SAFE-D

Surveillance of p**A**ncreatic health a**F**ter diab**E**tes **D**iagnosis

An interventional study to evaluate the cfDNA Pancreatic Cancer test (Avantect) in the early detection of pancreatic cancer in participants with newly diagnosed diabetes mellitus or newly elevated HbA1c

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COORDINATING CENTRE: Southampton Clinical Trials Unit

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FUNDER

This Study is primarily funded by ClearNote Health with additional financial support from Cancer Research UK Core funding at the Southampton Clinical Trials Unit.

Clinical Performance Study Protocol Information

This Clinical Performance Study Protocol (CPSP) describes the SAFE-D Study and provides information about procedures for entering participants. The CPSP should not be used as a guide for the treatment of other non-trial participants; every care was taken in its drafting, but corrections or modifications may be necessary. These will be circulated to investigators in the trial, but study locations entering participants for the first time are advised to contact Southampton Clinical Trials Unit to confirm they have the most recent version.

Compliance

This study will be conducted in compliance with the approved CPSP and will adhere to the principles outlined in the Medical Device Regulations 2002 (SI 2002 No.618), any subsequent modifications of the clinical trial regulations, GCP guidelines, ISO 20916:2024, the Sponsor's (and any other relevant) SOPs, and other regulatory requirements as amended.

LIST OF ABBREVIATIONS

5hmC	5-hydroxymethylcytosine
95% CI	95% Confidence Interval
AE	Adverse Event
BCT	Blood Collection Tube
BMI	Body Mass Index
cfDNA	Cell-free DNA
CAP	College of American Pathologists
CI	Chief Investigator
CPSP	Clinical Performance Study Protocol
CTIMP	Clinical Trials of Investigational Medicinal Products
CNV	Copy Number Variation
CRF	Case Report Form
CT	Computerized Tomography
DICOM	Digital Imaging and Communication in Medicine
DM	Diabetes Mellitus
DMP	Data Management Plan
DNA	Deoxyribonucleic acid
ECMC	Experimental Cancer Medicine Centres
EHR	Electronic Health Record
GCP	Good Clinical Practice
GP	General Practitioner
HbA1c	Haemoglobin A1c
HPB	Hepatobiliary
ICF	Informed Consent Form
IDMC	Independent Data Monitoring Committee
IPMN	Intraductal Papillary Mucinous Neoplasm
ILF	Investigator Location File
IVD	In Vitro Diagnostic Device
MCN	Mucinous cystic neoplasms
MDT	Multidisciplinary Team
MDST	Multidisciplinary Study Team
MHRA	Medicines and Healthcare products Regulatory Agency
MRCP	Magnetic Resonance Cholangiopancreatography
MRI	Magnetic Resonance Imaging
NIHR RRDN	National Institute of Health and Care Regional Research Delivery Network
NOD	New Onset Diabetes
NPV	Negative Predictive Value
PanIN	Pancreatic Intraepithelial Neoplasia
PC	Pancreatic Cancer
PIC	Participant Identification Centre
PID	Participant Identifiable Data
PIS	Participant Information Sheet
PPV	Positive Predictive Value
PV	Portal Vein
QNS	Quantity Not Sufficient
RDC	Rapid Diagnostic Centre
REC	Research Ethics Committee
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SCTU	Southampton Clinical Trials Unit

SDSC	Specialist Diabetes Service Centres
SEER	Surveillance, Epidemiology and End Results
LIV	Location Initiation Visit
SMA	Superior Mesenteric Artery
SMV	Superior Mesenteric Vein
SoC	Standard of Care
STAI	6-item Spielberger State Trait Anxiety Inventory
TMF	Trial Master File
TMG	Trial Management Group
TMP	Trial Monitoring Plan
TSC	Trial Steering Committee
QNS	Quantity Not Sufficient

KEYWORDS
Diabetes Mellitus, Early detection, Pancreatic Cancer, HbA1c, Epigenomics, 5hmC

CLINICAL PERFORMANCE STUDY SYNOPSIS

Short title	SAFE-D
Full title:	**S**urveillance of p**A**ncreatic health a**F**ter diab**E**tes **D**iagnosis

Population:	Up to 5,000 male and female participants between the age of 50-84 years with newly diagnosed type 2 diabetes mellitus and/or an elevated Haemoglobin A1c (HbA1c) (≥ 48 mmol/mol or 6.5%) within the previous six months across the UK.
Primary Objective:	• Pilot - evaluation of recruitment feasibility. If successful, this will be followed by the main study involving cumulative participant recruitment: • Main study – analysis of co-primaries sensitivity and specificity of Avantect Pancreatic Cancer Test v2 (referred to as Avantect Pancreatic Cancer Test or Avantect)
Secondary Objective:	• To evaluate the Avantect test in detecting pancreatic cancer across the pilot and main study combined in terms of: o Pancreatic cancer stage shift o Positive predictive value (PPV) o Negative predictive value (NPV) o Actual pancreatic cancer resectability rate • To evaluate the beneficial effect of the Avantect test in terms of: o Overall survival (time-to-event) o Time to pancreatic cancer diagnosis relative to new onset diabetes (NOD) diagnosis o Effect on state anxiety over time o Performance characteristics for high-grade neoplasia
Rationale	Pancreatic cancer is one of the most lethal common cancers (five-year survival 5-7%). Early detection and treatment could significantly improve overall survival. It is known that people who develop new type 2 diabetes are at higher-than-average risk for harbouring occult pancreatic cancer and there is currently no accepted clinical strategy for their surveillance. The Avantect Pancreatic Cancer Test is a multianalyte test that uses 5-hydroxymethylcytosine-based (5hmC) epigenomic signature and genomic profiles from cell-free DNA (cfDNA) isolated from the plasma of peripheral whole blood collected in Streck Cell Free DNA Blood Collection Tubes, combined with CA19-9 levels, for the qualitative detection of the presence or absence of an abnormal signal associated with pancreatic cancer. In this study, the test is intended to be used as an aid in the

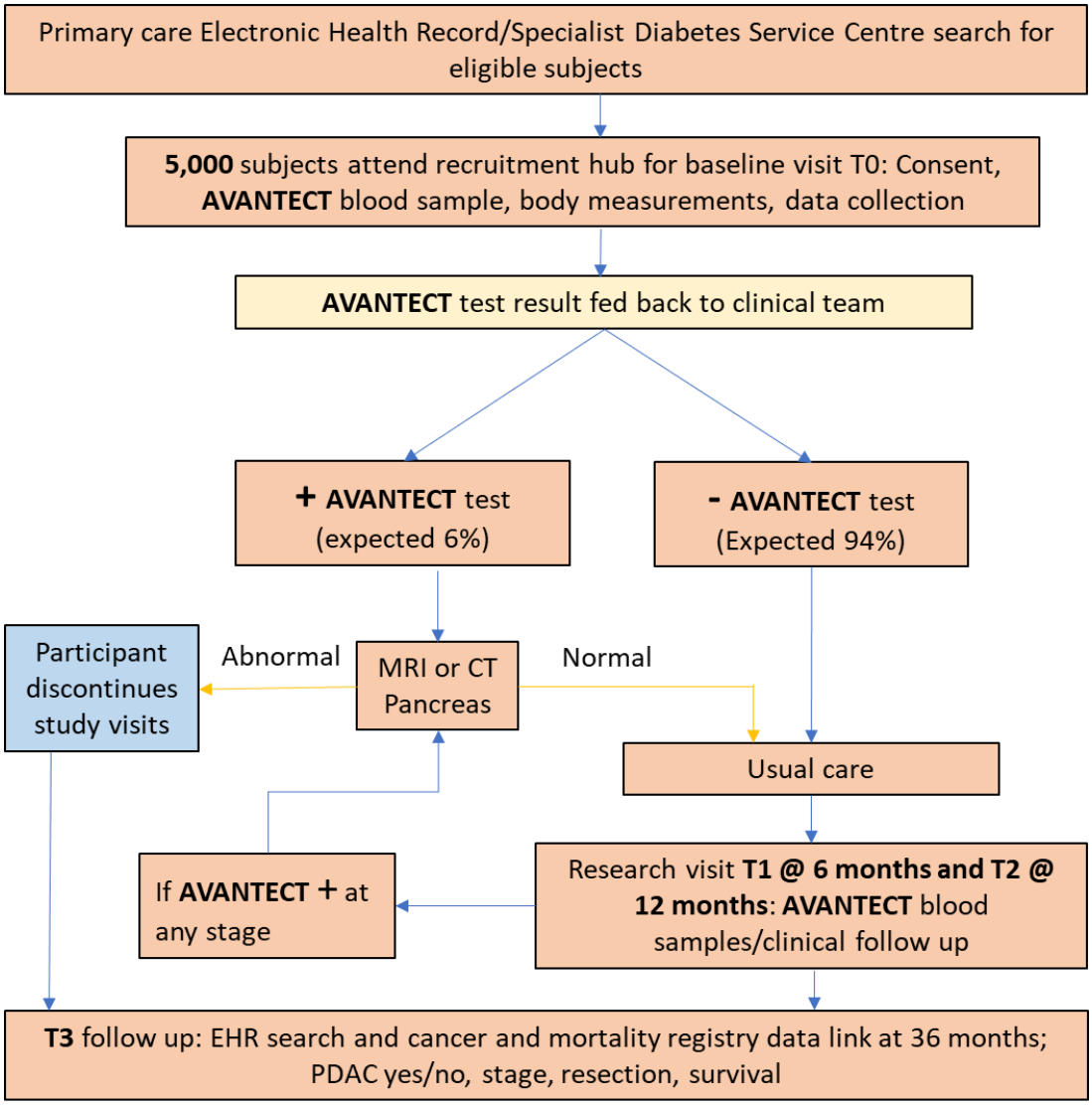
	earlier detection of pancreatic cancer in participants with new onset type 2 diabetes and/or raised Haemoglobin A1c (HbA1c) (≥ 48 mmol/mol or 6.5%) who are 50 – 84 years old and, following additional diagnostic imaging, could enable earlier treatment for pancreatic cancer which may increase survival rates.
Clinical Performance Study Design:	Prospective, interventional multicentre study
Sample size:	5,000 enrolled participants across the UK inclusive of pilot and main study participants. • Pilot: target up to 800 participants • Main Study: up to 5,000 participants including those enrolled in the pilot
Treatment/Intervention:	Avantect test performed within prioritied time frame with intent to share only "detected" test results with the participants and their General Practitioners (GPs) in parallel to making a referral to the local secondary care clinical team for further investigations. All test results will be included in primary endpoint analysis.
Number of specimens required per participant:	Three peripheral blood samples per participant (up to 30 mL in total) will be collected at three timepoints
Duration of the clinical performance study:	Participant involvement on trial: 3 visits over 12 months Length of remote follow-up collection for each participant: 36 months from consent Recruitment duration: 34 months Total study duration (including 12m for analysis and report writing): 6 years and 9 months

URL for Database:	https://www.imedidata.com
URL for randomisation (pilot phase only):	https://www.imedidata.com

Primary Study Endpoints:	Pilot: Recruitment rate Main study: Sensitivity and specificity of Avantect Pancreatic Cancer Test.
Secondary Study Endpoints:	Secondary endpoints (pilot and main study combined) will include PPV, NPV, proportion of pancreatic cancer patients undergoing surgical resection, pancreatic cancer stage shift and pancreatic cancer resectability rate.
Exploratory Endpoints	Overall survival (time-to-event)

	Time to pancreatic cancer diagnosis (NOD to pancreatic cancer diagnosis) 6-item Spielberger State Trait Anxiety Inventory (STAI) Performance characteristics for high-grade neoplasia
Total Number of Locations:	Up to 3,000 GP practices and up to 200 Specialist Diabetes Service Centres

TRIAL SCHEMA



1. INTRODUCTION

1.1 JUSTIFICATION FOR THE DESIGN OF THE CLINICAL PERFORMANCE STUDY

There is currently no accepted screening test for pancreatic cancer in average risk individuals (i.e., those without a known risk factor such as a constitutional mutation, multiple first-degree relatives with pancreatic cancer, or a pre-existing pancreatic cystic disease). Furthermore, among people who are known to have higher risk, no secondary, or risk-based screening test or procedure is widely accepted. Although it is known that people older than 50 years who develop type 2 diabetes mellitus (DM) are at higher-than-average risk for harbouring occult pancreatic cancer [1–4], there is currently no accepted clinical strategy for testing new onset diabetes (NOD) patients for the presence of pancreatic cancer (PC).

Initially SAFE-D was a two-arm randomised controlled trial with a nested pilot to evaluate the feasibility of continuation to a sample size of 15,000. Towards the end of the pilot, a decision was made in conjunction with the Independent Data Monitoring Committee (IDMC), Trial Management Group (TMG) and Trial Steering Committee (TSC) to continue the study with the removal of the control arm, with recruitment to a total sample size of 5,000. In order to define the success of endpoints that were intended to be compared between arms (resection rate, stage-shift, resectability), comparative clinical outcome data will be obtained from one or more external sources (see section 9.4.1 for more information).

1.2 RATIONALE (INCL. RISK-TO-BENEFIT) FOR IVD MEDICAL DEVICE UNDER INVESTIGATION

Research[5] shows that 5-hydroxymethylation changes in plasma-derived cell-free DNA (cfDNA) can be used for early detection of PC. 5-hydroxymethylcytosine (5hmC) is a stable epigenetic mark that arises as the first step of active demethylation of methylated-cytosine base in DNA by ten-eleven translocation enzymes, marking regions of active transcription and gene regulation[6]. Based on the technology developed[6], the Avantect blood-based test utilises 5hmC, fragmentation and copy number variation (CNV)-based biomarkers from cfDNA whose measures are associated with the detection of PC. The test employs state-of-the-art machine learning stacked ensemble modelling that combines multiple feature sets to predict the presence of PC using 5hmC-based epigenomic and genomic signatures in cfDNA. The ensemble model was trained and rigorously tested using 25 iterations of 10-fold outer cross validation. Specifically, for each fold in the outer folds, a model was trained on the in-fold data using further 10-fold cross validation and tested on the remaining out-of-fold data. The model parameters and classification score threshold was optimised during inner fold training. A classification score threshold that represented the 98% specificity in the training set was chosen. Version 1 of the model was validated in an independent cohort of 2,150 participants of

which 2,048 were non-cancers and 102 with PC. The performance of PC detection was at 66.7% sensitivity and 96.9% specificity with an early-stage PC (Stage I and II) sensitivity of 68.3%.

The Avantect Pancreatic Test version 2 is based on a next-generation sequencing (NGS)- technology and is intended for the qualitative detection of the presence or absence of a cancer-related multianalyte signal. The test uses plasma cell-free DNA (cfDNA) from peripheral blood to detect abnormal genomic and epigenomic signatures linked to pancreatic cancer. Epigenomic data is obtained via whole-genome sequencing of 5-hydroxymethyl cytosine (5hmC) enriched cfDNA, while genomic data comes from cfDNA fragmentomics. The updated model also incorporates plasma CA19-9 levels, adjusted based on fucosyltransferase gene genotyping. The test is intended for the qualitative detection, in NOD individuals, of the presence or absence of an abnormal 5hmC-based epigenomic and genomic signature in plasma cfDNA derived from peripheral whole blood collected in a Streck® blood collection tube (BCT). The Avantect test aids in identifying occult PC in participants with NOD who are 50 years old or older. These participants can then benefit from additional diagnostic imaging to rule out PC.
ClearNote Health feasibility data also suggests that the Avantect test may detect a subset of neoplastic cysts, including intraductal papillary mucinous neoplasms (IPMNs) and pancreatic intraepithelial neoplasms (PanINs). IPMNs of the pancreas and PanINs are PC precursors. Just as colon polyps can develop into colon cancer if left untreated, some IPMNs have the potential to become malignant, so it is important to diagnose and manage them early and appropriately before they develop into an invasive cancer.

People with NOD, an expanding subset of the UK population (about 240,000 patients diagnosed every year in England, according to the 2021 National Diabetes Audit)[7], are at increased risk for harbouring occult PC. Current standard of care fails to detect these cancers until it is too late. Avantect holds the promise of identifying people with NOD for whom further investigations may yield early detection of PC for a more successful intervention. Given existing clinical evidence that individuals with NOD have been linked to a higher incidence of PC, this study is designed to evaluate a novel non-invasive epigenomics-based test to detect pancreatic cancer earlier in people with NOD or a newly elevated HbA1c. With the use of such a non-invasive test the risk to the participants is negligible, however if proven to detect PC earlier, this could have significant survival benefits for both the study participants and future people with NOD or newly elevated HbA1c.

Pancreatic cancer is a Cancer Research UK area of unmet need with 5-year survival rates as low as 5%[8]. Other blood-based cancer detection studies are underway, such as Pathfinder, SYMPLIFY[9], and

NHS-Galleri[10], but these studies are evaluating multi-cancer detection tests. There are ongoing observational studies in PC detection, such as UK-EDI[11] but the SAFE-D study is a prospective interventional study in patients with newly diagnosed diabetes mellitus or elevated HbA1c who are at a higher-than-average risk of developing PC.

1.3 BENEFITS AND RISKS OF THE IVD MEDICAL DEVICE UNDER INVESTIGATION AND CLINICAL PERFORMANCE STUDY

1.3.1 Risks and anticipated adverse device effects

ClearNote Health has established requirements for managing product risks associated with the development and commercialisation of Avantect. Risks have been graded based on severity (grade 1-5, where 1 indicates negligible and 5 indicates catastrophic) probability of occurrence (grade 1-5, where 1 indicates an improbable and 5 a frequent occurrence) and detectability (grade 1-5, where 1 certainty of detection and 5 undetectable). Hazard analysis identified risks associated with collection of blood to be minimal (more details in Adverse Events section 8). With respect to the Avantect test itself, the primary risk relates to a false assay result (i.e., a false positive or a false negative result). All Avantect "detected" cases will require an MRI or CT-scan. Rare adverse events associated with MRI are described in Adverse Event Section 8.

Risks associated with the clinical performance study have been assessed in the SAFE-D Trial Risk Assessment.

2. CLINICAL PERFORMANCE STUDY OBJECTIVES AND ENDPOINTS

2.1 PRIMARY STUDY OBJECTIVES

The study will be divided into a pilot and the main study:

- Pilot: The goal of the six-month pilot is to determine if the enrolment strategy (identifying eligible participants via commercial recruitment platforms, NIHR Research Delivery Network Primary Care Networks and Specialist Diabetes Service Centres (SDSC)) is adequate, and to identify barriers and develop mitigation strategies to improve recruitment. Participants may also self-refer to the study following viewing study information found on the study website or displayed in Primary Care locations. The pilot will also assess the BMI distribution to determine whether body mass index (BMI) should be included as eligibility criteria in the main study. We will aim to open up to 450 Participant Identification Centres (PICs) during the pilot and at least 30 recruitment hubs where participants can attend for study visits (also referred to as locations).
- The pilot will be considered successful if:
    - Recruitment rate is greater than 10% of invitation to enrolment, or

    - 800 participants are enrolled, or
    - Enrolment is greater than an average of 133 participants per month in the last three months of pilot
- The feasibility of continuation to the main study will be assessed by the TSC based on recruitment during the pilot
- The main study will enrol up to a total of 5,000 participants with the primary objective to evaluate sensitivity and specificity of the Avantect test in detecting pancreatic cancer in participants.

2.2 PRIMARY ENDPOINTS:

- Pilot: Recruitment rate - number of individuals enrolled into the study divided by the number of individuals invited to participate.
    - Recruitment rate to be greater than 10% of invitation to enrolment OR
    - 800 participants are enrolled OR
    - Enrolment is greater than an average of 133 participants per month in the last 3 months of the pilot.
- Main study:
    - Sensitivity of Avantect test for detecting PC – number of individuals with one or more Avantect “detected” test results and PC divided by the number of individuals with PC.
    - Specificity of Avantect test for ruling out PC – number of individuals with no Avantect “detected” test results, at least one Avantect “not detected” test result and no diagnosis of PC divided by the number of individuals with no diagnosis of PC.

2.3 SECONDARY STUDY OBJECTIVES AND ENDPOINTS

To evaluate the Avantect test in detecting pancreatic cancer in the entire study cohort (Pilot + Main Study combined) in terms of:

- PPV
- NPV
- Proportion of pancreatic cancer patient undergoing surgical resection – compared to suitable clinical outcome source data
- Stage shift (the proportion of pancreatic cancers diagnosed at stage I/II out of all pancreatic cancers) - compared to suitable clinical outcome source data
- Resectability rate – number of individuals with PC deemed resectable by the study multidisciplinary team (MDST) divided by the number of PCs.

2.4 TABLE OF ENDPOINTS/OUTCOMES

PILOT

	Objective	Outcome Measures	Summary method(s)
Primary	To determine the recruitment rate	Recruitment rate	• Percentage recruited of all participants invited • Number of individuals recruited per month

MAIN STUDY (analysis inclusive of pilot):

	Objective	Outcome Measures	Summary method(s)
Primary	To estimate the sensitivity of the Avantect test in detecting PC	Sensitivity	Percentage with PC diagnosed who have an Avantect "detected" result
	To estimate the specificity of the Avantect test in ruling out PC	Specificity	Percentage without PC diagnosed who have one or more Avantect "not detected" results and no Avantect "detected" results
Secondary	To estimate the PPV of Avantect for detecting PC	PPV	Percentage with an Avantect "detected" result who have PC diagnosed
	To estimate the NPV of Avantect for ruling out PC	NPV	Percentage of individuals with no Avantect "detected" test results who have no diagnosis of PC
	To estimate the proportion of PCs that are resected	Resection rate	Percentage with PC who underwent resection - compared to suitable clinical outcome source data

	To determine the effect of the Avantect test on PC stage shift	Stage shift	Percentage of PCs diagnosed at stage I/II – compared to suitable clinical outcome source data
	To estimate the proportion of PCs deemed resectable	Resectability	Percentage of PCs deemed resectable by the study MDST
Exploratory	To estimate the time from NOD diagnosis to PC diagnosis	Time to diagnosis	Kaplan-Meier curve Hazard ratio compared to suitable clinical outcome source data
	To estimate the overall survival of study participants	Overall Survival	Kaplan-Meier curve Hazard ratio compared to suitable clinical outcome source data
	Assess the effect of the Avantect test on state anxiety over time	6-item STAI	T-test or non-parametric alternative if suitable
	To investigate the performance characteristics for high-grade neoplasia	Sensitivity Specificity PPV NPV	As described above, but disease positive is defined as PC and/or high-grade mucinous cysts and non-cases defined as no pancreatic cancer or high-grade mucinous cysts. This will be repeated where high-grade mucinous cysts are considered as disease positive and PCs are excluded.

2.5 DEFINITION OF END OF STUDY

The end of study for individual participants will occur when one of the following events occurs:

- All participant's final data has been captured.
- The participant is discovered ineligible over the course of the study.
- The participant withdraws consent (at any point of the study).
- The participant dies.

The definition for the overall end of study is the completion of all sample analysis and the collection and cleaning of all participant follow up data.

3. IVD MEDICAL DEVICE UNDER INVESTIGATION AND COMPARATOR

3.1 NAME OF THE INVESTIGATIONAL IVD DEVICE

Avantect Pancreatic Cancer Test v2.0

3.2 MANUFACTURER OF THE INVESTIGATIONAL IVD DEVICE

ClearNote Health, 10578 Science Centre Drive, San Diego, California, 92121, USA.

3.3 INTENDED PURPOSE AND USE OF THE INVESTIGATIONAL IVD DEVICE

The device is designed to report qualitatively the presence or absence of an abnormal epigenomic and genomic signature that is consistent with the signature in patients with pancreatic cancer. The Avantect test utilises plasma cfDNA to assess whether an individual has a signal associated with the presence of pancreatic cancer. The test uses whole blood collected using Streck Cell-Free DNA BCTs provided in the specimen collection kit. Plasma is isolated from whole blood according to ClearNote Health Standard Operating Procedures (SOPs) from which cfDNA is then extracted. This epigenomic and genomic signature is derived from whole-genome shotgun sequencing of 5hmC enriched cfDNA and total cfDNA employed to detect aberrant changes in 5hmC, cfDNA fragment size and copy number. Avantect testing will only be performed at a single location, at ClearNote Health, San Diego, CA. The test includes specimen collection kit, Avantect test reagents, software, and procedures for the analysis of the epigenomic and genomic signature in cfDNA from plasma. 10 ng of cfDNA is used to generate sequencing libraries. Data from sequenced libraries are processed using a proprietary bioinformatics pipeline developed to detect abnormal epigenomic and genomic signature consistent with pancreatic cancer.

3.4 TRAINING AND EXPERIENCE REQUIRED

The high complexity portion of the Avantect test that includes the isolation of cfDNA to create enrichment libraries for the delivery of a patient report is carried out at ClearNote Health following training SOP in accordance with the US Clinical Laboratory Improvement Amendments licensure and College of American Pathologists accreditation requirements.

The low complexity portion of the Avantect test that includes blood collection and plasma isolation. Blood collection will be executed by study locations according to Laboratory Manual. Plasma isolation will be executed by the Southampton Experimental Cancer Medicine Centres (ECMC) translational team according to specific SOP.

All study location personnel performing blood collection procedures will undergo training (e.g. via the study LIV) and can only perform these tasks when training is complete and duties have been assigned and signed off on the study delegation log.

All study personnel performing plasma isolation procedures will undergo training and can only perform these tasks when training is complete and documented in the study delegation log.

3.5 DEVICE ACCOUNTABILITY

See Appendix IV

4. OVERALL TRIAL DESIGN

A prospective, interventional multicentre cohort study with a pilot followed by a main study. Selected pre-existing conditions of interest, STAI, body measurements and blood samples will be collected at enrolment (Baseline (T0)), and at 6 months intervals (T1 and T2)). Three cancer and mortality registry searches will be undertaken by the SCTU study team to assess any cancer diagnosed and deaths during the Follow-up study period (T3) (Figure 1). The cancer registry database will be interrogated using any “C-codes and D-codes” available and data from any cancer type will be collected. Peer reviewed published data by the study team[12] has shown that the vast majority of pancreatic cancer patients are diagnosed, in NOD participants, within 12 -18 months from type 2 diabetes diagnosis. Therefore, the study strategy is to test participants at baseline (T0) (within 200 days from diabetes diagnosis or initial elevated HbA1c) and thereafter at 6 and 12 months (+/- 4 weeks) from T0 to ensure that the Avantect test is used in the period before pancreatic cancer symptoms usually present.

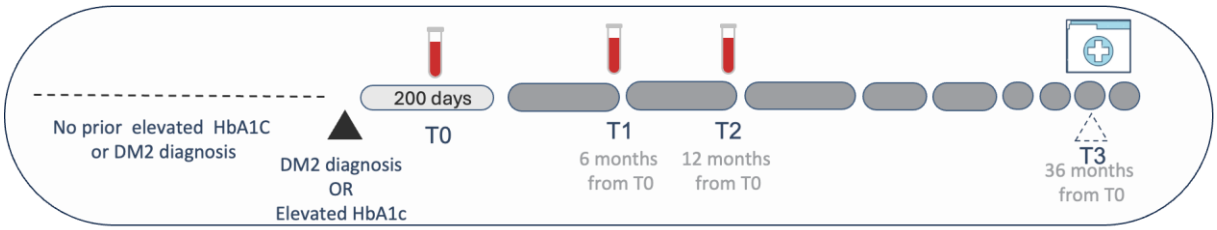


Figure 1: SAFE-D visit schedule figure

5. SELECTION AND ENROLMENT OF PARTICIPANTS

5.1 PARTICIPANT ENROLMENT

Participants will be approached to take part in SAFE-D via their GP or SDSC. Electronic Health Record (EHR) searches will be undertaken by the study team at participating GP practices and participants with a recent diagnosis of type 2 DM and/or initial elevated HbA1c (≥ 48 mmol/mol or 6.5%) (within 200 days) will be eligible for enrolment. Participants attending SDSCs will also be eligible for enrolment if meeting inclusion and exclusion criteria. In addition, participants self-referring for the study via the SAFE-D booking website may be enrolled providing evidence of meeting inclusion and exclusion criteria is provided. Participants who sign the consent form will be considered enrolled.

The study is expected to enrol 5,000 participants over 34 months, including a ten-month pilot study to evaluate recruitment feasibility and to estimate the number of participating study locations required. Participants will remain in the study for 12 months, attending study visits at enrolment (baseline (T0)) and at six (+/- 4 weeks) (T1) and 12 months (+/- 4 weeks) (T2) post enrolment. There may be planned recruitment stops between the Pilot and the main study to allow for a data driven 'stop-go' decision should this decision not be concluded in the lead up to the main study. Total study duration is expected to be 6 years and 9 months including 12 months for analysis and report writing.

5.2 CONSENT

The Principal Investigator (PI) retains overall responsibility for the conduct of the research at their study location, including the taking of informed consent of participants. They must ensure that any person delegated responsibility to participate in the informed consent process is duly authorised, trained, and competent to participate.

Consent to enter the trial must be sought from each participant. Information about the study will be available on the study website where participants will also be able to book their initial T0

appointment to attend a local recruitment hub (specified local GP practice or any other facility staffed and equipped for participant interactions, consenting and blood sample collection, including the participant home where part of standard local practice) if they are interested to take part. At the time of the T0 appointment, the clinical study teams at the hub will provide each participant with a full explanation of the study, a Participant Information Sheet (PIS), and answer any questions before consent is taken. Informed consent must be obtained prior to the participant undergoing procedures that are specifically for the purpose of the trial.

To ensure that all participants enrolled in the Pilot phase of the study are aware of the redesign they will also be reconsented at their next study visit.

The right of the participant to refuse to participate without giving reasons must be respected.

After the participant has entered the trial, the clinician remains free to give alternative care to that specified in the CPSP at any stage if he/she feels it is in the participant's best interest, but the reasons for doing so should be recorded.

All participants are free to withdraw at any time from the study procedures without giving reasons and without prejudicing further treatment. Participants must be provided with point of contact where they may obtain further information about the study.

Upon completion of the informed consent form (ICF), a copy will be given to the participant, a copy stored in the participant's medical records, the original filed in the location trial file and a copy of the ICF be sent to the Southampton Clinical Trials Unit (SCTU) using secure transfer systems, such as monitorSCTU@securemail.soton.ac.uk, to allow for central monitoring.

5.3 INCLUSION CRITERIA

1. 50 – 84 years of age at the time of enrolment (within year of birth, not month of birth)
2. Confirmed type 2 DM diagnosis established within the last 200 days or an initial elevated HbA1c ≥ 48 mmol/mol or 6.5% obtained within the last 200 days . This includes people who have a first elevated HbA1c (≥ 48 mmol/mol or 6.5%) within the last 200 days, even if subsequent HbAc1 measurements return to the the normal range.
3. Willing to provide up to 30 mL of blood for each study visit
4. Willing and eligible to undergo MRI or CT scan
5. Understands the study process and is willing to take part in the study and sign the ICF

5.4 EXCLUSION CRITERIA

6. Prior type 1 or type 2 DM diagnosis or an initial HbA1c ≥ 48 mmol/mol or 6.5% obtained prior to the 200-day inclusion window, except gestational elevated HbA1c.
7. A history of pancreatic cancer, pancreatic neuroendocrine tumour (pNET) or Pancreatitis
8. Under investigation for or confirmed pancreatic cancer
9. Under investigation/surveillance for pancreatic cyst
10. Any known pancreatic surgery (not including ERCP), or other major surgery requiring anaesthesia within 3 months
11. Any invasive solid or haematological cancer in the past 3 years, including cancer recurrence after treatment in the last 3 years
12. BMI > 40 at the time of consent
13. Blood transfusion within 1 month
14. Solid organ transplant recipient
15. Currently pregnant
16. Needing dialysis

Participants enrolled under a previous Protocol version remain in the study even if later changes render them ineligible; updated criteria affect only new participants.

6. SPECIMENS

Three peripheral blood samples will be collected from consenting participants according to the study schedule of observations and procedures

- Peripheral blood for SAFE-D study related testing or future research - 2 STRECK tubes (20 mL)
- Peripheral blood for future metabolomic research testing – 1 Lithium Heparin tube (6 mL)

Blood collection kits comprehensive of Avantect and metabolomic testing tubes will be provided to the collection locations (see section 6.1 for storage and analysis of clinical samples).
A detailed Laboratory Manual will be provided to study locations which will include details regarding sample preparation, handling, shipping and tracking.

6.1 SAMPLE HANDLING

At each study timepoint 2x10 mL Streck® tubes and 1x6 mL lithium heparin tube will be collected from participants. The 2x10 mL Streck® tubes will be used for the Avantect test or for future approved reaserch, and 1x6 mL lithium heparin will be used for the evaluation of a pancreatic cancer metabolomic signature.

All blood samples will be posted overnight according to Laboratory Manual using study specific boxes equivalent to Royal Mail Safeboxes, to the agreed laboratory: University of Southampton ECMC translational team. Samples will be sent from study locations pseudo-anonymised and fully labelled with a participant and time-point specific kit ID number together with a test requisition form allowing for participant specific reconciliation once received by the ECMC translational team. All study locations will keep a record of all samples collected, stored, and shipped.

Lithium heparin samples will be processed according to the SAFE-D specific SOP at the ECMC translational facility and stored for future research within the SAFE-D study (or future ethically approved research).

If more information comes to light which renders an enrolled participant ineligible, their already collected samples will be removed from any planned study testing and any generated data removed from study analysis. Any remaining samples will be kept for potential future ethically approved research as per participant consent. For participants that withdraw consent, see section 7.12.

6.2 SAMPLE REBLEED REQUEST

In the event of postal delays, any Streck sample received by the Southampton ECMC translational team after seven days from date of blood collection will be deemed unsuitable for Avantect testing and participants may be asked to undergo repeat blood draw. If repeat T0 draw is requested it must be completed while the participant is still within 200 days from diabetes diagnosis or initial elevated HbA1c. If T1 or T2 repeat blood collection is requested, it must be within 90 days of the initial sample collection date at that visit timepoint (T1 or T2). A repeat draw can also be requested if a sample is damaged during transport or if it is deemed unlikely to generate an Avantect results, such as haemolysed plasma or low plasma volume (<4mL in total).

Streck® tubes will be processed to plasma within 24 hours of receipt at the ECMC translational facility by trained operators and shipped at agreed frequencies as per the Laboratory Manual to ClearNote Health centralised laboratory (San Diego, California, USA). Streck plasma samples will be analysed and results will be generated within 14 business days of receipt of arriving at Clearnote Health and "detected" test results will be reported to SCTU team by providing Avantect test results via an excel file and individual participant reports via secure file sharing (Safesend.soton.ac.uk). In the event of a sample failing predefined Avantect metrics, (expected failure rate is ~4%), the participant will be asked to return for a repeated draw (if the participant is still within the 90 days time frame from the original blood draw). If the failure happens at T0 and no blood could be collected while the participant is still within 200 days of the diabetes diagnosis or initial elevated HbA1c the participant

will be asked to come back at T1. If the failure happens at T1 or T2 and no re-draw was performed, the participant will remain in study.

7. STUDY PROCEDURES

7.1 SCHEDULE OF OBSERVATIONS AND PROCEDURES

Visit:	Baseline (T0)	T1[f]	T2[g]	T3
Time:	Within 200 days from type 2 diabetes diagnosis or initial elevated HbA1c	6 months (+/- 4 weeks) after T0	12 months (+/- 4 weeks) after T0	Three occasions over the study duration from consent (T0)
Eligibility evaluation	X			
Informed consent	X			
Participant Data Collection Interview[a]	X			
STAI questionnaire[b]	X	X	X	
Blood sample collection[c]	X	X	X	
Body measurements[d]	X	X	X	
Electronic Health Record Review[e]	X	X	X	
Cancer and mortality registry review				X

NB: The participant/legal representative is free to withdraw consent at any time without providing a reason. When withdrawn, the participant will continue to receive standard clinical care. Follow up data will continue to be collected (unless the participant/legal representative has specifically stated that they do not want this to happen).

a: sex, ethnicity, selected pre-existing conditions of interest, family history of cancer, smoking, vaping, alcohol use

b: 6-item STAI, this data can also be collected over the phone should a participant be unavailable for an in-person visit.

c: 2x10 mL Streck® tubes, 1x6 mL lithium heparin tube

d: height, weight, waist circumference

e: review of selected pre-existing conditions of interest from EHR summaries when available or other evidence such as NHS App.

f: For missed appointment at T1; participants remain on study and attends study visit T2 and follow-up period

g: For missed appointment at T2; participants remain on study for follow-up period

7.2 RECRUITMENT METHOD EVALUATION IN THE PILOT

During the Pilot study, participants will be identified via the strategies described below with an aim to inform the study design for the main study.

- **From GP practices identified through a commercial participant recruitment platform**

Commercial recruitment platform collaborators will search participant EHR at participating GP practices (Participant Identification Centres (PICs)) on a regular basis throughout the study and provide GPs with a short-list of eligible participants. GPs will contact these eligible participants via text, email or letter inviting them to participate with a link to the study website (https://safe-d.uk / Home - Safe-D Clinical Study) where they can access the PIS and further information. Interested participants can book their T0 appointment at a conveniently located recruitment hub (specified local GP practice or other appropriate locations) via the website or call a member of the clinical study team at the hub for more information and help to book the appointment. Members of the clinical study team may contact consenting participants to offer assistance with booking an appointment. Optional reminder invites may be sent to invited participants.

- **From GP practices identified through National Institute of Health and Care Research Regional Research Delivery Networks (NIHR RRDN)**

Participant EHR will be searched by staff at participating GP practices (PICs) identified through the National Institute of Health and Care Research Regional Research Delivery Networks (NIHR RRDN). EHRs will be searched on a regular basis throughout the study and eligible participants will be contacted via text, email or letter inviting them to participate with a link to the study website where they can access the PIS and further information. Interested participants can book their T0 appointment at a conveniently located recruitment hub (specified local GP practice or other appropriate locations) via the website or contact a member of the clinical study team at the hub for more information and help to book the appointment. Members of the clinical study team may contact consenting participants to offer assistance with booking an appointment. Optional reminder invites may be sent to invited participants.

- **From Specialist Diabetes Service Centres**

Newly diagnosed diabetes patients referred to SDSCs will be invited to take part in the study. Eligible participants will be contacted by SDSC staff via email or letter, or in person at the time of the

educational session, inviting them to participate with a directions to the study website where they can access the PIS and further information. Interested participants can book their T0 appointment at a conveniently located recruitment hub (specified local GP practice or other appropriate locations) via the website or call a member of the clinical study team at the hub for more information and help to book the appointment. Members of the clinical study team may contact consenting participants to offer assistance with booking an appointment. Optional reminder invites may be sent to invited participants.

- **Self-referral**

Participants may also self-refer to the study if they become aware of the study through, but not limited to, viewing study information found on the study website, on social media or displayed in Primary Care locations. Interested participants can book their T0 appointment at a conveniently located recruitment hub (specified local GP practice or other appropriate locations) via the website or call a member of the clinical study team at the hub for more information and help to book the appointment. Self-referring participants are required to bring proof of date of initial elevated HbA1c to confirm their eligibility. Members of the clinical study team may contact consenting participants to offer assistance with booking an appointment.

7.3 PARTICIPANT SCREENING PROCEDURES

Frequent reviews of GP electronic health records and SDSC records will be undertaken by commercial recruitment platform collaborators or local research teams to identify eligible participants. Identified eligible participants will be contacted by text, email or letter, or approached in person when attending SDSC or similar diabetes educational sessions, with study information and invited to participate.

7.3.1 Screen Failures

Participants with whom the SAFE-D study is discussed but who do not enter the study will be documented in the screening log maintained at each participating study location, together with reasons for exclusion/decline. The screening log will be filed in the Investigator Location File (ILF) and shared on a regular basis with the SCTU study team via using secure transfer systems.

7.4 REGISTRATION PROCEDURES

Following informed consent, participants will be assigned a unique participant identification number via an independent, web-based system (www.imedidata.com) by a member of the clinical study team at the hub. This will be in the format of SFD-####-##### with the first four digits consisting of the

location code, and the last five digits consisting of sequential numbering provided through imedidata.com. The participant identification number will be added to the signed consent form.

7.5 TRIAL PROCEDURES

7.5.1 Timepoint T0

At enrolment visit participants will give informed consent to participate in the study and complete the following:

Sample collection

- 2x10 mL Streck® tubes
- 1x6 mL lithium heparin

Data collection at study locations and transferred securely to SCTU

- NHS number
- Date of birth

Contact details (name, postal and email address) for a select number of participants (to be defined) who have consented to taking part in optional further research related to the health questionnaire.

Data collection at study locations and entered into study database (Medidata RAVE)

- Height, weight and waist measurements
- 6-item STAI questionnaire
- Selected pre-existing conditions of interest, concomitant medications, family history, alcohol and smoking status

After T0 visit, GPs will be notified if participants under their care are taking part in the study.

7.5.2 Timepoint T1 (6 months +/- 4 weeks after T0):

Sample Collection:

- 2x10 mL Streck® tubes
- 1x6 mL lithium heparin

Data Collection:

- 6-item STAI Inventory questionnaire. This data can also be collected over the phone should a participant be unavailable for an in-person visit.
- Selected pre-existing conditions of interest and concomitant medications, in person or from EHRs.
- Weight and waist measurements

7.5.3 Timepoint T2 (12 months +/- 4 weeks after T0):

Sample Collection:

- 2x10 mL Streck® tubes
- 1x6 mL lithium heparin

Data Collection:

- 6-item STAI Inventory questionnaire. This data can also be collected over the phone should a participant be unavailable for an in-person visit.
- Selected pre-existing conditions of interest and concomitant medications, in person or from EHRs.
- Weight and waist measurements

7.5.4 Timepoint T3 (2 years after T2)

T3 refers to the three years of follow-up (following recruitment at T0) which will be collected via linkage with the cancer and mortality registry. At the time of writing the cancer registry is managed by the National Cancer Registration and Analysis Service which sits within NHS England, and the mortality register is managed by the Office for National Statistics but can be accessed through NHS England. Cancer and mortality registry data will still be required and sought even if the owner of the dataset changes in the future. A cancer and mortality registry download will be obtained on up to three occasions, including: once 5,000 participants have been recruited and at 3 years post last participant recruited.

Data Collection from Cancer Registry:

- Any cancer diagnosis (ICD10 C00-D48)
- Date of cancer diagnosis
- Site of cancer diagnosis
- Stage of cancer at diagnosis
- Histology of cancer
- Survival status
- Cancer treatments

Data Collection from Mortality Registry:

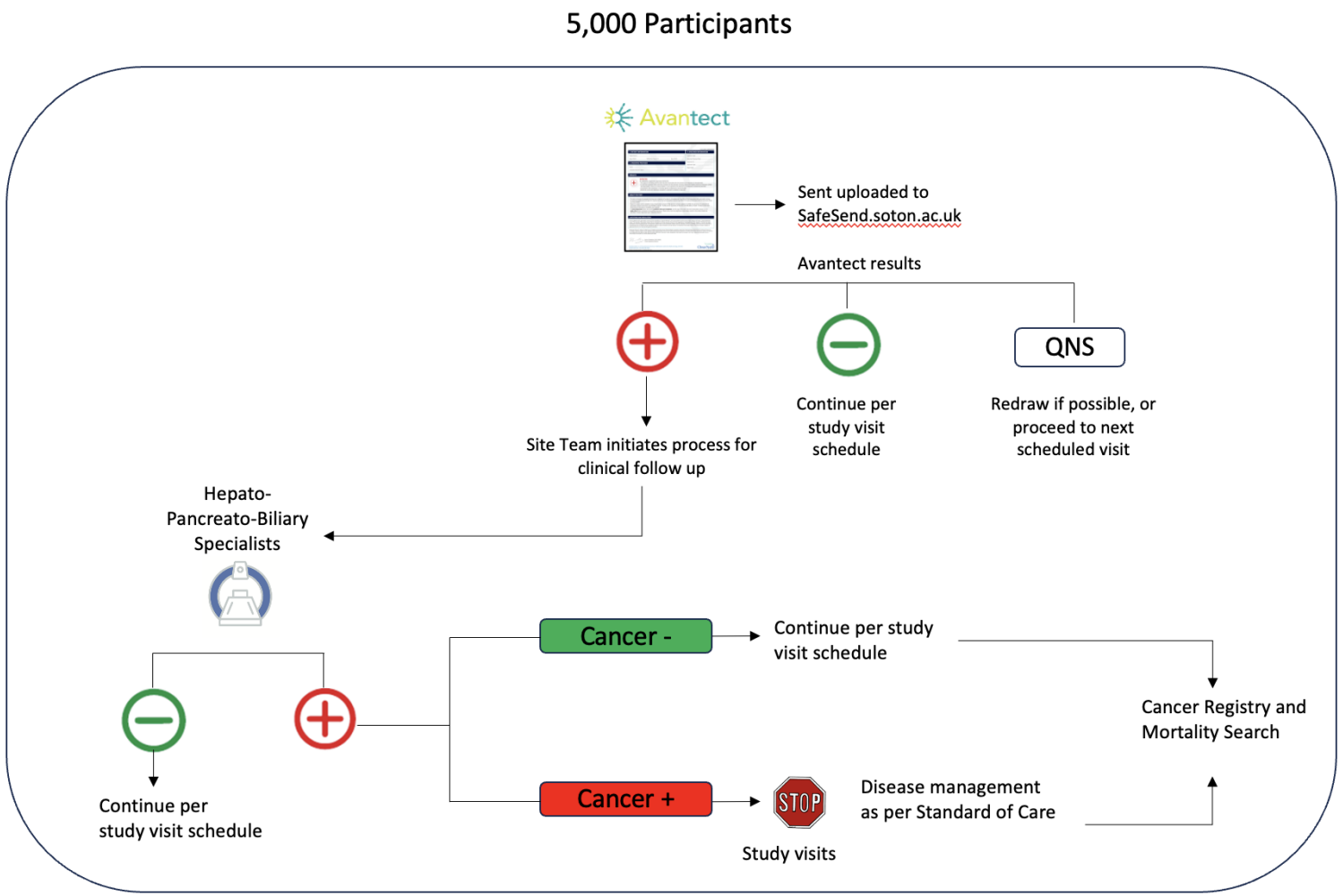
- Date of death
- Causes of death

The local study location team will collect and keep NHS number, address and contact details (including 1 or 2 phone numbers and an email address) from all participants. NHS numbers and dates of birth for all participants will be shared securely by study location to the SCTU. SCTU will then pass on the NHS numbers and dates of birth to the administrators at the registries to allow them to perform registry searches on three occasions during the study. The local study location team will also share with the SCTU study team, via secure email, the contact details (name, postal and email address) for a select number of participants (numbers to be defined) who have consented to optional further research questionnaire.

Addresses will be used by study locations to contact participants with any Avantect "Detected" results by post. Phone numbers will be used by study locations to contact participants if required throughout the study, including contacting participants to inform them of a "Detected" Avantect test if deemed more appropriate than by post alone (at the discretion of the clinical team).

NHS numbers should be shared with the SCTU study team securely either via secure email such as monitorSCTU@securemail.soton.ac.uk or SafeSend (https://safesend.soton.ac.uk/). SafeSend is a safe and secure (data protection compliant) mechanism for the study locations to send the relevant contact information to the SAFE-D email account as it is hosted by the University of Southampton and supports both in-transit and at-rest encryption. Whilst stored at the SCTU, details will be stored securely in a restricted access folder on the University of Southampton managed resource fileshare, in accordance with all applicable data protection regulations.

7.6 AVANTECT TEST RESULT MANAGEMENT SCHEMA



7.7 AVANTECT OUTCOMES AND FOLLOW UP

7.7.1. Detected

The CI will request the SAFE-D study location team to notify participants with Avantect “detected” test results and their GPs of the result via letter and an optional phone call (at the descretion of the clinical study team). The CI will also request the study location team to arrange for further investigation pancreas MRI or CT via an urgent suspected cancer referral (tumour specific pathway referral) to local hepatobiliary (HPB) service Local Collaborator or via rapid diagnostic centres or the participants own GP if no direct links with HPB centre are available. In either case, pancreas MRI or CT imaging will be scheduled as per standard of care for suspected cancer pathway. While every effort will be made to ensure that only eligible participants are enrolled, in the unlikely event that a participant with a "detected" test result is subsequently found to be ineligible, they will also be referred for further pancreas investigations out of duty of care.

If participant with Avantect “detected” test result is unable or unwilling to undergo imaging of pancreas, the participant will be removed from further Avantect testing, but will be included in the analysis and any cancer and mortality registry searches.

7.7.2. Not detected

Participants who have an Avantect “not detected” test result will not be informed of their result and will continue with study schedule of observations and procedures.

7.7.3. Quantity Not Sufficient (QNS)

In the event of a sample without adequate cfDNA concentration, a pancreatic cancer classification cannot be provided and a QNS report will be generated. The participant will be invited to provide a repeat blood sample within the predefined study timepoints (see Section 6.1).

7.8 IMAGING RESULTS

Following imaging, the imaging reports and any subsequent biopsy or resection pathology reports for all participants undergoing further investigations will be collected as part of the study clinical data from local scanning hospitals via the UHS Radiology and clinical team and transferred to the study MDST. The study MDST reviews the images and the de-identified imaging reports and any subsequent de-identified biopsy or resection pathology reports are shared with the SCTU for uploaded to RAVE. The SCTU informs the study location PI of the outcome and requests for participant to either continue or end participation on the study depending on imaging outcomes as described below.

7.8.1 Normal imaging outcome

If imaging did not show signs of pancreatic cancer or pancreatic cystic lesion with high grade dysplasia and/or neoplasia then the participant will continue with the remaining study visits.

7.8.2 Abnormal imaging outcome

Participants referred for imaging who have abnormal imaging results will be returned to routine clinical care (via local HPB team) for further clinical management as per current NHS practice.

If pancreatic cancer, other solid pancreatic lesion or other cancer type is identified based on imaging and biopsy, is performed then de-identified imaging reports and any subsequent de-identified biopsy or resection pathology reports will be collected and uploaded to RAVE as part of the study clinical data. Participant would discontinue further study blood collections. Diagnoses will be based on reports of pathologic evaluation performed at the treating institute. Digital Imaging and Communication in Medicine (DICOM) images will be obtained and reviewed at the end of the study phase as a quality control measure. If cyst fluid is sampled the de-identified cytology and any cyst fluid chemistry lab reports will be obtained and included in study data.

If imaging is abnormal and no biopsy or surgery is planned, de-identified imaging reports will be provided and uploaded to RAVE as part of study data and the cancer and mortality registry searches will be completed as planned. Participants with abnormal imaging results (suggestive of cancer) will discontinue further blood collection, but cancer and mortality registry searches will be completed as planned.

7.8.3 Abnormal imaging outcome showing pancreatic cystic lesion

For abnormal imaging outcomes showing a pancreatic cystic lesion, European or local guidelines will be followed.

IPMN or Mucinous cystic neoplasms (MCN) that, after surgical and histopathological evaluation, show a high-grade dysplasia phenotype will be considered as pancreatic cancer[12]. Otherwise, low grade dysplasia and other non-mucinous cystic lesions will not be considered as pancreatic cancer.

Participants for whom pancreatic cysts have been found by MRI/CT, and surveillance has been recommended, will continue study visits as scheduled and will be considered as non-pancreatic cancer outcome regardless of the size of the cyst until proven otherwise by pathological examination (Appendix III)

7.8.4 Abnormal imaging outcome showing suspicion of pancreatic cancer

For abnormal MRI imaging outcomes showing suspicion of pancreatic cancer, it is standard of care to perform a follow up CT scan to evaluate resectability (staging CT scan), and endoscopic ultrasound scans (EUS) depending on the local HPB MDT. Therefore, for any abnormal MRIs showing suspicion for cancer a contrast staging CT scan will be ordered by the local HPB centre according to NICE guidelines G18. Standard of care CT and MRI imaging reports will be provided to the multidisciplinary study team (MDST) as clinical study data, which will be assessed according to NCNN guidelines v1 2023 and will inform on resectability status. Decisions about resectability status will be determined by the local HPB MDT. To determine resectability for the study endpoint, the MRI and CT scans will be reviewed by the MDST and will neither influence participant care nor be fed back to the local MDT team unless the study MDST outcome contradicts local MDT decision in a way that affects participant management.

Table 1. Definition of borderline resectable pancreatic cancer as assessed by contrast CT pancreas protocol.

	Feature	Requirement
Resectable	a. Normal tissue plane between tumour and vessels b. No evidence of metastatic disease.	a and b
Borderline resectable	a. Loss of normal tissue plane between tumour and vessels. b. Venous involvement (contact and or distortion) of the (Superior Mesenteric Vein) SMV, (Portal Vein) PV or SMV-PV confluence – allowing surgical reconstruction. c. Tumour abutment <180° of the (Superior Mesenteric Artery) SMA or coeliac axis. d. No evidence of metastatic disease.	a and/or b or c and d
Unresectable	a. Encasement/contact of SMA or coeliac axis of >180°. b. Long segment involvement/occlusion of the SMV, PV or SMV-PV confluence with no reconstruction possible. c. Encasement of the hepatic artery. d. Confirmed metastatic disease.	one or more of a, b, c, d

7.8.5 Indeterminate imaging outcome

If the imaging is indeterminate and not clearly abnormal, the following scenario would apply:

- If imaging is indeterminate at T0, the participant will continue the study and undergo T1 visit. Subsequent follow-up imaging (as part of MDT decisions) reports will be collected as part of study data. Cancer and mortality registry records will be reviewed as planned.
- If indeterminate at T1, imaging reports will be collected as part of study data and participant will undergo T2 visit. Cancer and mortality registry records will be reviewed as planned.
- If indeterminate at T2, imaging reports will be collected as part of study data. Cancer and mortality registry records will be reviewed as planned.

7.9 DEFINITION OF BIOPSY OUTCOMES

The categories of clinical diagnostic follow-up findings are defined as follows:

- Histologic findings show pancreatic cancer, any stage (I-IV) based on American Joint Committee on Cancer (AJCC) v8.0.
- Histologic findings are indeterminate
- Histologic findings are consistent with pre-neoplastic lesions (IPMNs, mucinous cystadenoma or with pancreatic intraepithelial neoplasia (PanINs)).
- Histologic findings are consistent with an inflammatory process (benign disease)

Overall, the reference method will be histopathologic confirmation of PC, and/or definitive imaging diagnosis of PC.

7.10 DEVELOPMENT OF OTHER CANCER TYPES AND INCIDENTAL FINDINGS

In the event of any significant incidental findings on imaging found by local MDT, these findings should be acted upon by the local clinical team according to their processes.

For participants diagnosed with other cancers unrelated to the pancreas or other incidental findings during the study, pathology reports and imaging will be collected when available.
Participants diagnosed with other cancer types will discontinue further Avantect tests. Cancer and mortality registry searches will occur as planned.

7.11 TRIAL INTERVENTION DISCONTINUATION AND PARTICIPANT WITHDRAWAL

Participants with abnormal imaging results (cancer diagnosis) will discontinue further study visits but cancer and mortality registry searches will be completed as planned.

Participants will be able to withdraw from the study at any time and this will be recorded on the study database. It should be ascertained and documented whether the participant wishes to;

1. withdraw from future study procedures but allows for new data/information to be collected and already collected data and samples to be retained for analysis.
2. withdraw from future study procedures including collection of new data but allows for already collected data and samples to be retained for analysis.
3. completely withdraw, i.e. withdraw from future study procedures and requests that any remaining samples are disposed of and no further data will be collected.

Any withdrawal from the study should be recorded as end of study for the participant in the relevant eCRF and in their medical record. For level 2 and 3 withdrawals no further data should be collected for this participant. Already collected data will be retained to protect the validity of the study in line with HRA guidance.

If participants withdraw consent for further study procedures but are willing to continue sharing information (level 1), it would remain useful for the trial team to continue to collect any routine data (i.e., data that can be collected with no impact on the participant beyond standard clinical care/follow-up), and this will continue unless the participant explicitly requests otherwise. In the case of a level 1 withdrawal, cancer registry and mortality data is expected to be collected from NHS England as outlined in section 7.6.4.

In any case, participants who completely withdraw or withdraw only from further study procedures should revert to standard clinical care/follow-up as deemed by the responsible clinician.

8. SAFETY

8.1 DEFINITIONS

Standard BS ISO 20916:2019 (in combination with the UK Medical Device Regulations 2002, as amended) provides the following definitions relating to adverse events in medical device trials:

Device deficiency	Inadequacy of an investigational medical device with respect to its identity, quality, durability, reliability, usability, safety or performance. *Device deficiencies include malfunctions[1], use errors[2], and inadequacy in the information supplied by the manufacturer including labelling.* *These include deficiencies related to both the investigational medical device, or the comparator*

Adverse Event (AE)	Any untoward medical occurrence, inappropriate participant management decision, unintended disease or injury or any untoward clinical signs (including an abnormal laboratory finding) in participants, users or other persons with any connection to study related activities, whether or not related to the IVD medical device under investigation (and whether anticipated or unanticipated). *Adverse events can be cause by e.g. insufficient or inadequate instructions for use, deployment, installation, operation, or any malfunction or deterioration of the IVD medical device under investigation. This includes events related to the investigational medical device or comparator. For participants, this includes events related to all procedures involved. For users or other persons, this is restricted to events related to the use of investigational medical devices.* *False negative or false positive results are not considered adverse events unless inappropriate participant management decisions are made based on those false results.*
Serious Adverse Event (SAE)	Any adverse event that led to any of the following: • Death • A life-threatening illness of injury • A permanent impairment of a body structure or body function including chronic diseases • In-patient or prolonged hospitalisation • Medical or surgical intervention to prevent a life-threatening illness or injury or permanent impairment to a body structure or a body function • Foetal distress, foetal death, a congenital abnormality, or birth defect including physical or mental impairment *Planned hospitalisation for a pre-existing condition, or a procedure required by the Clinical Performance Study Protocol without serious deterioration in health, is not considered a serious adverse event*
Adverse Device Effect (ADE)	Adverse event related to the use of an IVD medical device under investigation. *This includes any adverse event resulting from insufficient or inadequate instructions for use, installation, operation, or any malfunction of the IVD medical device under investigation. This includes any event resulting from use error or from intentional misuse of the IVD medical device under investigation.*
Serious Adverse Device Effect (SADE)	Adverse device effect that has resulted in any of the consequences characteristic of a serious adverse event.
Anticipated Serious Adverse Device Effect (ASADE)	Serious adverse device effect (SADE) which by its nature, incidence, severity, or outcome **has been** identified in the manufacturers' risk analysis report, and listed in either the clinical performance study protocol, or Investigator brochure.
Unanticipated Serious Adverse Device Effect (USADE)	Serious adverse device effect (SADE) which by its nature, incidence, severity, or outcome **has not been** identified in the risk analysis report, and listed in either the clinical performance study protocol, or Investigator brochure.

[1] failure of an investigational medical device to perform in accordance with its intended purpose when used in accordance with the IFU, CPSP, or IB

[2] act or omission of an act that results in an IVD medical device output which differs from that intended by the manufacturer or expected by the user:

a. includes the inability of the user to complete a task

b. users may or may not be aware that a use error has occurred

c. can result from a mismatch between the characteristics of the user, the user interface, task, or use environment

d. an unexpected physiological response of the participant is not by itself considered use error

E. *a malfunction of an IVD medical device that causes an unexpected result is not considered a use error*

8.2 TRIAL SPECIFIC REQUIREMENTS

8.2.1 Adverse Events

a) Recording in medical records:

All Adverse Events (AEs) from the date of informed consent to the end of participation in the trial (i.e. 12 months to T2, or date of participant withdrawal) should be recorded in the *participant's medical records* as per usual practice.

b) Recording Adverse Events in trial eCRF:

The following adverse events are expected and do not require reporting in the eCRF. However:

1) if they are continued for more than one week, then these should be entered as adverse events in the eCRF, *or*
2) if the event meets the criteria of 'serious' as defined in section 8.1, then it must be reported in the eCRF and should also follow the process for reporting as a Serious Adverse Event

- Related to blood collection:
  - Pain, bleeding, bruising, swelling, or haematoma at site
  - low blood pressure
  - fainting at time of collection
  - headache
  - blood clot formation
  - infection at the site where skin is punctured by the needle (very rarely)
- Related to MRI or CT:
  - Allergic reaction to contrast
  - nausea due to contrast
  - panic attack
  - abdominal pain
  - contrast reactions (incl. contrast-induced nephropathy [CIN], acute kidney injury [AKI]) in participants with pre-existing kidney failure

Any other adverse events not listed above that are considered related to the study procedures (blood collection and imaging) and occurring within 7 days of each visit (excl. T3) must be recorded in the eCRF.
Events with an onset occurring after 7 days post-visit should not be recorded as AEs in the eCRF.

8.2.2 Device Deficiencies

Occurring at study locations: related to blood sampling kits
All device deficiencies (related to the blood sampling kits) occurring at clinical locations and related to a specific participant will be collected on the device deficiency eCRF. All other device deficiencies occurring at clinical locations that are NOT related to a specific participant will be collected on a paper "Device Deficiency – Non-participant related" form in the ILF.

Trial clinicians at the samples collection location (i.e. Hub) will assess if the participant-related deficiencies are *reportable*. Reportable device deficiencies are those that ***might*** have led to an SAE if:

i. suitable actions had not been taken, or
ii. intervention had not been made, or
iii. if circumstances had been less fortunate

Any device deficiency that fulfils the reportable criteria above must be reported to SCTU using the Serious Adverse Event Report Form for assessment and onward reporting as appropriate.

Occurring at labs: related to blood samples or Avantect test
Device deficiencies occurring at either the ECMC translational facility (involving blood sample tubes) or ClearNote Health (involving the Avantect lab assay under investigation) will be recorded outside of the RAVE database (both labs will be provided with written instructions for reporting of all safety events) and reported to the manufacturer within required timelines. Due to the design of the trial, there is no feedback loop in which a device deficiency occurring at either laboratory could lead to an SAE, and as such, clinicians will not assess these events and they will not be reported to MHRA. This is detailed in the Trial Risk Assessment.

8.2.3 Seriousness

For any adverse events occurring, a complete assessment of the seriousness must always be assessed by a medically qualified doctor who is registered on the delegation of responsibility log (this is usually the investigator).

All adverse events (whether related to study procedures or not) that fulfil the criteria definition of 'serious' in section 8.1, must be reported to SCTU using the Serious Adverse Event Report Form as per section 8.5.1.3

8.2.4 Exceptions

For the purposes of this trial, the following **SAEs do not** require reporting to SCTU using the Serious Adverse Event Report Form:

- Hospitalisations for elective treatment of a pre-existing condition (the pre-existing condition needs to have been captured within the selected pre-existing conditions of interest CRF and/or the participant's medical records).

For clarity, only events that are related to treatment should be reported to SCTU.

8.3 CAUSALITY

A complete assessment of the causality must always be made by a medically qualified doctor who is registered on the delegation of responsibility log; this is usually the investigator.

If any doubt about the causality exists, the local investigator should inform SCTU who will notify the Chief Investigator. Other clinicians may be asked for advice in these cases.

In the case of discrepant views on causality, SCTU will classify the event as per the worst-case classification and if onward reporting is required, the MHRA and/or Research Ethics Committee (REC) will be informed of both parties' points of view.

Relationship	Description	Denoted
Not related	Relationship to the device or procedures can be excluded when: • The event is not a known side effect of the product category the device belongs to, or of similar devices and procedures • The event has no temporal relationship with the use of the investigational device or the procedures • The event does not follow a known response pattern to the medical device, and is biologically implausible • The discontinuation of medical device application (or the reduction of the level of activation/exposure [when clinically feasible]) and reintroduction of its use (or increase the level of activation/exposure), do not impact on the serious event • The event involves a body-site or an organ not expected to be affected by the device or procedure • The serious event can be attributed to another cause (e.g. an underlying or concurrent illness/clinical condition, an effect of another device, drug, treatment or other risk factors) • The event does not depend on a false result given by the investigational device used for diagnosis, when applicable	SAE

	• Harms to the participant are not clearly due to use error *In order to establish the non-relatedness, not all the criteria listed above might be met at the same time, depending on the type of device/procedures and the serious event.*	
Unlikely	The relationship with the use of the device seems not relevant and/or the event can be reasonably explained by another cause, but additional information may be obtained	SAE
Possible	The relationship with the use of the investigational device is weak but cannot be ruled out completely. Alternative causes are also possible (e.g. an underlying or concurrent illness/clinical condition or/and an effect of another device, drug or treatment). *Cases where relatedness cannot be assessed or no information has been obtained should also be classified as possible.*	Anticipated or Unanticipated Serious Adverse Device Effect (USADE or ASADE)
Probable	The relationship with the use of the investigational device seems relevant and/or the event cannot reasonably be explained by another cause, but additional information may be obtained.	Anticipated or Unanticipated Serious Adverse Device Effect (ASADE or USADE)

Causal relationship	The serious event is associated with the investigational device or with procedures beyond reasonable doubt when:
	• The event is a known side effect of the product category the device belongs to or of similar devices and procedures
	• The event has a temporal relationship with investigational device use/application or procedures
	• The event involves a body-site or organ that
	  ○ The investigational device or procedures are applied to;
	  ○ The investigational device of procedures have an effect on
	• The serious event follows a known response pattern to the medical device (if the response pattern is previously known)
	• The discontinuation of medical device application (or reduction of the level of activation/exposure) and reintroduction of its use (or increase of the level of activation/exposure) impacts on the serious event (when clinically feasible)
	• Other possible causes (e.g. an underlying or concurrent illness/clinical condition or/and an effect of another device, drug or treatment) have been adequately ruled out
	• Harm to the participant is due to error in use
	• The event depends on a false result given by the investigational device used for diagnosis (when applicable)
	In order to establish the non-relatedness, not all the criteria listed above might be met at the same time,
		Anticipated or Unanticipated Serious Adverse Device Effect (ASADE or USADE)

	depending on the type of device/procedures and the serious event.	

8.4 EXPECTEDNESS

There are no adverse events that are expected to meet the definition criteria for seriousness; therefore all **serious** adverse events will be 'unexpected'.

The nature and/or severity of the event should be considered when making the assessment of expectedness. If these factors are not consistent with the current information available, then the AE or device deficiency should be recorded as 'unexpected'.

8.5 REPORTING PROCEDURES

Any questions concerning adverse event reporting should be directed to the SCTU in the first instance. Study locations (i.e. Hubs) at which participant blood samples are collected, as well as both labs (the ECMC translational facility and ClearNote Health) will receive written instructions and a tailored flow chart to assist in reporting procedures of all safety events.

8.5.1 Reporting Details

8.5.1.1 Adverse Events

All AEs should be recorded in the participant's medical records, and all related AEs (Adverse Device Effects - ADEs) should be reported in the trial eCRF as per the trial specific requirements listed in Section 8.2.

8.5.1.2 Device Deficiencies

All device deficiencies of an investigational device must be documented throughout the clinical investigation. These will be recorded as detailed in section 8.2.2. If a device deficiency meets the reportable criteria detailed in section 8.2.2. (and do not meet the exceptions listed in 8.2.2.), it must also be reported using the reporting process in section 8.5.1.3 below.

8.5.1.3 Serious Adverse Events

For all reportable SAEs and device deficiencies, an SAE report form should be completed with as much detail as possible (including any relevant anonymised treatment forms and/or investigation reports) and emailed to SCTU immediately but at least within 3 days of study location becoming aware of the event.

Or

Contact SCTU by phone for advice and then email a scanned copy of the SAE report form completed as above.

SAE REPORTING CONTACT DETAILS

Please email a copy of the SAE form to
SCTU within 3 days of becoming aware of the event

Email: ctu@soton.ac.uk

FAO: Quality and Regulatory Team

For further assistance: Tel: 023 8120 5154 (Mon to Fri 09:00 – 17:00)

The event term should be the most appropriate medical term or concept (which the SCTU will code to MedDRA) and grades given in accordance with the National Cancer Institute (NCI) CTCAE v5.

Additional information should be provided as soon as possible as it is received if all information was not included at the time of reporting.

As per regulatory and local SCTU procedures, all SAEs and device deficiencies that might have led to an SAE as detailed in section 8.2.2 will be reported to the REC, if the event was:

- 'Related' – i.e., resulted from the administration of any of the research procedures; and
- 'Unexpected' – i.e., an event that is not listed in the CPSP as an expected occurrence.

8.5.1.4 Reporting Timelines

All reportable AEs and SAEs should be reported from the date of informed consent up to 7 days after each study procedure.

All unresolved adverse events should be followed by the investigator until one of the end of trial criteria is met (i.e. lost to follow up, withdrawal etc.). At the last scheduled visit, the investigator should instruct each participant to report any subsequent event(s) that the participant, or the participant's general practitioner, believes might reasonably be related to participation in this trial. The investigator should notify the trial sponsor of any death or adverse event occurring at any time after a participant has discontinued or terminated trial participation that may reasonably be related to this trial.

8.5.2 Pre-existing Conditions

Pre-existing conditions (prior to informed consent) should not be reported as an AE unless the conditions worsen during the trial. The condition, however, must be reported on the selected pre-existing conditions of interest eCRF or clearly documented in the participant's medical record.

8.5.3 Pregnancy

Given the deemed low risk of the intervention on pregnancy, pregnancy data will not be collected in the trial. If a participant becomes pregnant whilst taking part in the trial, they become ineligible to remain in the trial and will be followed up as per standard care.

8.6 RESPONSIBILITIES

8.6.1 Principal Investigator (PI)

The PI, or medically qualified doctor who is registered on the delegation of responsibility log, is responsible for:

1. Using medical judgement in assigning seriousness, causality and if requested, whether the event/reaction was anticipated using the Reference Safety Information approved for the trial.
2. Ensuring that all SAEs and reportable device deficiencies are recorded and reported to the SCTU immediately, or at a least within 72 hours, of becoming aware of the event and provide further follow-up information as soon as available. Ensuring that SAEs are followed up with the SCTU if a record of receipt is not received within 1 working day of initial reporting.
3. Ensuring that all AEs are recorded and that ADEs are reported to the SCTU in line with the requirements of the CPSP.

8.6.2 Chief Investigator (CI) / delegate or independent clinical reviewer:

The CI, or delegated clinical reviewer, is responsible for:

1. Clinical oversight of the safety of patients participating in the trial, including an ongoing review of the risk / benefit.
2. Using medical judgement in assigning the event's seriousness, causality and whether if requested, the event was anticipated (in line with the Reference Safety Information) where it has not been possible to obtain local medical assessment.
3. Using medical judgement in assigning whether an event was anticipated and if requested, assessing expectedness in line with the Reference Safety Information.

4. Immediate review of all USADEs.
5. Review of specific events in accordance with the trial risk assessment and CPSP as required.
6. Upon request review Medical Dictionary for Regulatory Activities (MedDRA) or Body System coding to all events.

8.6.3 Sponsor / delegate

The Sponsor, or delegate, is responsible for:

1. Central data collection and verification of device deficiencies, AEs, and SAEs and USADEs according to the CPSP onto a database.
2. Reporting safety information to the CI, delegate or independent clinical reviewer for the ongoing assessment of the risk / benefit of the trial.
3. Checking causally related events against the approved RSI, in place at time of event onset.
4. Reporting safety information to the independent oversight committees identified for the trial
5. Sharing of all reported serious adverse events and device deficiencies with the manufacturer (or UK Responsible Person).
6. Notification to the manufacturer within 1 working day of any SAE where:
    - Direct involvement of manufacturer test is suspected
    - Causality cannot be ruled out
    - Device deficiency / malfunction is implicated
7. Ensuring expedited reporting of related and unexpected serious adverse events to the REC within the required timelines.
8. Notifying Investigators of related and unexpected serious adverse events that occur within the trial.
9. Notifying PIs of updates to the Reference Safety Information for the trial.

8.6.4 The ECMC translational Facility and ClearNote Health laboratory

Each laboratory is responsible for recording any device deficiencies occurring at their respective laboratories onto a CRF and sharing these with SCTU on an ad-hoc basis (at least quarterly) as requested for onward reporting to manufacturer within the required timelines. SCTU will be required to report device deficiencies to REC if they also lead to a related and unexpected SAE.

8.7 REPORTING URGENT SAFETY MEASURES

If any urgent safety measures are taken the CI/Sponsor shall immediately, and in any event no later than 3 days from the date the measures are taken, give written notice to the MHRA and REC of the measures taken and the circumstances giving rise to those measures.

9. STATISTICS AND DATA ANALYSES

9.1 CROSS-OVER OF PILOT STUDY PARTICIPANTS

Participants recruited during the pilot phase of the study were randomised to the control or intervention arm (1:1 ratio) via an independent, web-based system (www.imedidata.com). Samples from intervention arm participants were sent for expedited testing on the Avantect Pancreatic Cancer test v1, whereas control arm samples were stored for potential future Avantect testing or future approved research purposes. All participants remained blinded unless a “detected” result was found in participants from the intervention arm, in which case they and their GP were informed and further investigation by pancreas MRI scan was arranged.

Following recruitment feasibility assessments as part of the Pilot objectives, the decision to redesign the SAFE-D study to a single arm intervention cohort study evaluating the upgraded Avantect v2 test was taken by the TSC with support of other oversight groups. In the new study design, all samples, including those stored from the control arm will be shipped to ClearNote Health for testing using Avantect v2. The testing of control arm samples with Avantect v2 will enable the conversion of these participants to the main study intervention arm.

To allow all participants to benefit from test updates, the upgraded Avantect v2 will be used for all collected samples as well as subsequent study visits according to the CPSD as described here. This includes re-analysis of participants’ samples already analysed with the previous version of the Avantect test as part of the pilot study. For absolute clarity only Avantect test v2 results will be included in the study analysis once all collected samples from participants recruited to both study arms in the Pilot study have been reanalysed on Avantect test v2. Any “detected” results will be acted on as described in section 7.8.1, with the exception of samples that have already returned a “detected” result. Participants with samples returning a “Detected” results will be referred for MRI or CT scan.

All participants will be informed of the study redesign via letter from study location staff. This will inform of the intention to analyse (control arm) or reanalyse (intervention arm) their already

collected samples on the upgraded Avantect test v2 unless the participant withdraws from the study within 2 weeks of receiving the letter. If we have not heard back within this time limit, the samples will be analysed. The updated PIS will be included in the communications and participants will be reminded that they have the option to withdraw from the study at anytime should they wish.

9.2 SAMPLE SIZE

Upon conclusion of the pilot, further recruitment to the study will occur. Participants in the pilot study will continue to have their data analysed. The final analysis includes two co-primary endpoints:

1. sensitivity (of the Avantect test),
2. specificity (of the Avantect test)

The anticipated prevalence of a pancreatic cancer diagnosis within 3-years of follow-up within this population is 0.8%[3]. Conservative estimates place the anticipated sensitivity of the Avantect test at 82.6% sensitivity and 95% specificity in the detection of PC. Under usual care in the UK, 10-20%[13,14] of pancreatic cancer patients receive surgery with curative intent due to the majority (80%) presenting at Stage III or Stage IV[15]. Data from the CAPS cohort[16] in the US has demonstrated that it is possible to reduce the proportion of patients presenting with late stage disease if surveillance testing is conducted on at-risk subgroups, thus improving the availability of curative resection as a treatment strategy. It is anticipated that the Avantect v2 test will increase the proportion of pancreatic cancers eligible for resection compared to standard care.

With two co-primary endpoints, each endpoint must be reached for an overall successful result. To achieve an overall power of 90%, the power for each endpoint should be $90\%^{(1/2)}$ = 94.9%. Following guidance from Korevaar and colleagues[17], the analysis will consist of a one-sided test at a cumulative alpha of 0.05 at the final analysis.

Both co-primaries are metrics of test accuracy. Individuals with at least one ‘Detected’ result will be treated as a ‘positive’ prediction for the purpose of calculating sensitivity. Individuals with at least one ‘Not detected’ result and no ‘Detected’ results will be treated as a ‘negative’ prediction for the purpose of calculating specificity. In practice test results will not be available for all participants due to machine failure, insufficient blood sample quality, shipping or processing, or participants being unable to provide a blood sample. To reduce the number of participants where no test results are available, three collection time points are included. In the case where a blood draw did not occur or the sample was not analysable following a scheduled visit, a repeat blood draw will be arranged. The expected proportion of participants who are expected to not have a single Avantect result is 5%.

Based on feedback from the FDA, the sample size calculations are driven by being able to rule out a test sensitivity lower than 56% and rule out a specificitity lower than 85%. Using the PropTestPower function in the R package EnvStats, it was determined that 38 individuals with pancreatic cancer are required to rule out a sensitivity lower than 56% with an expected sensitivity of 80% at 94.9% power and an alpha of 0.05. At an incidence of 0.8%, the recruitment target is 4,750, which increases to 5,000 with allowing for 5% loss to arrive at the Per Protocol population (see section 9.4) leads to the following confusion matrix:

		Diagnostic status	
		Has PC diagnosis	Does not have PC diagnosis
Avantect test expected result	Detected	31	236
	Not detected	7	4,476
	No valid results or lost to follow-up	2	248
	Total	40	4,960

With 38 cases of pancreatic cancer of which 31/38 = 81.6% were detected by the Avantect test, this would be sufficient to rule out a sensitivity lower than 56% at 95.1% power. With 4,712 (4,476 + 236) individuals without a pancreatic cancer diagnosis and an Avantect result of which 4,476/4,512 = 95% are expected to have no 'detected' Avantect test results, more than 99% power is achieved to rule out a specificity lower than 92%.

9.3 STUDY TIMEPOINTS

There will be three timepoints for blood collection: at baseline (T0) [within 200 days of diabetes diagnosis], 6 months +/- 4 weeks post-baseline (T1), and 12 months +/- 4 weeks from baseline (T2). For each study timepoint, the Avantect test will be conducted. Collected samples will be assessed as soon as possible within 14 business days of receipt of samples in the analysing laboratory at ClearNote Health. Those with positive test results (test result = Avantect "detected") will undergo diagnostic pancreas imaging.

9.4 STATISTICAL ANALYSIS PLAN (SAP)

This study will be analysed using the principles of the International Conference on Harmonisation E9 guidelines and reported according to the CONSORT guidelines. A full and detailed statistical analysis

plan will be developed prior to the final analysis of the study. The main features of which are described here.

All analyses will be conducted on a Per Protocol population, which is defined as individuals with at least one analysable Avantect test result (i.e. either “Detected” or “Not detected”) and linked to the cancer registry or local equivalent to determine if pancreatic cancer was diagnosed. It is expected that 95% of the population will qualify for the Per Protocol population. The final analysis will be carried out after 3-year follow-up data has been collected for all 5,000 participants.

The co-primary outcomes are Avantect sensitivity and specificity in detecting PC. Sensitivity is defined as the proportion of participants with one (or more) Avantect “detected” test results who have pancreatic cancer diagnosed via imaging in relation to all individuals who had pancreatic cancer diagnosed. Specificity is defined as the proportion of participants with one or more Avantect “not detected” test results, and no Avantect “detected” results, who did not have a pancreatic cancer diagnosis in relation to all individuals who did not have a pancreatic cancer diagnosis. For all co-primary endpoints, a logistic model will be used to estimate uncertainty. Co-primaries will be presented alongside one-sided 95% confidence intervals.

At the final analysis, the sensitivity co-primary will be considered successful if a sensitivity of 39% can be ruled out with a one-sided p-value of 0.05 among participants. The specificity co-primary will be considered successful if a specificity of 92% can be ruled out with a one-sided p-value of 0.05.

9.4.1 Source of comparative clinical outcome data

With the re-design of the SAFE-D study to a single-arm interventional study, clinical outcomes (resection rate, stage-shift, resectability) can no longer be compared between arms. Resectability requires that imaging be reviewed by the study MDST, and therefore it is not possible to obtain comparative clinical outcome data. Resection rate and stage-shift will be collected from routine data sources or cohort studies over the same time period as the SAFE-D study for comparison. Ideally those datasets would be restricted to be similar to the SAFE-D study population, in size and characteristics, to provide a fair comparison. Then the 95% lower-bound of the one-sided interval for the point estimate in the SAFE-D study will be compared with the point estimate from the comparative data to test whether this outcome was ‘improved’ for SAFE-D participants.

Data sources for comparative clinical outcome data may include (but are not limited to): the cancer registry, the Clinical Practice Research Datalink, Our Future Health, the UK Biobank.

9.4.2 Secondary outcomes

PPV in detecting PC - With a sample size of 5,000, PC prevalence of 0.8%, and 5% lost from the per protocol population, there will be an expected 261 individuals with an Avantect "detected" result. 9.6% (25/261) are expected to have a PC. PPV will be considered successful if a null PPV of 5% can be ruled out at a one-sided p-value of 0.05.

NPV in ruling out PC - With a sample size of 5,000, PC prevalence of 0.8%, and 5% lost from the per protocol population, there will be an expected 4,489 individuals without an Avantect "detected" result. 99.6% (4,476/4,489) are expected to not have a diagnosis of PC. NPV will be considered successful if a null NPV of 99% can be ruled out at a one-sided p-value of 0.05.

Resection rate of PC - The analysis will be conducted by comparing the proportion of PC cases that underwent resection as a treatment modality between SAFE-D participants and the point-estimate of the proportion from comparative data (see section 9.4.1 above). Resection rate will be considered successful if the lower-bound of the 95% one-sided proportion in SAFE-D participants is higher than the proportion from comparative data.

Stage shift - The analysis will be conducted by comparing the proportion of PC cases diagnosed at stage I/II out of all participants diagnosed with PC between SAFE-D participants and the point-estimate of the proportion from comparative data (see section 9.4.1 above). Stage shift will be considered successful if the lower-bound of the 95% one-sided proportion in SAFE-D participants is higher than the proportion from comparative data.

Resectability – The analysis will be conducted by presenting the proportion of PC cases considered resectable by the study MDST. There is no success criteria for resectability as there will not be comparable clinical data.

For analyses of exploratory outcomes, the following applies:
Time-to-event outcomes (time to PC diagnosis and overall survival) will be analysed using a Cox regression model, comparing individuals in the study with a suitable clinical outcome data source. This will be supported by a Kaplan-Meier plot, median survival (and 95% confidence interval), and estimates of 3-year survival (alongside the corresponding 95% confidence interval).

The 6-item STAI will be analysed using a t-test or non-parametric suitable alternative if data are not normally distributed.

Performance characteristics for high-grade neoplasia include sensitivity, specificity, PPV and NPV. They will be analysed as described above, when high-grade neoplasia is also considered as Disease Positive, and when high-grade neoplasia alone (with the exclusion of pancreatic cancer) is considered as Disease Positive.

Unless otherwise stated, continuous data will be presented as means and standard deviations and analysed using a linear regression modelling framework. If data are skewed, medians and ranges will be presented. To analyse skewed data we will attempt to find a suitable transformation to allow a linear modelling approach. If this is not possible, we will explore whether another suitable parametric distrbution fits the data. If not, a non-parametric approach, such as quantile regression, will be used. Binary data will be reported in terms of odds ratios and analysed using logistic regression modelling, unless otherwise stated.

10. REGULATORY COMPLIANCE

10.1 CLINICAL TRIAL AUTHORISATION

This study has a favourable REC opinion and the IVD device under investigation has been registered with the UK competent authority (Medicines and Healthcare products Regulatory Agency [MHRA]) as an IVD medical device for performance evaluation. The trial has been designed in accordance with the principles of Good Clinical Practice (GCP).

10.2 DEVIATIONS AND SERIOUS BREACHES

10.2.1 Clinical Performance Study Protocol (CPSP) Compliance

A CPSP deviation is any noncompliance with the trial CPSP, GCP, or Manual of Procedure requirements. The investigator is not allowed to deviate from the CPSP, except when a deviation is necessary to protect participant's rights, safety and well-being, or the scientific integrity of the clinical performance study. Any deviation occurring at study locations or at the processing or analysis labs should be reported to the SCTU immediately. As a result of deviations SCTU will advise of and/or undertake any corrective and preventative actions as appropriate. Deviations from the CPSP which are found to frequently recur are not acceptable, will require immediate action and could potentially be classified as a serious breach.

Manufacturers (or SCTU if delegated in the Task Allocation Matrix) must notify the MHRA of all deviations relating to UK study locations as soon as they have been made aware of them. Details

about the nature of the deviation, when it occurred, where it occurred, and any proposed corrective and preventative actions should be provided. MHRA provides details on how to report deviations to them; if this is delegated to SCTU, then local processes will be followed.

10.2.2 Serious Breaches

A "serious breach" is a breach which is likely to effect to a significant degree –

- The safety or physical or mental integrity of the participants of the trial; or
- The scientific value of the trial.

All serious protocol deviations/violations and serious breaches of GCP and/or the trial protocol will immediately be reported to the regulatory authorities and other organisations, as required.

10.3 MODIFICATIONS

The CPSP, PIS, ICF and other participant information or other study documents (e.g. Instructions for Use) shall be amended as needed throughout the study in accordance with local SCTU written procedures for the control of documents and document changes. Proposed modifications to the CPSP will be reviewed and authorised locally in accordance with SCTU procedures. Any modifications to the CPSP, PIS and ICF shall be notified to the REC and will only be implemented once clinical performance study authorisation has been received.

Local SCTU procedures will be followed in the event that the clinical performance study requires either a temporary halt, or early termination. In the event of early termination of the clinical performance study, there will be no requirement for additional follow-up or continued care for study participants.

11. ETHICAL CONSIDERATIONS

The trial will be conducted in accordance with the recommendations for physicians involved in research on human participants adopted by the 18th World Medical Assembly, Helsinki 1964 as revised and recognised by governing laws and EU Directives. Each participant's consent to participate in the trial should be obtained after a full explanation has been given of treatment options, including the conventional and generally accepted methods of treatment. The right of the participant to refuse to participate in the trial without giving reasons must be respected.

After the participant has entered the trial, the clinician may give alternative treatment to that specified in the CPSP, at any stage, if they feel it to be in the best interest of the participant. However, reasons for doing so should be recorded and the participant will remain within the trial for the purpose of follow-up and data analysis according to the treatment option to which they have

been allocated. Similarly, the participant remains free to withdraw at any time from CPSP treatment and trial follow-up without giving reasons and without prejudicing their further treatment.

11.1 RESEARCH ETHICS COMMITTEE (REC) REVIEW AND REPORT

The Clinical Performance Study Protocol has received the favourable opinion of a Research Ethics Committee or Institutional Review Board (IRB) in the approved national participating countries.

Within one year after the end of trial, the Chief Investigator will submit a final report with the results, including any publication/abstracts, to the REC.

11.2 SPECIFIC ETHICAL CONSIDERATIONS

None.

11.3 INFORMED CONSENT PROCESS

Informed consent is a process that is initiated prior to an individual agreeing to participate in a trial and continues throughout the individual's participation. In obtaining and documenting informed consent, the investigator should comply with applicable regulatory requirements and adhere to the principles of GCP.

Discussion of objectives, risks and inconveniences of the trial and the conditions under which it is to be conducted are to be provided to the participant by appropriately delegated staff with knowledge in obtaining informed consent with reference to the participant information leaflet. This information will emphasise that participation in the trial is voluntary and that the participant may withdraw from the trial at any time and for any reason. The participant will be given the opportunity to ask any questions that may arise and provided the opportunity to discuss the trial with family members, friend or an independent healthcare professional outside of the research team and time to consider the information prior to agreeing to participate.

11.4 DATA PROTECTION AND CONFIDENTIALITY

SCTU will preserve the confidentiality of participants taking part in the study. The investigator must ensure that participant's anonymity will be maintained and that their identities are protected from unauthorised parties.

Participants' identification data will be required for the registration process.

Participant confidentiality will be ensured by using a trial identification number to identify a participant. Centres will maintain a master list of their participants linking the participant's name to their study identification number. This list will only be accessible to authorised members of the study team. Participant case records and files may be inspected by members of the SCTU, Sponsor and other regulatory bodies as required.

Any data or samples transferred from the centre will be identified by the study identification number only.

Participant data held electronically by the SCTU will be stored securely in a restricted access folder on the University of Southampton managed resource fileshare, in accordance with all applicable data protection regulations. Only authorised members of the study team will have access to participant data.

Databases will only be accessed by authorised personnel using specific passwords. Electronic participant data will only be identified by their study identification number. All data will be handled in accordance with current data protection regulations, including General Data Protection Regulation (GDPR).

Participants will not be identified in any study reports or publications.

12. SPONSOR

SCTU, Chief Investigator and other appropriate organisations have been delegated specific duties by the Sponsor University Hospital Southampton NHS Foundation Trust and this is documented in the trial task allocation matrix.

The duties assigned to the trial locations (NHS Trusts or others taking part in this study) are detailed in the Non-Commercial Agreement or other appropriate study location-specific agreement.

12.1 INDEMNITY

For NHS sponsored research HSG (96) 48 reference no.2 applies. If there is negligent harm during the clinical trial when the NHS body owes a duty of care to the person harmed, NHS Indemnity covers NHS staff, medical academic staff with honorary contracts, and those conducting the study. NHS Indemnity does not offer no-fault compensation and is unable to agree in advance to pay compensation for non-negligent harm. Ex-gratia payments may be considered in the case of a claim.

12.2 FUNDING

ClearNote Health is funding this study. Cancer Research UK provide core funding for SCTU.

12.3 STUDY LOCATION PAYMENTS

The payments assigned to the trial locations (NHS Trusts or others taking part in this study) are detailed in the Non-Commercial Agreement.

12.4 PARTICIPANT PAYMENTS

Participants will not be paid for participation in this study. However, participants with a "detected" test result requiring further investigations by pancreas MRI or CT scan will be able to claim for costs contributing towards covering travel expenses to the HPB centre where the scan will be performed.

13. TRIAL OVERSIGHT GROUPS

The day-to-day management of the trial will be co-ordinated through the SCTU and oversight will be maintained by the Trial Management Group, the Trial Steering Committee and the Independent Data Monitoring Committee.

13.1 TRIAL MANAGEMENT GROUP (TMG)

The TMG is responsible for overseeing progress of the study, including both the clinical and practical aspects. The Chair of the TMG will be the Director of Southampton Clinical Trials Unit.

The SAFE-D TMG charter defines the membership, terms of reference, roles, responsibilities, authority, decision-making and relationships of the TMG, including the timing of meetings, frequency and format of meetings and relationships with other trial committees.

13.2 TRIAL STEERING COMMITTEE (TSC)

The TSC act as the oversight body on behalf of the Sponsor and Funder. The majority of members of the TSC, including the chair, should be independent of the study.

The TSC charter defines the membership, terms of reference, roles, responsibilities, authority, decision-making and relationships of the TSC, including the timing of meetings, frequency and format of meetings and relationships with other study committees.

13.3 INDEPENDENT DATA MONITORING COMMITTEE (IDMC)

The aim of the IDMC is to safeguard the interests of trial participants, monitor the main outcome measures including safety and efficacy, and monitor the overall conduct of the study.

The SAFE-D IDMC charter defines the membership, terms of reference, roles, responsibilities, authority, decision-making and relationships of the IDMC, including the timing of meetings, methods of providing information to and from the IDMC, frequency and format of meetings, statistical issues and relationships with other trial committees.

13.4 THE SAFE-D MULTIDISCIPLINARY STUDY TEAM (MDST)

The multidisciplinary study team will include a pancreatic surgeon and a radiologist with experience in interpreting pancreatic scans.

The MDST is responsible for verifying all study related imaging scans to provide standardised quality assurance. The MDST will meet quarterly and generate a report of their findings. MDST will not interfere with the local HPB outcome or management plans (unless a significant finding can provide useful information to the participant care).

14. DATA MANAGEMENT

Participant data will be entered remotely at the study location and retained in accordance with the current Data Protection Regulations. The PI is responsible for ensuring the accuracy, completeness, and timeliness of the data entered.

The participant data is pseudo-anonymised by assigning each participant a participant identifier code which is used to identify the participant during the study and for any participant-specific clarification between the SCTU and study location. The study location retains a participant identification code list which is only available to location staff. Each sample will have a unique code linking the sample to the applicable timepoint.

The PIS and ICF will outline the participant data to be collected and how it will be managed or might be shared, including handling of all Participant Identifiable Data (PID) and sensitive PID adhering to relevant data protection law.

Trained personnel with specific roles assigned will be granted access to the electronic case report forms (eCRF). The eCRF includes built-in validation rules, edit checks, and audit trails to ensure data integrity, accuracy, and completeness. eCRF completion guidelines will be provided to the investigator locations to aid data entry of participant information.

Only the Investigator and personnel authorised by them should enter or change data in the eCRFs. When requested, laboratory data must be transcribed, with all investigator observations entered into the eCRF. ClearNote Health Avantect Test reports will be sent to SCTU.

A Data Management Plan (DMP) providing full details of the study specific data management strategy including data flows, data cleaning processes and central monitoring activities. Timelines for key tasks will be specified in the DMP and shared with study locations during the Location Initiation Visits.

Data queries will either be automatically generated within the eCRF, or manually raised by the study team, if required. All alterations made to the eCRF will be visible via an audit trail which provides the identity of the person who made the change, plus the date and time.
At the end of the study after all queries have been resolved and the database frozen, the PI will sign off to confirm the data integrity. The eCRFs will be archived according to SCTU policy and a PDF copy including all clinical and Meta data returned to the PI for each participant.

15. DATA SHARING REQUESTS FOR RESULTS THAT ARE AVAILABLE IN THE PUBLIC DOMAIN

In order to meet our ethical obligation to responsibly share data generated by clinical trials, SCTU operate a transparent data sharing request process. Clinical study data will be available upon completion of the study (after T3 timepoint) and after 24 months from publication of the final study data (stage 1 and stage 2) in a peer reviewed journal article.

Researchers interested in our data or samples are asked to complete the request for sample and data sharing form (CTU/FORM/5219) [template located on the SCTU website, www.southampton.ac.uk/ctu] to provide a brief research proposal on how they wish to use the data. It will include: the objectives, what data and/or samples are requested, timelines for use, intellectual property and publication rights, data release definition in the contract and participant informed consent etc. If considered necessary, a data sharing agreement from Sponsor may be required.

16. MONITORING

16.1 CENTRAL MONITORING

Data stored at SCTU will be checked for missing or unusual values (including range checks) and checked for consistency within participants over time.

Data queries on eCRFs will be raised to study location either automatically or manually by SCTU staff via the database. Study locations should respond to queries on the database and provide an explanation/resolution to any discrepancies within the required timeframe. Queries and responses are recorded within the database audit trail.

There are a number of monitoring principles in place at SCTU to ensure reliability and validity of the trial data, which are detailed in the trial monitoring plan.

The IDMC also have responsibility for specific central monitoring activities, as described in protocol section 13.3.

16.2 CLINICAL LOCATION MONITORING

As only sample collection and no Investigation Medicinal Product (IMP) is involved in the SAFE-D trial, no study location monitoring will be undertaken for source data verification. However, the study will be centrally monitored for appropriate consent taken, data integrity and sample tracking purposes as described in the Trial Monitoring Plan (TMP).

16.3 SOURCE DATA

Source documents are where data are first recorded, and from which participants' CRF data are obtained. These include, but are not limited to, GP and/or hospital records (from which selected pre-existing conditions of interest and previous and concurrent medication may be summarised), clinical and office charts, laboratory and pharmacy records, diaries, microfiches, radiographs, and correspondence.

The PI is responsible for maintaining the Investigator Source Location Agreement (CTU/FORM/5245) to detail location specific source data location information.

16.4 AUDITS AND INSPECTIONS

The study may be participant to inspection and audit by Southampton Clinical Trials Unit and Sponsor (University Hospital Southampton NHS Foundation Trust) and other regulatory bodies to ensure adherence to the principles of GCP, UK Policy Framework for Health and Social Care Research, applicable contracts/agreements and national regulations.

17. RECORD RETENTION AND ARCHIVING

Trial documents will be retained in a secure location during and after the trial has finished.

The PI or delegate must maintain adequate and accurate records to enable the conduct of the trial to be fully documented and the trial data to be subsequently verified. After trial closure the PI will maintain all source documents and trial related documents. All source documents will be retained for a period of 15 years following the end of the trial.

Study locations are responsible for archiving the ILF and participants' medical records.

The Sponsor is responsible for archiving the trial master file (TMF) and other relevant documentation.

18. PUBLICATION POLICY

Data from all centres will be analysed together and published as soon as possible. Evaluation of sensitivity and specificity of the Avantect test may also take place following completion of recruitment at T0 and prepared for potential publication.

Individual investigators may not publish data concerning their participants that are directly relevant to questions posed by the study until the TMG has published its report. The TMG will form the basis of the Writing Committee and advise on the nature of publications. All publications shall include a list of investigators, and if there are named authors, these should include the Chief Investigator, Co-Investigators, Study Manager, and Statistician(s) and PPI representatives involved in the study. Named authors will be agreed by the CI and Director of SCTU. If there are no named authors, then a 'writing committee' will be identified.

All publications shall include a list of contributors, and if there are named authors, these should include the study's Chief Investigator, Co-Investigator(s), Statistician(s) and Study Manager(s) involved at least. If there are no named authors (i.e. group authorship) then a writing committee will be identified that would usually include these people, at least. The ISRCTN number allocated to this study should be attached to any publications resulting from this study.

The members of the TMG should be listed with their affiliations in the Acknowledgements/Appendix of the main publication. Any competing interests will be declared in the publications relating to this study.

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20. APPENDICES

20.1 APPENDIX I

MRI and MRCP Minimal Sequence Recommended for SAFE-D study

Sequence, Imaging Plane	Scan Time	Slice Thickness (mm)	TR (ms)	TE (ms)
T2-weighted HASTE				
Axial	45 s	4	1100	90
Coronal	30 s	4	1100	90
MRCP				
2D slab coronal	20 s	40	2000	755
3Da coronal	4 min	1	2500	700
T1-weighted				
2D in and opposed phase axial	20 s	4	120	4.4/2.2
3D SPGR FS				
Axial precontrast	15 s	3	4	1.9
Axial postcontrastb	4 min	3	4	1.9
Coronal	1 min 15 s	1.7	3	1.1
DWIc/ADC, axial	3 min 30 s	5	4600	65

These sequences follow the PRECEDE Consortium recomandations[18]

FS = fat suppressed.

A. Three-dimensional T2-weighted MRCP plus maximum-intensity-projection images.

B . Gadolinium-based contrast agent (0.1 mmol/kg body weight). Post-contrast phases include arterial phase axial, venous phase axial, late venous phase axial, and late venous phase coronal.

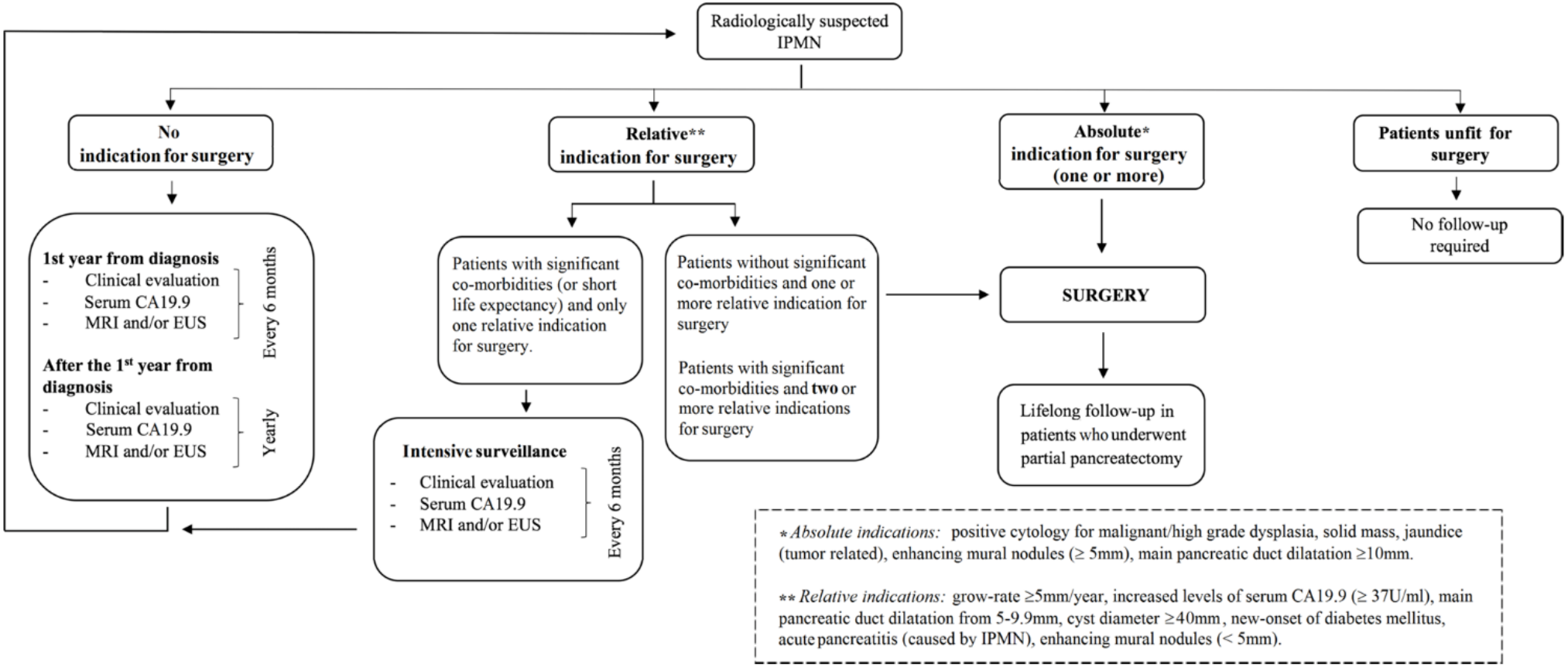
C. Including b values of 50, 500, and 800 s/mm2.

20.2 APPENDIX II

Standardization of MRI and MRCP Reporting	
1) Main pancreatic duct (MPD):	
Maximal caliber:	_____mm (location where measured: [head/body/tail])
Dilation Description [Normal/Segmental dilatation/Diffuse dilatation]:	
MPD stricture/abrupt cutoff (without obstructive cause):	[YES/NO]
If YES, Lcation	
2) Pancreatic parenchima:	
Describe: [Normal/Diffusely atrophic/Focally atrophic]	
3) Cystic lesion(s):	
Number of cystic lesions	[1/2–5/More than 5]
Lesion 1:	Describe most worrisome cystic lesion
If no worrisome lesion, reference the largest cystic lesion:	
Size:	Measure the longest dimension on axial or coronal T2-weighted image. Use MRCP maximum intensity projection or coronal thick slab as last resort
Location:	[Head/Body/Tail]
Duct communication:	[Present/Likely/Absent/Indeterminate]
Worrisome features	
Cyst ≥ 3 cm	[YES/NO]
Thickened enhanced cyst wall	[YES/NO]
Nonenhanced mural nodule	[YES/NO]
MPD 5–9 mm	[YES/NO]
Abrupt change in the MPD caliber with upstream pancreatic atrophy	[YES/NO]
High-risk stigmata	
Enhanced mural nodule	[YES/NO]
MPD ≥ 10 mm	[YES/NO]
4) Solid lesion:	
If present, use NCCN solid lesion reporting template[b]	
5) Peripancreatic abnormality:	
Fat stranding	[YES/NO]
Fluid collection	[YES/NO]
Lymphadenopathy	[YES/NO]
6) Additional abdominal findings:	

[b] https://www.nccn.org/professionals/physician_gls/pdf/pancreatic.pdf

20.3 APPENDIX III



20.4 APPENDIX IV

SAFE-D Medical Device Accountability

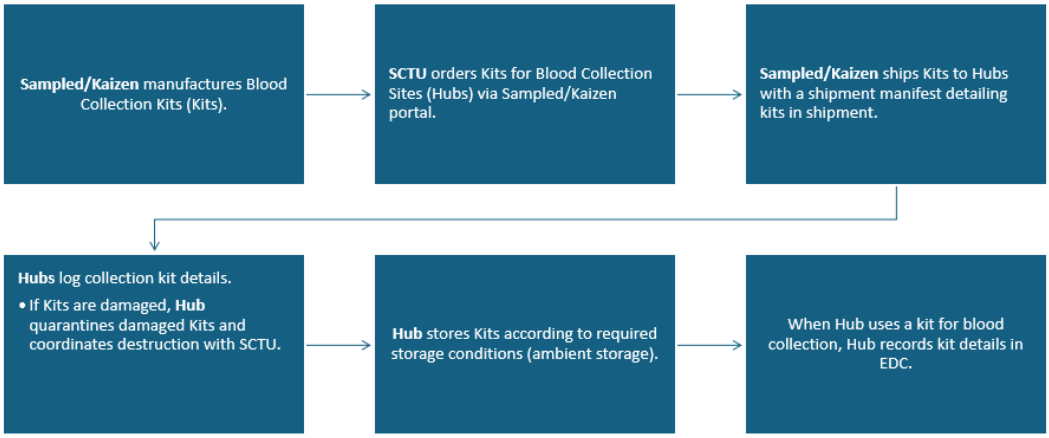
The investigational device for the SAFE-D clinical performance study consists of a laboratory assay (the in vitro diagnostic test) and (for the purposes of the clinical performance study) a blood collection kit (an accessory kit to the IVD device). The laboratory assay does not consist of a kit, but rather a number of reagents and laboratory consumables which are validated under College of American Pathologists (CAP) accreditation guidance as a Laboratory Developed Test. The critical reagents will be stored and managed by ClearNote Health according to manufacturers' instructions and clinical laboratory standard operating procedures.

The specimen collection kit consists of the products detailed in Table 1 below, of which the Streck and Lithium Heparin tubes are currently CE marked, available on the UK market and are not individual investigational products.

Table 1 - Constituent products of the SAFE-D sample collection kit

Product	**Supplier**	**Catalogue number/identifier**
2 x 10ml Streck blood collection tubes	*Streck*	*230244 (x1000)* *218997 (x100)*
1 Lithium Heparin 6ml blood collection tube	*BD (fisher scientific)*	*367885 (x1000)* *VS367885 (x100)*
Biohazard bag		
Absorbent wadding		
Test Requisition Form		
Royal Mail Safe Box or equivalent		
Bubble wrap		

Figure 1; Collection Kit Workflow below shows the flow of devices throughout the study. Once a kit is used for sample collection, it is no longer considered a device and is then managed as detailed in the Laboratory Manual, rather than covered in this Device Accountability document.



1. Equipment

a) Sample Shipment Manifest Template
b) Laboratory Information Management System (LIMS)
c) Medidata Rave Electronic Data Capture (EDC)

2. Manufacture of devices

2.1. Manufacturer details

The manufacturer of the device is ClearNote Health, Inc.
Address: 10578 Science Center Drive, Suite 210, San Diego, California, 92121, USA
Tel: (833) 258 7827
Email: customersuccess@clearnotehealth.com

The manufacture of the blood collection kit has been sub-contracted by ClearNote Health to Kaizen Bioservices.
Address: Highfield House, Cheadle Royal Business Park, Cheadle, Stockport, SK8 3GY
-+44 0800 640 9940
Email: www.kaizenbioservices.co.uk

2.2. Number of devices

The number of blood collection kits being manufactured for the purpose of the study is up to 15,000.

2.3. Documentation to be provided by manufacturer

Kaizen will provide kit quality reports and a shipment manifest to study locations with each shipment of kits. Shipment manifest will include: batch number, serial number, lot number, kit number, and expiry date.

2.4. Serial numbers of devices to be used

The blood collection kit lot number, expiry date and unique kit ID number will be on external packaging of kit. Within the kit, sterile blood collection tubes labelled with a unique identifier will be provided.

3. Labelling of medical devices

The collection kit will be labelled with a trial-specific label (bearing the regulatory statement "Device for Performance Evaluation Study") printed on the outer packaging. The blood collection tubes within the kit are UKCA/CE marked.

4. Shipping and receipt of medical devices from Kaizen to study locations

Blood collection kit shipments to blood collection locations will be managed by Southampton Clinical Trial Unit (SCTU). SCTU will order sample collection kits for the study locations via Kaizen portal and Kaizen will be responsible for the shipment of kits to the study locations via courier or Royal Mail.

Upon agreement of a mutually convenient date, the SCTU trial team will arrange for the blood collection kits to be sent to blood collection locations. The number of blood collection kits ordered for each study location will be based on recruitment projections. When collection kits need to be replenished, SCTU will place an order via the Kaizen portal and Kaizen will send the kits to the blood collection locations.

A list of all serial numbers, batch numbers, lot numbers, kit numbers and expiry dates will be included in each shipment manifest and will be available to SCTU via the Kaizen portal.

It is the responsibility of delegated study location staff to check the shipment, sign and scan the shipment manifest and send to SCTU via SAFE D email address (at safed@soton.ac.uk). A copy must be retained in the Investigator Location File. It is the study location's responsibility to maintain device accountability records and notify SCTU, via SAFE-D email, with details of any damaged or missing kits in the shipment.

If any kits are received at study locations in an unsuitable condition, they should be quarantined and kept separate from those that are useable. Unsuitable kits should be destroyed at the study location as per SOP and documented in the device accountability log.

The SCTU trial team will cross-reference shipment lists and confirmation emails from study locations to ensure that all devices have been received and that any faulty/unsuitable kits are recorded.

5. Storage of medical devices

Blood collection kits must be stored at ambient temperature and left unopened until use. Blood collection kits must only be used by delegated study location staff.

6. Usage and monitoring of medical devices

Kits may be selected at random for use by study location staff.

Study locations will track which collection kit is assigned to the participant and timepoint and ensure data are entered to Electronic Data Capture (EDC) forms. One kit must be used per collection. The tubes from multiple kits cannot be mixed and matched. If one component is faulty, the collection kit must be discarded and a new collection kit must be used. Deficient kits will be disposed of according to Section 7.

Kit-specific requirements:

- Once opened, the kits cannot be returned to stock.

- If one component of the kit is faulty, discard (and notify SCTU as per section 7), then discard the entire kit and use a new one.

7. Return or disposal of used medical devices

If a kit is used and experiences a device deficiency (e.g. vacuum in blood tube is not sufficient to allow blood draw) inform SCTU via SAFE-D email with

- kit serial number
- date the deficiency occurred
- description of the deficiency
- date the deficient device(s) were disposed of.

Kits must be disposed according to local waste policies, ensuring that sharps are correctly disposed of.

Unused device may not be disposed of without the prior written permission of SCTU.

8. Emergency recall of medical devices

In case of an emergency recall of the kits or components, SCTU standard operating procedures for product recall should be followed. Device accountability at the study location is the responsibility of the Investigator at each location. However, SCTU will coordinate any process for returns if applicable, and will issue instructions for any actions required at the study location, including quarantine, return, or disposal of blood collection kits.

9. Warnings / Notes / General Information / Safety

Study location investigators retain responsibility for device accountability at their locations. Accurate records of all device shipments and all devices destroyed must be documented and SCTU notified via email.

At the end of the study, it must be possible to reconcile delivery records with records of usage and destroyed stock.

21. SUMMARY OF SIGNIFICANT CHANGES TO THE PROTOCOL

Protocol date and version	Summary of significant changes
V1	New Production
V2 FEB 2025	• Updated the withdrawal process to not delete already collected data for participants that withdraw completely. • Changed the referral process from GPs to Research Hub team making the making the urgent suspected cancer referral. • Changed who send the letter of "Detected" result letter to participant and GP from SCTU to Research Hub team. • Removed the requirement of the SCTU team to hold names and addresses for participants with "Detected" result. • Changed that participants will be informed about incidental findings by GP to informed by local MDT team. • Addition of Self-referral as recruitment route • Inclusion of date of birth required for cancer and mortality registry searches
V3 25 MAR 2025	• Changed the review of Electronic Health Records to when available or participant self-reported. • Clarified Table 7.1 • Updated REC reference • Clarifications of AEs reporting in section 8.2.1 and 8.2.3
V4 31 JUL 2025	• Addition of self-referral option in Section 5.1 • Added Social Media to the self-referral path in section 7.2 • Changed wording to using secure transfer system, rather than specifically SafeSend in Section 5.2, 7.6.2 and 7.6.4 • Clarification that the exclusion criteria also includes confirmed pancreatic cancer or cyst in Section 5.4. • Addition of SAFE-D website address in Section 7.2 • Addition of data collection for participants who opt in to future health questionnaire related research in Section 7.6.1 and 7.6.4 • Clarification that the clinical study team may contact participants by phone to inform of a detected result in Section 7.6.4

V5 01 Dec 2025	• Clarification that the study population also includes individuals with a raised Haemoglobin A1c (HbA1c) (≥ 48 mmol/mol or 6.5%) instead of, or in addition to, a recent diagnosis of type 2 diabetes. • Clarification that members of the clinical study team may contact participants to offer assistance with booking an appointment. • Extension of the rebleed request window to 90 days from consent • Addition of a separate Sample Rebleed Request section 6.2 and rebleed request if it is deemed unlikely that an Avantect results can be generated (incl. <4mL in total or haemolysis plasma) • Extension of the time-frame for the T1 and T2 visit to 6 months or 12 months +/- 4 weeks, respectively • Addition of optional reminder invites sent to invited participants • Clarification that participants with a "detected" test result but later found to be ineligible will still be referred for pancreatic evaluation. • Clarification of device deficiency reporting in section 8.1 – 8.5.
V6 18 MAR 2026	• Study redesign to single arm interventional cohort study throughout including study title • Inclusion of upgraded Avantect v2 test including changes to Statistics and Data analysis section 9 • Reduction in sample size to 5,000 participants including changes to Stats section 9 • Moving pancreatic cancer respectability rate from primary to secondary objective • Self-reporting of type 2 diabetes diagnosis and/or elevated blood sugar levels removed. Now needs to be evidence based. • Initial elevated HbA1c >200 days excluded, except for gestational elevated HbA1c in section 5.3 • Addition of BMI >40 as exclusion criteria in section 5.4 • Removal of current chronic or acute oral or systemic steroids as exclusion in section 5.4 • Clarification of initial elevated HbA1c within 200 days of recruitment is included throughout. • Clarification of study participation if study visit missed (section 7.1)

	• Inclusion of collection of 6-item STAI data over the phone should a participant be unavailable for an in-person visit in section 7.1, 7.6.2 and 7.6.3. • Inclusion of more locations for study activities such as participants own home in section 5.2 • Clarification of recurrent EHRs searches throughout the study in section 7.2 • Clarification about how to share Screening Logs in section 7.3.1 • Removed randomisation from section 7.4 • Removed section 7.5 "Blinding and procedure for unblinding" • Clarification of referral paths (direct to HPB centre or via participants own GP) in section 7.7.1 • Removal of interim analysis throughout • Clarification that scan results from all scanned participants will be shared with the Study MDST in section 7.8 • Clarifications around how suspected pancreatic cancer found by study MDST are communicated with the local MDT. • Clarifications around the process for local MDT reporting of incidental findings to the participant in section 7.10 • Clarifications around data collection for the different withdrawal levels in section 7.11 • Updates to SAE reporting for device studies in section 8 • "Method of Randomisation" section replaced with a new section "Cross-over of Pilot study participants" (section 9.1) describing that collected and stored samples from all Pilot study participants will be analysed on the latest MHRA approved version of the Avantect test. • Removed CT scan only if MRI is contraindicated. Now states MRI or CT scan throughout. • Description of suitable clinical outcome data for comparisons in section 9.4.1 • Addition of participant payments as contribution toward travel costs for rebleeds and scans in section 12.4 • Addition of ability to evaluate and publish T0 data on test sensitivity and specificity in section 18

	• Changed site to location, amendment to modification and subject to participant throughout in line with new GCP regulations • Clarifications in Data Management section 14
V7 01-MAY-2026	• Reconsent of Pilot study enrolled participants at their next study visit was added to section 5.2. • Clarification that only Avantect test v2 results will be included in study analysis once all collected sample from participants recruited to both study arms of the Pilot study have been reanalysed on Avantect test v2, in Section 9.1. • More details around how participants will be informed about the study design change was added to Section 9.1. • Updated sample collection kit manufacturing company details.