint of the study is to compare the MRI metrics for liver fibroinflammation in those patients with type 2 diabetes at baseline vs. individuals who are healthy and non-diabetic. Values for the healthy, non-diabetics will be provided from data from the UK Biobank (UKBB)(30) or from other studies (31). Healthy individuals will be matched to the diabetic population based on gender, age and ethnicity. Analysis will be based on a two-sample, two-sided t-test.

The sample size required to perform a t-test with 90% power and alpha of 0.05 would require n=150. Based on MRI metric for liver fibroinflammation (cT1) this assumes:

- Detection of a 24.87 ms difference in cT1 in liver (This represents 50% of the difference in cT1 between self-reported diabetes vs healthy subgroups within the UK Biobank), based on unpublished data from Perspectum)
- SD of 42ms (pooled SD from self-reported diabetes and healthy subgroups within UKBB, based on unpublished data from Perspectum)
- 20% drop-out rate.

Secondary endpoints of the study include separate comparisons of MRI metrics for liver fat infiltration and volume in patients with type 2 diabetes vs. the same metrics in healthy, non-diabetic individuals. Values for the healthy, non-

diabetics will be provided from data from the UK Biobank (30) or or from other studies (31) and will be selected based on the matching of gender, age, ethnicity to the patients from this study with type 2 diabetes. Analysis will be based on two-sample, two-sided t-tests.

Based on MRI metric for liver fat infiltration (PDFF), the sample size required to perform the t-test with 90% power and alpha of 0.05 would require n=150. This assumes:

- Detection of a 2.4% difference in PDFF [This represents 63% of the difference in PDFF between self-reported diabetes vs healthy subgroups within UK Biobank, unpublished Perspectum]
- Measurement SD of 5.4% (Pooled SD from self-reported diabetes and healthy subgroups within UK Biobank, based on unpublished data from Perspectum)
- 20% drop-out rate.

Based on MRI metric for liver volume, the sample size required to perform the t-test with 90% power and alpha of 0.05 would require n=150. This assumes:

- Detection of a 0.084 L difference in liver volume in liver (This represents 6% of the pooled mean from UK Biobank data, unpublished Perspectum)
- Measurement SD of 0.289 L (pooled mean from UK Biobank data, unpublished Perspectum)
- 20% drop-out rate.

7. STUDY PROCEDURES

7.1. Recruitment

Participants will be identified from the community, primary care and secondary care diabetes; appointments; specifically, those patients with type 2 diabetes who are prescribed glucose lowering treatment as per their standard of care. A member of the clinical care team will provide potential participants with a study invitation letter and an accompanying Participant Information Leaflet (PIL) in the following places:

1) Liverpool Diabetes Partnership/ Aintree University Hospital (Liverpool University Hospitals NHS Foundation Trust)
2) The Oxford Centre for Diabetes, Endocrinology and Metabolism (OCDEM) based at the Churchill Hospital, the Horton Hospital and the John Radcliffe Hospital (Oxford University Hospitals NHS Foundation Trust)
3) The Royal Free London NHS Foundation Trust - Diabetes Department
4) Perspectum Ltd., Oxford

At each locality (Oxford, Liverpool, London catchment area of Royal Free NHS Foundation Trust), posters will be displayed around the hospitals, University departmental buildings and GP practices so that potential participants can also self-refer into the study by contacting the study team directly. The study will also be advertised on social media platforms (for example, Twitter and Facebook), Perspectum Ltd.'s website, hospital websites, newspapers and the Diabetes UK Patient Online Forum (forum.diabetes.org.uk). iWantGreatCare Ltd., a company that operates a patient experience data collection and analysis service, will also advertise the study by sharing the study poster via their website and will provide a website link to the Perspectum webpage for patients interested in participating in this research. The Perspectum webpage will provide a copy of the advertisement with details of how to contact us for further information.

A short film outlining the use of ATLAS in Perspectum's research will also be made available on Perspectum's MODIFY website and other social media platforms. We also plan to recruit through health awareness sessions in the local hospitals. Once a potential participant has been identified by any of these means and has expressed an interest in taking part in the study, they will be sent a Participant Information Leaflet (PIL) to read. They will be allowed as much time as they require to understand the details of the study and what's involved. Further to this, they will be given the opportunity to discuss the study with a member of the research team as part of the informed consent process.

7.2. Informed Consent

The participant must personally sign and date the latest approved version of the Informed Consent Form (ICF) before any study specific procedures are performed. This can be obtained via a hard copy or via the online consent platform that will be available to further prevent the spread of COVID-19.

Written and verbal versions of the Participant Information Leaflet (PIL) 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; and any risks involved in taking part. It will be clearly state that the participant is free to withdraw from the study at any time and for any reason without prejudice to future care, 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, the research team, 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 using the paper version of the Informed Consent Form or by using the online platform for obtaining Informed Consent. This will be followed by a dated signature of the person from the clinical study team who presented and obtained the Informed Consent.

7.3. Study Visits

In addition to the screening visit, there will be three dedicated study visits that are in addition to standard care for the participants. As far as possible we will endeavour to align study visits with clinic appointments or combine early visits, for the participants' convenience. As a precautionary measure and in an effort to prevent the further spread of COVID-19, participants will be asked to confirm whether they have experienced any of the documented symptoms prior to each study visit. Participants may also undergo a temperature measurement if necessary.

Appointments will be allocated to specific time slots to ensure minimal contact between staff and participants and so social distancing measures can be adhered to where possible. Social distancing will not be possible during some study assessments, such as blood tests.

Personal protective equipment (PPE) should be worn by all study staff in accordance with Public Health England guidance. This could include the use of items such as a plastic apron tied securely at the back, a surgical mask covering the nose, mouth and chin, and gloves. Suitable PPE can also be offered to participants, with special consideration for equipment used during imaging appointments. For example, ensure the metal strip is removed from the nose piece of surgical masks and replaced with tape, as per the guidance example in Appendix 1.

Table 1 illustrates what will happen at each study visit. Day 0 (Baseline) is defined as the day that the consented patient attends their diabetes clinic in order to participate in the study.

Activities	Screening visit	Visit 1: Baseline, Day 0	Visit 2: Within 21-days of Visit 1	Visit 3: 6-9 months after Visit 1	Follow Up phase at 1 year, 3 years and 5 years
Informed Consent	X				
COVID-19 check	X	X	X	X	X
Medical Record Review	X				
Concomitant Medication Check	X				
Medical History		X		X	
Anthropometrics		X		X	
Blood Sample		X		X	
Urine Sample		X		X	
Multiparametric MRI Scan			X	X	
Echocardiogram (optional)			X		
Medical Record Data Collection		X	X	X	X
Potential supplememtary phone call to participant to: - clarify data that may not be clear from medical record -fill in missing data from medical record; -In case of Perspectum-recruited participants who have consented to medical record check, to complete Yrs 1,3,5,follow-up data collection					X
Patient Reported Outcome/Experience		X	X	X	

Measures (PROMs)/ PREMs)					
Clinician Reported Experience Outcomes				X	

Table 1 *- Study visits and measurements*

7.3.1. Standard study visit – assessments

Medical history (~10 min)

We will obtain a full medical history including age, diabetes presentation, diabetes complications, diabetes duration, previous and current diabetes medication, current medication regime, family history, smoking history, alcohol history, ethnicity, history of cardiovascular disease, QRISK score, history of kidney disease, history of liver disease and record of any other co-morbidities the patient may have.

We will confirm that the participant has no contraindications for MRI (e.g. pregnancy, pacemaker or other metallic unfixed implanted device, metallic fragments, extensive tattoos, severe claustrophobia, metal in clothing). A resting blood pressure measurement will be taken.

All measurements will be recorded on the study participant's Case Report Form (CRF).

Anthropometric measurements (5 min)

We will measure the height and weight of the participant to calculate BMI and also take hip and waist circumference.

Blood sample (10 min)

Routine bloods will be performed as per standard-of-care for T2D or its complications and will include: HbA1c, serum creatinine, electrolytes, lipids, FBC (full blood count), LFT (liver function tests that include aspartate transaminase and alanine transaminase) and gamma glutamyl transferase (GGT). eGFR will also be calculated.

A further blood sample of approximately 10 ml will be taken to measure additional circulating biomarkers [such as the enhanced liver fibrosis test (ELF), N-terminal levels of type III procollagen (P3NP), pancreatic lipase, cystatin C, serum albumin, high sensitivity C-reactive protein, NT-proBNP and uric acid] and optional genetic testing for NAFLD or T2D associated genetic variants. Consent for genetic testing and to place blood samples in the biobank at Liverpool, Royal Free London or Oxford for future testing will be optional for all participants for up to 7 years after baseline to enable evaluation after full study completion.

Biomarker	Key organ(s)
HbA1c	Various/pancreas
Lipids	Various
GGT	Liver (various)

Full Blood Count	Various
LFT, including AST and ALT	Liver
Serum Creatinine	Kidney
Urine Albumin Creatinine Ratio	Kidney
Electrolytes	Kidney

Table 2 - *Standard of care circulating biomarkers in study*

Urine sample (10 min)
Routine urine sample collection will be performed as per standard of care to measure urine dipstick and urine albumin creatinine ratio.

MRI Scan (~30min)
All participants will undergo a standardised imaging protocol (ATLAS) in an MRI scanner. At the time of initial consent, participants will be asked for their consent to have their images de-identified and stored. The MRI scan is not painful or risky, but a small minority of people feel claustrophobic. If this is apparent during screening, we will advise the patient to not participate. If this becomes apparent during a scan, we will stop the scan and take them out.

The MRI scans will be performed exclusively for research purposes and are not routinely looked at by a clinician. If a study investigator suspects an incidental finding, then they will follow the Perspectum Ltd incidental findings standard operating procedure (please refer to section 13.1 of this protocol). Blood pressure measurement may be taken at the same visit.

OPTIONAL Echocardiogram (~30min)
Participants may undergo a standardised transthoracic echocardiogram (ECHO) protocol using an ultrasound machine at visit 2. Participants will be asked for their consent to have de-identified images stored at the time of initial consent. The ECHO scans will be performed exclusively for research purposes and are not routinely looked at by a clinician. If a study investigator suspects an incidental finding, then they will follow the University of Liverpool incidental findings standard operating procedure.

Patient reported experience and outcome measures (~10min)
All participants will be asked to complete a questionnaire on a hand-held tablet at the end of all active study visits (or on their mobile phone/online). They will be asked to describe their experience within the clinical care setting and the impact of their prescribed treatment course.

7.3.2. Outcome data collection

Participants will be asked to give written consent to allow the study team to access their primary care and hospital medical records. Data will be collected to assess outcome data pertaining to cardiovascular, kidney, liver and diabetes related clinical events, as well as any further complications and hospital admissions. Primary care medical records will be reviewed at 1, 3 and 5-year timepoints following the baseline visit. In the majority of cases, follow-up data at years

1,3 and 5 will be entered from participants' medical records. However, some participants may receive a short telephone call to clarify any data which may be unclear or, to supply data which may be missing, from their medical record. All participants recruited and scanned at Perspectum Ltd. in Oxford (an approved non-NHS clinical study site) will complete their years 1, 3 and 5 follow-up medical history over the telephone: although all participants have consented to a medical records review during the study, medical records are not available to staff outwith the NHS. Thus self-reported data will be collected from these participants.

7.3.3. Withdrawing from the study

Each participant has the right to withdraw from the study at any time. In addition, the Investigator may discontinue a participant from the study at any time if they deem it necessary for reasons that might include:

- Ineligibility (arising during the study)
- Significant protocol deviation
- Significant non-compliance with study requirements
- Withdrawal of consent
- Loss to follow up

Data already collected from the study participants will be included in the analysis. Withdrawn participants will be replaced. The reason for withdrawal (if provided) will be recorded in the CRF.

8. DEFINITION OF END OF STUDY

The end of the study will be the date that 5-year outcome data is obtained on the last recruited study participant. Active participation will end when the last recruited participant attends their 6 to 9 month visit (Visit 3).

9. INTERVENTIONS

There will be no intervention to the standard of care these patients receive. However, consented participants will be asked to make two study visits where a multiparametric MRI scan will be performed – these visits will be defined as visit 2 and visit 3. An optional echocardiogram may be included at Visit 2. The example guidelines provided in Appendix 1 should be taken into consideration when imaging research participants to ensure the safety of both staff and participants, whilst helping to further prevent the spread of COVID-19.

10. DATA

10.1. Data Collection and Management

All MRI imaging data will be pseudonymised before being uploaded to the custom-built data management system at Perspectum Ltd. No other parties will be able to access identifiable information (with the exception of the study team who will upload the data).

Relevant medical history and demographics will be extracted from the patients' medical notes by a local study investigator and subsequently entered into an eCRF. The blood and urine samples will be processed at the local clinical site laboratory and the results entered into the eCRF by the local study team.

All paper documents containing personal data (e.g. informed consent forms) will be stored securely and only accessible by local study staff and authorised personnel. The study investigator is responsible for keeping these documents in a secure and accessible format to ensure that, in case of an emergency, patients can be identified and contacted. The

enrolment log that links a participant's study ID to their personal information will be kept for 5 years after study completion or until ethical approval terminates, whichever is sooner (please refer to section 11).

All study data will be stored for a minimum of five years after the end of the study in line with GCP recommendations.

10.2. Analysis plan

Descriptive statistics will be used to summarise subject characteristics. Summary data will be calculated for MRI metric values (Table 3). Normality will be determined by use of the Shapiro-Wilk test. Results will be expressed as means with standard deviation (SD) for continuous variables and as numbers and percentages for categorical variables.

Analysis of variance will be used to test for differences between multiple groups.

The primary endpoint will be a comparison of MRI metric values for fibro-inflammation in the liver compared to a matched non-diabetic control group from the UK Biobank(30) or from other studies (31) (Table 3). This will be assessed with a two-sample, two-sided t-test. Secondary endpoints include a comparison of individual MRI metric values [summarised in table 3 below] in individual organ associated with T2D and its comorbidities [summarised in table 3 below] at baseline (visit 1/visit 2) compared to a matched non-diabetic control group from the UK Biobank or other studies. These will also be assessed with two sample, two-sided t-tests. Additionally, the prevalence of mean liver PDFF and / or mean liver cT1 above NAFLD thresholds in the study cohort will be compared to the matched non-diabetic control group, using a Chi-squared test.

MRI metric	Organ(s) or Location(s)	Associated organ characteristic
For primary endpoint		
cT1	Liver	Fibro-Inflammation
For secondary endpoints		
Diameter of Aorta	Heart	Local Blood Flow
Aortic Distensibility	Heart	Elasticity of Aorta
T1	Spleen, Kidney, Pancreas	Fibro-Inflammation
T2*	Spleen	Iron Level
PDFF	Liver, Spleen, Pancreas	Fat content
Volume	Liver, Spleen, Kidney, Pancreas	Size
Optional exploratory endpoint metrics		
T2* Gradient	Kidney	Oxygenation
D	Kidney	Glomerular Filtration
PDFF	Kidney	Fat Content

Volume of Visceral Adipose Tissue (VAT)	Abdomen	Fat Content
Abdominal Subcutaneous Adipose Tissue Volume (ASAT)	Abdomen	Fat Content
Skeletal Muscle Index	Abdomen	Muscle Content

Table 3 *- MRI metrics in relevant organs*

Change from baseline in MRI metrics values at 6 to 9-months post-treatment will be assessed as secondary endpoints in each organ. These will be assessed with linear mixed effects model with an interaction variable of time. The change from baseline in proportion of patients at 6 to 9 months with mean PDFF and / or mean cT1 above NAFLD thresholds, across the whole study cohort, will be assessed using Chi-squared tests. Equivalent changes from baseline at 6 to 9 months will be assessed for HbA1c (glycaemic control), and other circulating biomarkers utilised in the clinical pathway for T2D, NASH and CKD [serum creatinine and eGFR (kidney), urine albumin creatinine ratio (kidney), lipids (NALFD), LFT (liver)], using linear mixed effects to assess changes over time. Odds ratios will be calculated by logistic regression analysis in relation to cardiovascular, liver, pancreatic and kidney-related events and or death, including hospital admissions, at 1, 3 and 5 years from baseline.

Exploratory endpoints will investigate the potential influence of glycaemic control/weight and of glucose/lowering therapies (oral/injectable agents) on prevalence of abnormality based on thresholds set from the healthy controls and on rate of progression for both biochemical and MRI-metrics, in subgroup analyses (including subgroups with abnormalities in multiple organs). Multiple testing will be corrected with Bonferroni correction. In addition, analysis of covariance will provide estimates of MRI metrics, adjusting for potential confounders such as baseline MRI metric, type of co-morbidity, type of therapeutic, HbA1c values, anthropometric measures and organ-specific circulating biomarker values as covariates. Similarly, additional associations of MRI metrics to biomarkers that are optional [for example left ventricular strain from the ECHO] or not in standard of care [for example pancreatic lipase] may be analysed, if evaluated locally or from stored, consented additional blood samples. Thresholds will be set based on Kaplan–Meier analysis to establish the proportions of patients in different MRI metric categories that remain free of diabetes-related events in the follow-up period. Differences between the curves will be compared using the log-rank test.

The results will be expressed as effect sizes and 95% confidence intervals (95% CI). Spearman and/or Pearson's correlations will be calculated to test associations between categorical and / or continuous variables, for example significant correlations between MRI metrics and weight, and between MRI metrics and biochemical metrics. To determine the diagnostic utility of MRI in these cohorts for assessing organ dysfunction, receiver-operating characteristic analyses will be carried out.

11. SAFETY REPORTING

11.1. Definition of Serious Adverse Events

This study is an observational longitudinal study and there is no intervention. Therefore, the risk of the occurrence of a Serious Adverse Event is minimal.

In relation to this study, a Serious Adverse Event would be any untoward medical occurrence immediately before, during or subsequent to the study visit. This would be classed as a Serious Adverse Event if it:

- results in death
- is life-threatening
- requires hospitalisation (outpatient and inpatient)
- results in persistent or significant disability/incapacity

Other 'important medical events' may also be considered serious if they jeopardise the participant or require an intervention to prevent one of the above consequences.

11.2. Reporting Procedures for Serious Adverse Events

A serious adverse event (SAE) occurring to a participant should be reported to the Research Ethics Committee (REC) that gave a favourable opinion for 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). All SAEs must also be reported to local regulatory teams in line with local requirements.

There are no anticipated 'related' serious adverse events from this study.

12. ETHICAL AND REGULATORY CONSIDERATIONS

12.1. Declaration of Helsinki

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

12.2. Guidelines for Good Clinical Practice

The Investigator will ensure that this study is conducted in full conformity with relevant regulations and with the Guidelines for Good Clinical Practice.

12.3. Approvals

The protocol, informed consent form, participant information sheet and any proposed advertising material will be submitted to an appropriate REC, HRA and host institution(s) 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.

Approval will also be sought locally by all participating sites.

12.4. Reporting

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

12.5. Participant Confidentiality

The study staff will ensure that the participants' privacy is maintained. Data shall be pseudonymised such that the participants will be identified only by a study ID number on the CRF and any electronic database. All documents will be stored securely and only accessible by study staff and authorised personnel. The study will comply with the General Data Protection Regulation (GDPR).

The named investigators will have access to all pseudonymised data from the study. Students and collaborators may be given access to pseudonymised data under the supervision of the named investigators.

12.6. Potential Risks of Procedures

MRI

MRI is a safe and non-invasive technique with no known risk when appropriately supervised. It does not involve ionising radiation (X-rays). Potential participants with ferromagnetic objects in their bodies or with implanted devices which can be damaged by the MRI magnet, cannot be scanned and so will be excluded. To minimise this risk, all participants before entering the scanner room complete a standard MRI safety screening interview and are screened for such objects. The MRI scanner is noisy and hence participants will be given earplugs and protective headphones. Some people find that being in the scanner is claustrophobic, and therefore participants will be given the opportunity to view the scanner prior to consenting to the study. The participant will be able to contact the operators throughout the scan via a microphone and hand buzzer. They will be able to indicate should they wish the scan to cease. All study sites are fully equipped for resuscitation (including defibrillation) in the unlikely event of a medical emergency during scanning.

Phlebotomy

Common risks associated with phlebotomy are pain during the procedure and bruising (with associated pain afterwards). These risks will be minimised by ensuring that all staff are fully trained in phlebotomy. Bruising after the event will also be reduced by promptly applying pressure on the puncture site after the needle is withdrawn. All participants will be fully informed about these risks in the Participant Information Leaflet (PIL). The worry associated with taking blood may cause some participants to feel unwell or faint before, during or after the procedure. The risk associated with this will be reduced by having an adequately equipped facility for performing the blood taking procedure and having a staff member trained in basic life support. Although phlebotomy is a very safe procedure, it does create a puncture wound on the skin which may very rarely lead to infection around the puncture site. The risk of this will be minimised by ensuring strict hygiene during the procedure and by not recruiting participants who are at increased risk of infection. In the event that a participant reports symptom of an infection (local redness, swelling, pain or discharge of pus), they should be referred to their GP or to A+E urgently.

ECHO

ECHO is a form of ultrasound assessment and there are no known risks associated with ultrasound scanning.

12.7. Expenses and Benefits

Reasonable travel expenses for all study specific visits (outside of standard of care) that are additional to normal care will be reimbursed on production of receipts, or a mileage allowance provided as appropriate. Expenses will also be provided for one companion, if applicable.

Participants will receive a formal letter of thanks and study feedback after completion of their last face-to-face visit, and around the time of their 1-year follow-up. The letter will provide details on study progress, recent study publications and some basic healthy lifestyle guidance. A copy of a participant's LiverMultiScan Reports from baseline and 6-9-month follow-up MRI scans will also be included, with guidance on how to interpret the metrics of cT1 and PDFF.

13. OTHER ETHICAL CONSIDERATIONS

13.1. Incidental findings

Scans are carried out for research purposes only and are not a replacement for clinical diagnosis. In addition, existing disease may not be detected. If a suspected incidental finding is discovered, scans (MRI or optional ECHO) will be screened for technical artefacts by a relevantly trained specialist and where a perceived incidental finding is noted, it will be managed following the investigation-specific Incidental Findings Management Plan. If a site or local imaging facility has a bespoke Incidental Findings Management Standard Operating Procedure, this will be followed. In all other cases, Perspectum's Incidental Findings Management Plan will be followed, and the scans will be reviewed by an expert reviewer (a radiologist) to assess for clinical significance. In the event that a potentially clinically significant incidental finding is discovered, this will be communicated to the relevant site's Principal Investigator who will discuss this with the participant and, if appropriate, the finding will be referred to their GP and/or specialist consultant for further investigation as necessary.

13.2. Participant comfort and dignity

While most people do not experience discomfort in an MRI environment, the enclosed space of the scanner can potentially feel uncomfortable, especially for more elderly participants. Discomfort from lying still for a long period of time will be minimised with comfortable padding and positioning. People with a history of claustrophobia will be excluded from participation in the study. Participants will be given a chance to see the scanner before the study starts. Whilst in the scanner, participants will be able to use the alarm button if they wish to communicate with the operator or to interrupt the scanning. All participants would be introduced carefully to the scanner and allowed to leave at any stage, should they wish to do so. Once in the scanner, participants would be able to indicate immediately if they wish the scanning to cease by squeezing a bulb placed in their hands, or by requesting it verbally. As the MRI scanner is noisy, participants would be given earplugs and acoustically shielded headphones to minimize the noise and aid communication between participants and investigators.

Participants will be asked to wear a gown for the MRI scan. To help maintain participant dignity they will be asked to leave their underwear on, provided it is not made of synthetic material and has no metal parts (e.g. zips, bras clasps or studs). The gowns are designed to cover participants and preserve their modesty while remaining loose in the scanner to avoid potential burns from synthetic clothing. Participants will be asked to change in a changing room near to the scanner and will be given a locker to securely store their belongings. If they are unable to change into the gown by themselves a member of staff will be on hand to offer assistance.

The example guidance provided in Appendix 1 should be taken into consideration when imaging research participants and have been provided as a result of the COVID-19 pandemic. These guidelines provide details of further precautionary measures that could be put in place to ensure the comfort and safety of both staff and participants. Appendix 1 provides example guidance on additional PPE; study visit management and participant management. These guidelines are optional and can be considered alongside local protocols for imaging research participants.

13.3. Pregnancy in participants

Although there is no evidence that MRI scans cause harm to unborn babies, as a precaution clinical MRI scans are not usually recommended during pregnancy, particularly in the first three months. MRI for research purposes provides no benefit to the mother or unborn child and therefore research MRIs are not performed on women who may be pregnant. As part of screening for the MRI, women will be asked if they are pregnant, or if there is any chance that they could be. If there is any uncertainty, a urine test will be carried out prior to the MRI examination to rule out pregnancy.

14. DATA HANDLING AND RECORD KEEPING

Direct access to study data will be granted to local research teams and authorised representatives from the Sponsor and host institution for the purposes of monitoring and/or audit of the study to ensure compliance with regulations. At the time of recruitment, each participant will be assigned a unique Study ID that contains no personal or identifying information about them. This will be how they are identified throughout the study and only the enrolment log will contain personal and identifiable data that links the Study ID to the study participant.

The enrolment log for each site will be stored securely (password protected) with restricted access to authorised members of the study team only. Study data collected (measurements, outcomes etc.) will be stored in a pseudonymised format using the assigned Study ID only and kept on a separate database to the enrolment log in line with GCP guidelines. Only data outlined on the case report forms will be collected and entered into the electronic data capture study database by members of the research team. Training on how to use the study database shall be provided by the Sponsor or another appropriately qualified member of the study team. In addition to using strict version control of the study database to prevent duplication and errors, quality checks of data entered including consistency, missing data and unusual values, shall be performed by the study manager and a data manager from Perspectum Ltd.

All collected study data will be carefully reviewed and 'cleaned' before any final analysis and database lock is undertaken. The reason for any excluded data or data changed after database lock will be described in detail in the end of study report. Study data collected (measurements, outcomes, etc.) will be stored in a pseudonymised format using the assigned Study ID only and kept on a separate platform to the link between Study ID and participant identifiable data, in line with GCP guidelines.

Perspectum's chosen on-line eConsent platform will be utilised to aid in the Informed Consent Process. This on-line platform allows potential participants to consider and engage remotely with the participant information leaflet and informed consent form. Reducing the exchange of paper documentation, in turn, reduces any risk of SARS-CoV-2 transmission. The highly infectious nature of this new coronavirus is recognised and, therefore, all measures will be taken to lessen the risk of transmission. The link between the participant's name and Study ID will be housed within the eConsent platform, which is compliant to ISO27001 and 21CFR11. This information will be stored securely (password protected) with restricted access only to authorised members of the study team.

All paper documents containing personal data (e.g. informed consent forms) will be stored securely in a locked cabinet behind locked or ID accessed doors. Documents will be only accessible by study staff and authorised personnel. The local principal investigator is responsible for keeping these documents in a secure and accessible location to ensure that, in any case of an emergency, participants can be identified and contacted readily. The enrolment log containing the linking personal data to the study ID will be kept for up to 5 years after study completion or until ethical approval terminates, whichever is sooner.

The study will comply with GDPR and relevant privacy legislation, please refer to section 12. As part of the informed consent process, participants will authorise the pseudonymous collection, use and disclosure of their study data by the study investigators and by those persons who need that information for the purposes of the study, including the commercial sponsor of the study, Perspectum.

The pseudonymised MRI DICOM files will be uploaded to Perspectum data transfer system called Perspectum Portal. Perspectum Portal is compliant with GDPR laws. Our data security infrastructure is supported by an ISO 27001, ISO 9001 and ISO 13485 compliant quality management system designed around a defence-in-depth approach with multiple

layers of redundancy, surveillance, physical access controls and audit logs. Access to the Perspectum Portal is controlled and secured by Secure Sockets Layer (SSL) encryption mandating a HTTPS protocol for web-based data transmissions to prevent eavesdropping, tampering and forgery. All data is encrypted while in storage in Perspectum Portal and routinely backed-up to an alternative secondary physical location to ensure service continuity. Perspectum Portal is hosted by Amazon Web Services (AWS), a market-leading provider of cloud platform solutions who employ rigorous and sophisticated security processes to safeguard data privacy from malicious or accidental incident. No project partner will be able to access identifiable information (with the exception of the study team who will upload the data).

15. QUALITY ASSURANCE PROCEDURES

The study will be monitored, and/or audited in accordance with the current approved protocol, GCP, relevant regulations and standard operating procedures. Direct access to the study data will be granted to authorised representatives from the Sponsor and host institution(s) for the purposes of monitoring to ensure compliance with regulations. A monitoring plan will be established for this study and circulated to the local study teams.

16. FINANCING AND INSURANCE

The study will be financed for 2-years by Innovate UK (grant reference: 26512). The remaining study period will be funded by Perspectum Ltd.

Perspectum has in place a specialist insurance policy which operates in the event of a participant suffering harm as a result of their involvement in the study (CNA Hardy Policy number 10351211).

NHS indemnity operates in respect to the clinical treatment that is provided.

Negligent Harm

Indemnity and/or compensation for negligent harm arising specifically from an accidental injury for which the Perspectum is legally liable as the Research Sponsor will be covered by Perspectum.

Non-Negligent Harm

Indemnity and/or compensation for harm arising specifically from an accidental injury and occurring as a consequence of the Research Subjects' participation in the study may be covered by Perspectum.

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APPENDIX 1: EXAMPLE GUIDELINES FOR MRI IMAGING IN CONSIDERATION OF COVID-19

COVID-19 is the clinical syndrome resulting from infection with a novel coronavirus, the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), which was first identified in December 2019. SARS-CoV-2 has since been declared a global pandemic by the World Health Organization.

It is therefore necessary to consider the following safety aspects when imaging a research participant during the COVID-19 pandemic:

- The virus is transmitted through contact with endothelium (mouth, nose, eyes)
- Transmission occurs through droplets and contaminated surfaces
- Aerosol transmission possible over longer distances (>1m)

Whilst the MRI procedure itself is not aerosol generating, it is important to remember that:

- In a pandemic, all participants should be considered carriers
- Healthcare staff need efficient personal protective equipment (PPE)

Personal Protective Equipment (PPE)

To ensure both participant and staff safety, appropriate PPE should be worn during the imaging process. It is important to consider the type of PPE appropriate for MRI imaging specifically.

An appropriate PPE kit would consist of:

Staff (e.g. MRI operator)

- Mask or respirator
- Gloves (consider two pairs each time)
- Face shield or googles
- Long sleeved disposable surgical gown
- Head caps
- Shoe covering

Research participant

- Mask (ensuring the nasal metal band has been removed and adhesive tape is used across the bridge of the nose)
- Gloves
- Gown

Options for PPE vary, depending on requirements. Table 1 provides alternative mask and respirator options.

Table 1: Masks and respirators

FFP3 (European standard) respirators filter **99%** of particles. **FFP2** respirators are specified to filter **94%** of particles
The **N99** (American standard) respirator is an alternative to the FFP3 and filters **99%** of particles
An **N95** respirator is specified to filter **95%** of particles and is a close equivalent to the FFP2 Other equivalents: • KN95 (China) • P2 (Australia/New Zealand) • DF FFR (Japan)
The **Type IIR** (European Standard) fluid resistant surgical mask is the “regular” surgical mask often used in clinical settings
The **Level 2** (American standard) fluid resistant surgical mask is equivalent to the Type IIR

Availability may dictate the use of specific items however Table 2 provides recommendations for masks to use for both staff and participants during MRI imaging.

Table 2: Mask/respirator recommendations for staff and participants

Participant	Staff (e.g. Operator)
Type IIR/Level 2 Fluid Resistant Mask 	Respirators (N95 non-valved FFP3 valved) 
Loose fitting covers nose and mouth	**Tight fitting** creates a facial seal
One-way protection captures bodily fluid e.g. cough/sneeze leaving the wearer of the mask	**Non-valved** provides **two-way protection** to filter inflow and outflow of air
"R" denotes that the mask is fluid resistant	Respirators may have additional letters (e.g. FFP3**R** FFP3**D**) to denote the following: **"R"** = reusable **"NR"** = Non-reusable **"D"** = passed the dolomite dust clogging test and is suitable for >8 hours use depending on surrounding conditions

Staff Management

Healthcare and office staff should be reduced to the minimum necessary.

Scheduling for appointments should allocate enough time between scans to allow for proper cleaning of the MRI scan room and all tools/devices utilised.

- Workstation area should be treated similarly; constant cleaning of desktops, phones, door handles, keyboards etc. should be performed between operators
- Sufficient time should be allotted for surfaces to dry after disinfection

Participant Management

Prioritising participant study visits

The usual clinical indications for the triage of imaging would be to defer elective exams, schedule imaging based on urgency and to have a tailored protocol to tailor to clinical indications whilst limiting time waste.

For research scans during COVID-19, the above should be taken into account whilst also considering the following protocol:

- Schedule non-active COVID-19 participants who are clear from symptoms and/or risk factors
- Postpone non-active COVID-19 participants who have shown symptoms and/or risk factors for at least 14 days; then re-assess symptoms and risk factors
- Do not schedule imaging for active COVID-19 participants, unless it affects the direct management of their care

Prior to study visit

Screen participants for active COVID-19 prior to scheduling their study visit where possible. This could include asking the participant if they have recently developed or had any of the documented symptoms or have been exposed to certain risk factors (e.g. recent travels or recent close contact with active subjects).

During study visit

Screen participant again by confirming any changes in their health and if they have developed any symptoms or been exposed to any risk factors since the appointment was scheduled. It may be necessary to postpone the procedure based on the participants current health status.

It is important to maintain social distancing where possible (in accordance with latest government guidelines). The following considerations are recommended to help comply with social distancing:

- Reduce the capacity of the waiting rooms/research areas
- Minimise time in waiting room by ensuring sufficient time between appointments/visits.
- Schedule less participants per clinic to ensure sufficient time between scans to allow time for:
    - Participant to get ready for visit (e.g. getting changed into gown and appropriate PPE)
    - Participant to complete safety questionnaire and addressing any concerns (if any)
    - Participant time to prepare for departure after completing the scanning procedure
    - The scanning room, workstation and equipment to dry after disinfection

Scanning procedure

Participant

Make sure that the participant is wearing PPE even during the MRI (mask, gown and glove), ensuring the surgical mask is fluid resistant (level 2 - type IIR) and that the nasal metal band has been removed and adhesive tape used across the bridge of the nose instead.

Operator(s)

Ideally two operators should be present during the MRI procedure:

- One operator in full PPE would take care of managing the participant
    - preparation
    - safety questionnaire
    - positioning on the MR table
- The other operator should be scanning
    - Potentially wearing a lower level of PPE but keeping in mind that, in case of emergency, should be able to be in full PPE in matter of seconds to help out the other operator sliding the participant out of the scanner and start any emergency procedure according to the standard operating procedure in place. This means that at least a clean full PPE kit should be available in the scanning room

During the scanning session, the operator in full PPE managing the participant, should simply be able to wait at an adequate distance without touching the workstation or other common surfaces; particularly advised in case of claustrophobic participants.

Post scanning

The operator in full PPE appointed for the management of the participant will:

- Escort the participant in the changing room
- Disinfect the MR scan room, including everything that has been used during the scanning procedure, for example:
    - Scanner bore (MRI safe cleaning wands suggested)
    - Scanner table
    - All coils used
    - All pads/cushion used

    - Headphones, emergency buzzer
    - Door handles
    - ECG/PPG devices
    - Infusion pumps
- Allow enough time for the surfaces to dry after disinfection between participants
    - Thirty minutes should be sufficient, depending on the agent used (the bore fan may be Increased to maximum to accelerate the process)
    - Allow fresh air to flow into the MR scan room between participants (without compromising MR safety)

Additional Notes

- It is worth considering having hand sanitisers, gloves and surgical masks available in the reception area so that participants can be warned to use these safety precautions immediately at the entrance and without any particular interaction with the front-desk personnel
- Signage with explanations and/or rules may be useful in all areas (e.g. how to sanitise your hand, how to wear gloves, how to wear a mask or *"wearing the mask is a mandatory requirement for the entire length of your visit in these premises"*)
- It is worth considering avoiding scheduling Research participants with underlying severe medical conditions; any chances to avoid an emergency situation should be taken.