SAFE-D

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

A randomised trial to evaluate the cfDNA Pancreatic Cancer test (Avantect) in the early detection of pancreatic cancer in patients with newly diagnosed diabetes mellitus

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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 amendments may be necessary. These will be circulated to investigators in the trial, but sites 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 amendments of the clinical trial regulations, GCP guidelines, ISO 20916:2024, the Sponsor's (and any other relevant) SOPs, and other regulatory requirements as amended.

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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
IDMC	Independent Data Monitoring Committee
DMP	Data Management Plan
DNA	Deoxyribonucleic acid
EHR	Electronic Health Record
GCP	Good Clinical Practice
GP	General Practitioner
HbA1c	Haemoglobin A1c
HPB	Hepatobiliary
ICF	Informed Consent Form
IPMN	Intraductal Papillary Mucinous Neoplasm
ISF	Investigator Site 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	Patient 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
SIV	Site 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 15,000 male and female participants between the age of 50-84 years with newly diagnosed type II diabetes mellitus (within previous six months) across the UK.
Primary Objective:	• Pilot - evaluation of recruitment feasibility. If successful, this will be followed by two study stages involving cumulative participant recruitment: • Study stage 1 – interim analysis of co-primaries sensitivity and specificity of Avantect test for pancreatic cancer, pancreatic cancer resectability rate • Study stage 2 – final analysis of co-primaries sensitivity and specificity of Avantect test for pancreatic cancer, pancreatic cancer resectability rate
Secondary Objective:	• To evaluate the Avantect test in detecting pancreatic cancer across the pilot, study stage 1 and study stage 2 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 cancer (five-year survival 5-7%). Early detection and treatment could significantly improve overall survival. It is known that people who develop new type II 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 intended for the qualitative detection of the presence or absence of an abnormal 5-hydroxymethylcytosine (5hmC)-based epigenomic and genomic signature in plasma cell-free DNA (cfDNA) derived from peripheral whole blood collected in a Streck® blood collection tube. The Avantect test may aid in

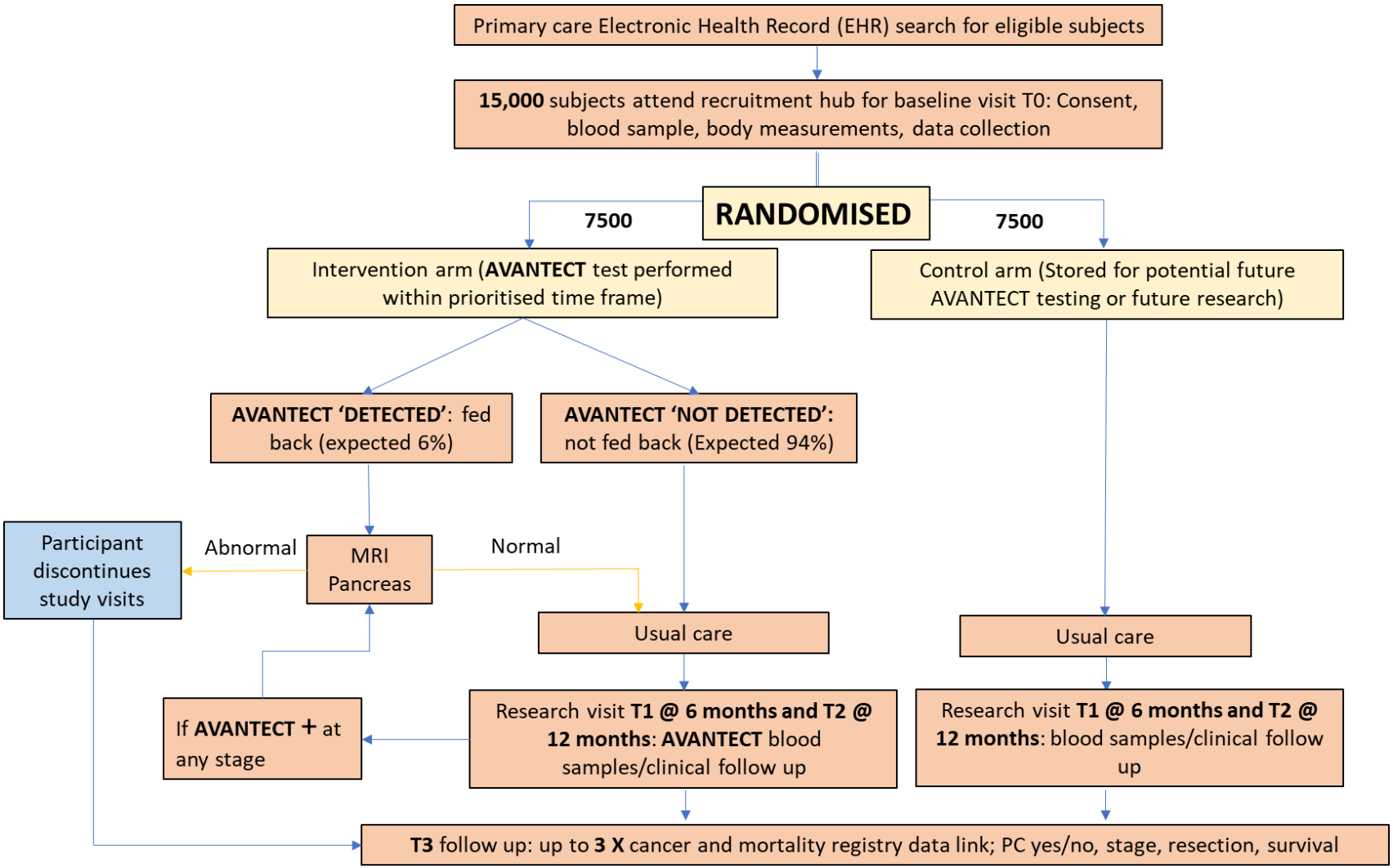
	identifying occult pancreatic cancer in patients with new onset type II diabetes who are 50 – 84 years old and, following additional diagnostic imaging, could enable earlier treatment for pancreatic cancer which may increase survival rates.
Clinical Performance Study Design:	Prospective, single blinded interventional randomised multicentre study
Sample size:	Up to 15,000 participants across the UK in the following stages: • Pilot: target 800 participants • Study stage 1: up to an additional 5,600 participants • Study stage 2: up to an additional 8,600 participants There will be a data driven 'stop-go' decision at the end of each stage before progressing to the next stage.
Treatment/Intervention:	Participants will be blindly randomised into two arms; • Intervention arm: 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. • Control arm (Standard of Care [SoC] arm): Participants will receive the current standard of care for diabetes management. Samples will be used for potential future Avantect testing and/or future research.
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: 36 months Total study duration (including 12m analysis and report writing): 7 years

URL for Database:	https://www.imedidata.com
URL for randomisation:	https://www.imedidata.com

Primary Study Endpoints:	Pilot: Recruitment rate Study stage 1 & 2: Sensitivity and specificity of Avantect test for detecting pancreatic cancer, pancreatic cancer resectability rate

Secondary Study Endpoints:	Secondary endpoints (pilot and study stage 1 and 2 combined) will include pancreatic cancer stage shift, PPV, NPV and proportion of pancreatic cancer patients undergoing surgical resection
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 Sites:	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 II 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).

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. 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%.

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.

The ClearNote Health Avantect pancreatic cancer 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 patients with NOD who are 50 years old or older. These patients can then benefit from additional diagnostic imaging to rule out PC.

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 early and improve resection rate. 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 trial participants and future newly diagnosed diabetes mellitus patients.

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 randomised single blinded interventional study in patients with newly diagnosed diabetes mellitus 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 (CT-scan only if MRI is contraindicated). 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 two stages:

- Pilot: The goal of the six-month pilot is to determine if the enrolment strategy (identifying eligible subjects 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 study stage 1 and 2. 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 sites).
- 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 study stage 1 and 2 will be assessed by the Trial Steering Committee based on recruitment during the pilot
- Study stage 1 will enrol an additional 5,600 NOD participants with the primary objective to evaluate sensitivity and specificity of the Avantect test in detecting pancreatic cancer in 3,200 intervention arm participants with 1 year of follow-up for futility and efficacy.
- Study stage 2 will enrol an additional 8,600 participants to make a total of 15,000 NOD participants with the primary objectives of evaluating sensitivity and specificity of the Avantect test in detecting pancreatic cancer in intervention arm participants, and comparing the proportion of pancreatic cancers deemed resectable across the intervention and control arms.

2.2 PRIMARY ENDPOINTS:

- Pilot: Recruitment rate - number of NOD 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 patients per month in the last 3 months of the pilot.
- Study stage 1 and 2:
    - Sensitivity of Avantect test for detecting PC – number of individuals in the intervention arm with one or more Avantect "detected" test results and PC divided by the number of individuals in the intervention arm with PC.
    - Specificity of Avantect test for ruling out PC – number of individuals in the intervention arm 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 in the intervention arm with no diagnosis of PC.
    - Resectability rate – number of individuals with PC deemed resectable by the study multidisciplinary team (MDT) divided by the number of PCs.

2.3 SECONDARY STUDY OBJECTIVES AND ENDPOINTS

To evaluate the Avantect test in detecting pancreatic cancer in the entire study cohort (Pilot + Study Stage 1 + Study stage 2 combined) in terms of:

- Stage shift (the proportion of pancreatic cancers diagnosed at stage I/II out of all pancreatic cancers) - compared between arms
- PPV – intervention arm only
- NPV – intervention arm only
- Proportion of pancreatic cancer patient undergoing surgical resection – compared between arms

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

STUDY STAGE 1 and 2 (analysis inclusive of pilot):

	Objective	Outcome Measures	Summary method(s)
Primary	To estimate the proportion of PCs deemed resectable	Resectability rate	Percentage of PCs deemed resectable by the study MDT [compared between arms]
	To estimate the sensitivity of the Avantect test in detecting PC	Sensitivity	Percentage with PC diagnosed who have an Avantect "detected" result [within intervention arm]
	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 [within intervention arm]
Secondary	To determine the effect of the Avantect test on PC stage shift	Stage shift	Percentage of PCs diagnosed at stage I/II [compared between arms]
	To estimate the PPV of Avantect for detecting PC	PPV	Percentage with an Avantect "detected" result who have PC diagnosed [within intervention arm]

	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 [within intervention arm]
	To estimate the proportion of PCs that are resected	Resection	Percentage with PC who underwent resection [compared between arms]
Exploratory	To estimate the time from NOD diagnosis to PC diagnosis	Time to diagnosis	Kaplan-Meier curve Hazard ratio [within intervention arm]
	To estimate the overall survival of study participants	Overall Survival	Kaplan-Meier curve Hazard ratio [compared between arms]
	Assess the effect of the Avantect test on state anxiety over time	6-item STAI	T-test or non-parametric alternative if suitable [compared between arms]
	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. [within intervention arm]

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

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 site, 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 sites according to Laboratory Manual. Plasma isolation will be executed by the WISH Laboratory according to specific SOP.

All study site personnel performing blood collection procedures will undergo training (e.g. via the study SIV) 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, single blinded interventional randomised controlled multicentre study with a pilot followed by 2 stages of recruitment. 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). 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 subjects, within 12 -18 months from type 2 diabetes diagnosis. Therefore, the study strategy is to test NOD patients at baseline (T0) (within 6 months from diabetes diagnosis) and thereafter at 6 and 12 months from T0 to ensure that the Avantect test is used in the period before pancreatic cancer symptoms usually present.

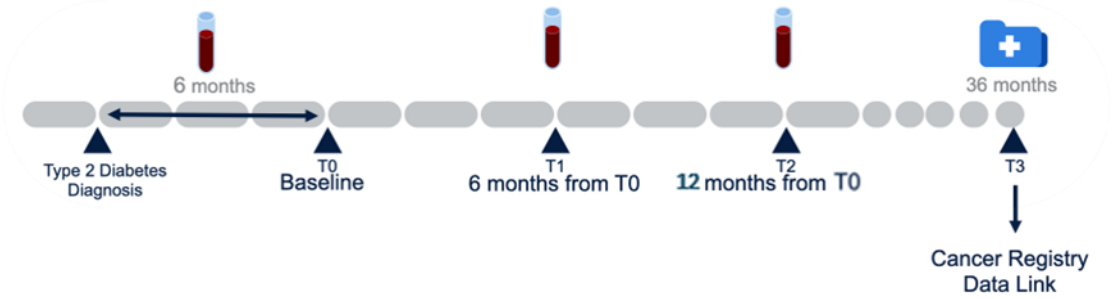


Figure 1: SAFE-D visit schedule figure

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 subjects with a recent diagnosis of DM (within six months) will be eligible for enrolment. Subjects attending SDSCs will also be eligible for enrolment. In addition, participants may self-refer for the study via the SAFE-D booking website. Participants who sign the consent form will be considered enrolled.

The study is expected to enrol 15,000 participants over 36 months, including a six-month pilot study to evaluate recruitment feasibility and to estimate the number of participating sites required, and an interim analysis for futility and efficacy (Stage 1). Participants will remain in the study for 12 months, attending study visits at enrolment (baseline (T0)) and at six (T1) and 12 months (T2) post enrolment. There may be planned recruitment stops between the Pilot and Stage 1 of the study to allow for a data driven 'stop-go' decision should this decision not be concluded in the lead up to Stage 1. Recruitment will continue once the Stage 1 interim analysis requirements have been met and will continue unless that analysis concludes that the intervention is futile. Total study duration is expected to be 7 years 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 site, 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 other facility staffed and equipped for participant interactions, consenting and blood sample collection) 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, 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.

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, a copy will be given to the participant, a copy stored in the participant's medical notes, the original filed in the site trial file and a copy of the consent form be sent to the Southampton Clinical Trials Unit (SCTU) using secure transfer systems, such as the University of Southampton's SafeSend service, 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. Haemoglobin A1c (HbA1c) ≥ 48 or 6.5% and/or confirmed type II DM diagnosed within the last 180 days (+20 days flexibility allowance)
3. Willing to provide up to 30 mL of blood for each study visit
4. Willing and eligible to undergo MRI scan (or CT scan if MRI is contraindicated)
5. Understands the study process and is willing to take part in the study and sign the informed consent form

5.4 EXCLUSION CRITERIA

6. Prior type I or type II DM diagnosis > 6 months
7. A history of pancreatic cancer, pancreatic neuroendocrine tumour (pNET) or Pancreatitis
8. Under investigation for or confirmed pancreatic cancer / pancreatic cyst

9. Any known pancreatic surgery (not including ERCP), or other major surgery requiring anaesthesia within 3 months
10. Any invasive solid or haematological cancer in the past 3 years, including cancer recurrence after treatment in the last 3 years
11. Current chronic or acute oral or systemic steroid use within 3 months of initial HbA1c or diabetes diagnosis (estimate rather than accurate)
12. Blood transfusion within 1 month
13. Solid organ transplant recipient
14. Currently pregnant
15. Needing dialysis

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 sites. (See section 6.1 for storage and analysis of clinical samples)
A detailed Laboratory Manual will be provided to sites 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 future reaserch depending on the study arm, 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 WISH Laboratory. Samples will be sent from sites pseudo-anonymised and fully labelled with a patient and time-point specific kit ID number together with a test requisition form allowing for patient specific reconciliation once received at the WISH laboratory. All sites will keep a record of all samples collected, stored, and shipped. A detailed Laboratory Manual will be provided to sites which will include details regarding sample preparation, handling, shipping and tracking.

In the event of postal delays, any Streck sample received at WISH laboratory 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 6 months from diabetes diagnosis. If T1 or T2 repeat blood collection is requested, it must be within 28 days of the initial sample collection date. A repeat draw can also be requested if a sample is damage during transport.

Streck® tubes will be processed to plasma within 24 hours of receipt in the WISH laboratory 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 collected from patients randomised to the invervention arm 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 patient 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 28 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 6 months of diabetes diagnosis timeframe 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. For participants assigned to the control arm, samples will be kept for future potential Avantect testing and/or future research.

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

7. STUDY PROCEDURES

7.1 SCHEDULE OF OBSERVATIONS AND PROCEDURES

Visit:	Baseline (T0)	T1	T2	T3
Time:	Within 6 months from Diabetes mellitus (DM) diagnosis*	6 months after T0	12 months after T0	Three occasions over the study duration from consent (T0)
Eligibility evaluation	X			

Informed consent	X			
Patient 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).

*In the SAFE-D study "date of DM diagnosis" refers to the elevated HbA1c date

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

b: 6-item STAI

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 participant self-reported.

7.2 RECRUITMENT METHODS

Participants will be identified via the strategies described below.

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

Commercial recruitment platform collaborators will search patient EHR at participating GP practices (Participant Identification Centres (PICs)) and contact eligible subjects 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 participant information sheet (PIS) and further information. Interested subjects 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.

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

Patient 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). Eligible subjects 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 subjects 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.

- **From Specialist Diabetes Service Centres**

Newly diagnosed diabetes patients referred to SDSCs will be invited to take part in the study. Eligible subjects will be contacted by SDSC staff via email or letter inviting them to participate with a link to the study website where they can access the PIS and further information. Interested subjects 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-referral**

Participants may also self-refer to the study following viewing study information found on the study website, on social media or displayed in Primary Care locations. Interested subjects 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.

7.3 SUBJECT 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 subjects. Identified eligible subjects will be contacted by text, email or letter, or approached in person when attending SDSC, with study information and invited to participate.

7.3.1 Screen Failures

Patients 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 site, together with reasons for exclusion/decline. The screening log will be filed in the Investigator Site File (ISF).

7.4 REGISTRATION/RANDOMISATION PROCEDURES

Following informed consent, participants will be assigned a unique patient 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 site code, and the last five digits consisting of sequential numbering provided through imedidata.com. The patient identification number will be added to the signed consent form.

Following their T0 visit, participants will be randomised to the control or intervention arm (1:1 ratio) via www.imedidata.com by a member of the WISH Laboratory team as specified on the delegation log. Participants will not be informed which arm they have been randomised to. The randomisation list will be pre-generated with permuted blocks of differing lengths.

7.5 BLINDING AND PROCEDURES FOR UNBLINDING

7.5.1 Blinding

After the T0 visit, participants will be randomised to either intervention or control arm as described in 7.4. Participants will remain blinded to their allocation unless the condition stated in section 7.5.2 is met.

7.5.2 Planned Unblinding

Only participants in the intervention arm who have Avantect "detected" test results (and their GPs) will be informed of their Avantect test results.

7.6 TRIAL PROCEDURES

7.6.1 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 sites 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 sites 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, participants will be randomised to either the control or intervention arm. GPs will be notified if patients under their care are taking part in the study but will remain blinded at this stage.

7.6.2 Timepoint T1 (6 months after T0):

Sample Collection:

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

Data Collection:

- 6-item STAI Inventory questionnaire
- Selected pre-existing conditions of interest and concomitant medications
- Weight and waist measurements

7.6.3 Timepoint T2 (12 months after T0):

Sample Collection:

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

Data Collection:

- 6-item STAI Inventory questionnaire
- Selected pre-existing conditions of interest and concomitant medications
- Weight and waist measurements

7.6.4 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 three

occasions: once 6,400 participants have been recruited, once 15,000 participants have been recruited, and at 3 years post last participant recruited.

Data Collection from Cancer Registry:

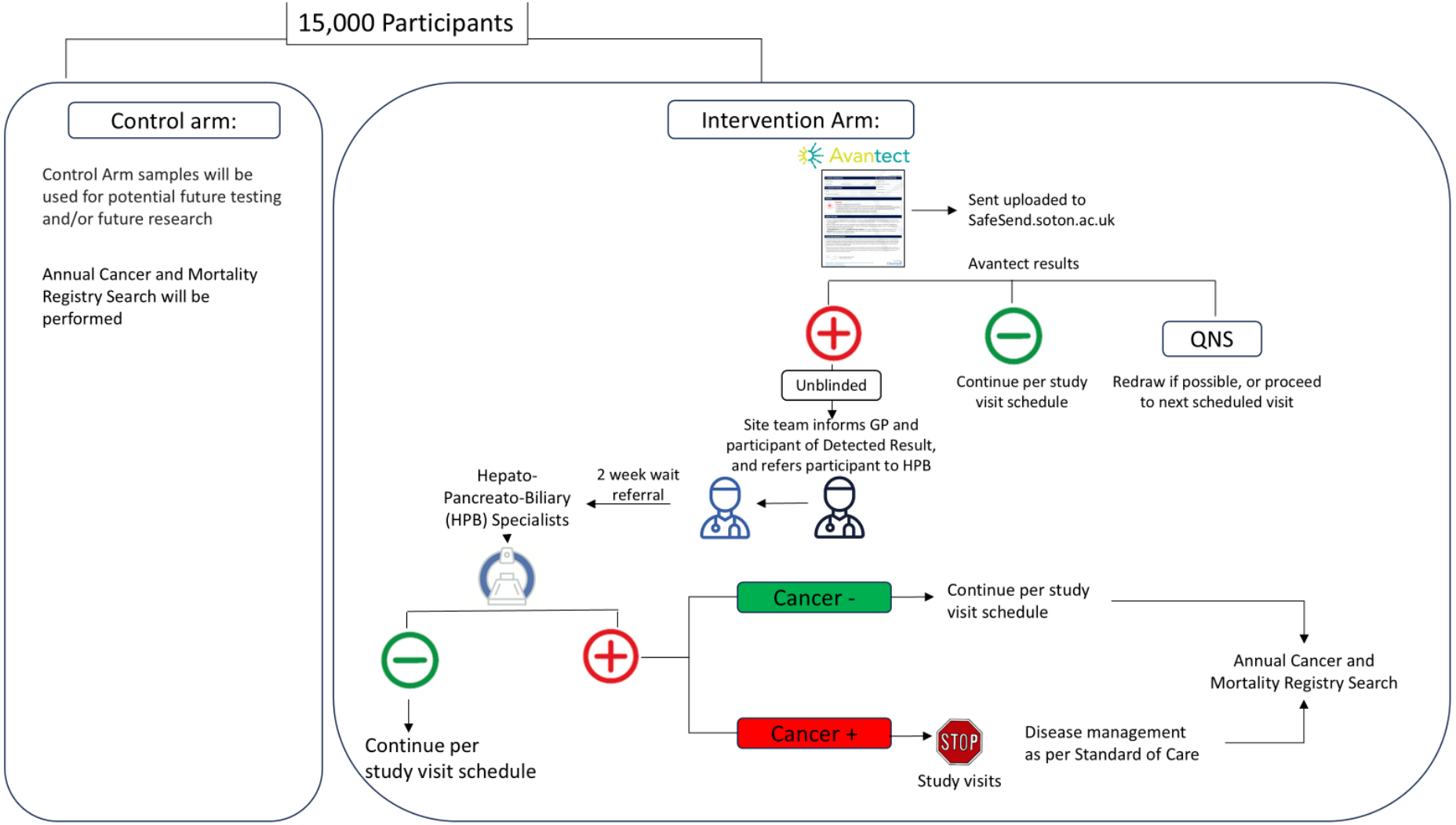
- Any cancer diagnosis (ICD10 C00-D48)
- Date of cancer diagnosis
- Site of cancer diagnosis
- Stage of cancer at diagnosis
- Histology of cancer
- Survival status
- Cancer treatments

Data Collection from Mortality Registry:

- Date of death
- Causes of death

The local site study 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 site 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 site 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 sites to contact participants with any Avantect "Detected" results by post. Phone numbers will be used by sites 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 sites 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.

7.7___ AVANTECT TEST RESULT MANAGEMENT SCHEMA



7.8 AVANTECT OUTCOMES AND FOLLOW UP FOR PARTICIPANTS IN THE INTERVENTIONAL ARM

7.8.1. Detected

The CI will request the SAFE-D site team to notify participants in the intervention arm 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 site team to arrange an urgent suspected cancer referral (tumour specific pathway referral) to local hepatobiliary (HPB) service Local Collaborator for a pancreas MRI (or CT if MRI is contraindicated) and imaging will be scheduled as per standard of care for suspected cancer pathway.

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

7.8.2. Not detected

Participants in the intervention arm 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.

7.8.3. 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).

7.9 IMAGING RESULTS

7.9.1 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.

7.9.2 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 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 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.

7.9.3 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 in the intervention arm with Avantect “detected” test results and 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)

7.9.4 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 ultra sound scans (EUS) depending on the local HPB multidisciplinary team (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 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 multidisciplinary team (MDT). To determine resectability for the study endpoint, the MRI and CT scans will be reviewed by the multidisciplinary study team (MDST) and will neither influence patient care nor be fed back to the local MDT team.

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.

7.9.5 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.
- 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.

7.10 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.

7.11 DEVELOPMENT OF OTHER CANCER TYPES AND INCIDENTAL FINDINGS

In the event of any significant incidental findings on imaging, the participant would be informed of such findings by the local PI and study team, who will also inform their GP with any follow up recommendations by the local MDT as per usual clinical care.

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.

7.12 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.

A complete withdrawal from the trial should be recorded as end of study for the participant in the relevant eCRF and in their medical record and 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 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 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 patient management decision, unintended disease or injury or any untoward clinical signs (including an abnormal laboratory finding) in subjects, 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 subjects, 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 patient 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 subject 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 notes:

All Adverse Events (AEs) from the date of informed consent to the end of participation in the trial should be recorded in the *patient's medical notes* as per usual practice.

b) Recording in trial database:

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 subjects with pre-existing kidney failure

Any other adverse events 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

Device deficiencies (related to the blood sampling kits) occurring at clinical sites will be collected on the device deficiency eCRF.

Trial clinicians will assess whether or not these *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

If the device deficiency fulfils the reportable criteria above, then the event will be reported to SCTU using the Serious Adverse Event Report Form for assessment and onward reporting as appropriate.

Device deficiencies occurring at either WISH Lab (involving blood sample tubes) or ClearNote Health (involving the Avantect lab assay under investigation) will be recorded on a CRF outside of the RAVE database (both labs will be provided with written instructions for reporting of all safety events). 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

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.

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 patient's medical notes).

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 • Harms to the subject 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.*	SAE
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	Anticipated or Unanticipated Serious Adverse Device Effect (ASADE or USADE)

	• 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 subject 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, 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. Sites at which participant blood samples are collected, as well as both labs (WISH Lab 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 patient's medical notes, 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 in the trial eCRF. If they meet the reportable criteria in section 8.2.2. (and do not meet the exceptions listed in 8.2.2.), these will also be reported as serious adverse events using the 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 site 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 MHRA. Additionally, SAEs 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 patient’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 patient becomes pregnant whilst participating 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). SCTU will report these to MHRA on behalf of the manufacturer.
6. Ensuring that the expedited reporting of SAEs and reportable device deficiencies to the Competent Authority (MHRA in the UK) via MORE portal, are within the required timelines.
7. Ensuring expedited reporting of related and unexpected serious adverse events to the REC within the required timelines.

8. Authoring and submission of Quarterly Summary Reports to the Competent Authority (MHRA in the UK) via MORE portal, within the required timelines.
9. Notifying Investigators of related and unexpected serious adverse events that occur within the trial.
10. Notifying PIs of updates to the Reference Safety Information for the trial.

8.6.4 WISH Laboratory and ClearNote Health laboratory

Each laboratory is responsible for:

1. 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 MHRA within the required timelines.

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.

8.8 QUARTERLY SAFETY REPORTS (QSR)

SCTU (on behalf of the manufacturer) will provide quarterly summary reports to the MHRA via the MORE portal, following internal standard operating procedures as well as the latest MHRA guidance. The first report is to be submitted as soon as possible after the end of the first quarter after the first patient sample has been tested. In this study, “first treatment” will be the day that the first patient has their first visit.

9 STATISTICS AND DATA ANALYSES

9.1 METHOD OF RANDOMISATION

Participants will be randomised to the control or intervention arm (1:1 ratio) via an independent, web-based system (www.imedidata.com) by a delegated member of the WISH laboratory team. The randomisation list will be pre-generated with permuted blocks of differing lengths. Participants will remain blinded until planned unblinding occurs (see section 7.5.2).

9.2 SAMPLE SIZE

Upon conclusion of the pilot, further recruitment to the study will occur with a planned interim analysis for futility and efficacy. Participants in the pilot study will continue to have their data analysed. The planned interim analysis is referred to as ‘stage 1’ analysis for convenience. The final analysis is referred to as ‘stage 2’ analysis. In each stage, there are three co-primary endpoints:

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

3. resectability of diagnosed PCs

In the stage 1 interim analysis, these endpoints will be assessed within the intervention arm, as more information will be available on the diagnostic status of this group. In the stage 2 final analysis, the sensitivity and specificity of the test will be estimated within the intervention arm, whereas resectability will be compared between the arms.

The anticipated prevalence of a pancreatic cancer diagnosis within 3-years of follow-up within this population is 1%[3]. Conservative estimates place the anticipated sensitivity of the Avantect test at 65% 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 hoped that the Avantect test can improve the resectability of pancreatic cancers from a rate of 14% in usual care to 40% in the intervention arm (just over a 2.5-fold increase).

With three 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 $90\%^{(1/3)}$ = 96.5%. Following guidance from Korevaar and colleagues[17], the analysis will consist of a one-sided test at an cumulative alpha of 0.05 at the final analysis. Because there is an interim analysis at stage 1 for efficacy and futility, the one-sided significance level changes at the interim and final analysis.

Two of the three co-primaries are metrics of test accuracy. 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 2.5%.

Using the PropTestPower function in the R package EnvStats, it was determined that 73 individuals with pancreatic cancer are required in each arm to detect a change of resectability from 14% in usual care to 40% in the intervention arm. At the stage 2 final analysis, allowing for interim analysis, the overall power would be 96.5%. Allowing for 2.5% loss to arrive at the Per Protocol population (see section 9.4), this increases to 75 cases per arm (150 total), which at an event rate of 1% leads to a recruitment target of 7,500 per arm (15,000 total). As only samples from the intervention arm are to

be tested for the purpose of the analysis, with an anticipated test sensitivity of 65% and specificity of 95%, this leads to the following confusion matrix in the intervention per protocol group (7,312):

		Diagnostic status	
		Has PC diagnosis	Does not have PC diagnosis
Avantect test result	Detected	48	362
	Not detected	25	6,877

With 73 cases of pancreatic cancer of which 48/73 = 65% were detected by the Avantect test, this would be sufficient to rule out a sensitivity lower than 42 % in the stage 2 final analysis at 96.5% power. On discussion with the FDA, a specificity of 92% would be considered acceptable within this clinical context. With 6,877 individuals without a pancreatic cancer diagnosis of which 6,877/7,239 = 95% are expected to be detected by the Avantect test, more than 99% power is achieved to rule out a specificity lower than 92%.

Definition of 'promising result' in study stage 1 to guide progression to study stage 2

An analysis for futility and efficacy will be conducted once 3,200 individuals randomised to the intervention arm have returned for the third blood-draw (T2) in order to obtain cancer outcome data from the cancer registry. This amounts to 43.8 % of the total information accural in the intervention arm, accounting for 2.5% not qualifying for the Per Protocol population (see 9.4; 3,200/7,312). All individuals with one or more Avantect "detected" test results will be included as positive predictions. Individuals whose Avantect test results are all "not detected" will be included as negative predictions. Based on a cumulative one-sided alpha of 0.05 and 96.5% power for the three co-primary outcomes, the futility and efficacy thresholds at stage 1 interim analysis are detailed in the table below. If all study endpoints are deemed futile, or in the scenario that all study endpoints are deemed efficacious the study will stop at this stage. If all of the study endpoints are deemed promising then the study will continue to stage 2. If there is a combination of results, the Trial Steering Committee (TSC) and IDMC will decide whether the study progresses to stage 2.

	Expected proportion	Futility threshold at stage 1	Promising result range at stage 1	Efficacy threshold at stage 1
Sensitivity	65%	<46.5%	46.5% to 63.1%	>63.1%
Specificity	95%	<92.0%	92.0% to 94.9%	>94.9%
Resectability	40%	<21.0%	21.0% to 38.1%	>38.1%

9.3 STUDY TIMEPOINTS

There will be three timepoints for blood collection: at baseline (T0), 6 months +/- 2 weeks post-baseline (T1), and 12 months +/- 2 weeks from baseline (T2). For each study timepoint, the Avantect test will be conducted. For samples collected from participants assigned to the intervention arm, the Avantect test 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") in the intervention arm will undergo diagnostic pancreas imaging. Samples collected from participants assigned to the Control arm will be stored for potential future Avantect testing or future research.

The study design comprises a pilot and two study stages:

- Stage 1 Analysis will be carried out 6 months after the T1 visit for 3,200 participants in the intervention arm. Only participants followed up for a minimum of 6 months after the T1 visit in the intervention arm will be included in this analysis.
- Stage 2 Analysis will be carried out after 3-year follow-up data has been collected for all 15,000 participants.

In addition, during the study annual readouts will be provided to the data monitoring committee to monitor study progress and inform on decisions to continue or stop the study.

The diagnostic performance of the Avantect test results will be summarised according to the pancreatic cancer diagnoses collected by the point of analysis. The stage shift, and resection rate of pancreatic cancer will be summarised by arm. For this purpose, a positive test at any timepoint will be considered a 'positive prediction' e.g., if a participant has a negative result at T0, but a positive result at T1, their overall prediction will be considered as at-risk of pancreatic cancer.

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. All individuals in the control arm will qualify for the Per Protocol population. Individuals in the intervention arm will qualify for the Per Protocol population if they have at least one analysable Avantect test result (i.e. either "Detected" or "Not detected"). Per Protocol population will be analysed according to the original randomisation

group even when other aspects of the protocol are not followed e.g.unplanned cross-over, study withdrawal. It is expected that 98.8% of the randomised population will qualify for the Per Protocol population.

The co-primary outcomes are Avantect sensitivity and specificity in detecting PC, and resectability rate. Sensitivity is defined as the proportion of participants in the intervention arm with one (or more) Avantect "detected" test results who have pancreatic cancer diagnosed via imaging in relation to all individuals in the intervention arm who had pancreatic cancer diagnosed. Specificity is defined as the proportion of participants in the intervention arm 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 in the intervention arm who did not have a pancreatic cancer diagnosis. Resectability is defined as the proportion of PCs deemed resectable by the study MDT divided by the number of PCs and will be compared between arms. For all co-primary endpoints, a logistic model will be used to estimate uncertainty. At the stage 1 interim analysis, due to alpha spending to reach a cumulative total alpha of 0.025 for each co-primary endpoint, a one-sided 98.6% confidence interval will be calculated to estimate the lower-bound of the observed proportion. At the stage 2 final analysis, a one-sided 98.5 % one-sided interval will be calculated instead. Co-primary endpoints will also be assessed for regular oversight meetings, where a one-sided 95% confidence interval will be used.

At the stage 1 interim analysis, co-primaries will be considered 'futile', 'promising' or 'efficacious' according to the following table:

	Expected proportion	Futility threshold at stage 1	Promising result range at stage 1	Efficacy threshold at stage 1
Sensitivity	65%	<46.5%	46.5% to 63.1%	>63.1%
Specificity	95%	<92.0%	92.0% to 94.9%	>94.9%
Resectability	40%	<21.0%	21.0% to 38.1%	>38.1%

At the stage 2 final analysis, the sensitivity co-primary will be considered successful if a sensitivity of 49% can be ruled out with a one-sided p-value of 0.03 among participants in the intervention arm. Specificity will be considered successful if a specificity of 92% can be ruled out with a one-sided p-value of 0.03 among participants in the intervention arm. Resectability will be considered successful if the resectability rate in the intervention arm is higher than the rate in the control arm at a one-sided p-value of 0.03.

Secondary outcomes, in order of importance, are defined as follows, which all are calculated with a minimum of 90% power:
Stage shift - The analysis will be conducted by comparing the proportion of PC cases diagnosed at stage I/II vs III/IV between the intervention and control arms. A proportion of 60% (44/73 PCs) is expected in the intervention arm versus 35% (26/73 PCs) in the control arm, which provides 90% power at a one-sided alpha of 0.05. Stage shift will be considered successful if the proportion in the intervention arm is higher than the rate in the control arm at a one-sided p-value of 0.05.

PPV in detecting PC - The analysis will be conducted within the intervention arm. With a sample size of 7,500, PC prevalence of 1%, and 2.5% lost from the per protocol population, there will be an expected 410 individuals with an Avantect "detected - abnormal" result. 11.6% (48/410) 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 - The analysis will be conducted within the intervention arm with a sample size of 7,500, PC prevalence of 1%, and 2.5% lost from the per protocol population, will be an expected 6,902 individuals without an Avantect "detected - abnormal" result. 99.6% (6,877/6,902) 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 resection between the intervention and control arms. With a sample size of 15,000, PC prevalence of 1%, and 2.5% lost to follow-up, there will be an expected 73 cases of PC in each arm. It is assumed that 5% of those deemed resectable will not undergo resection, for an expected rate of 38% (28/73) in the Intervention arm versus 13% (9/73) in the control arm. Resection rate will be considered successful if the proportion in the intervention arm is higher than the rate in the control arm at a one-sided p-value of 0.05.

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 to determine the hazard ratio (and 95% confidence interval) between groups. This will be supported by a Kaplan-Meier plot for each group, median survival (and 95% confidence intervals), and estimates of 3-year survival (T0-T3) (alongside the difference in proportions and 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. Two-sided p-values will be presented for exploratory outcomes.

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 subject's rights, safety and well-being, or the scientific integrity of the clinical performance study. Any deviation occurring at sites 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 sites 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 AMENDMENTS/MODIFICATIONS

The CPSP, PIS, informed consent form (ICF) and other subject 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 amendments to the CPSP will be reviewed and authorised locally in accordance with SCTU procedures. Any amendments 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 patient 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 sites (NHS Trusts or others taking part in this study) are detailed in the Non-Commercial Agreement or other appropriate site-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 SITE PAYMENTS

The payments assigned to the trial sites (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.

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 Trial Steering Committee (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 standardized 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 patient care).

14 DATA MANAGEMENT

Participant data will be entered remotely at site 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 SCTU and site. The site retains a participant identification code list which is only available to site 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 Patient 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). eCRF completion guidelines will be provided to the investigator sites 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 for the study will be available and a Study Schedule with planned and actual milestones, eCRF tracking and central monitoring for active study management created.

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 confirm the data integrity by electronically signing all the eCRFs. 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.

Data may be requested from the Data Access Committee at SCTU. Any request will be considered on a monthly basis.

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 web site, 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 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 site either automatically or manually by SCTU staff via the database. Sites 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 SITE MONITORING

As only sample collection and no Investigation Medicinal Product (IMP) is involved in the SAFE-D trial, no site 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 site 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.

Sites are responsible for archiving the ISF 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.

Individual investigators may not publish data concerning their patients 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). Postcontrast phases include arterial phase axial, venous phase axial, late venous phase axial, and late venous phase coronal.

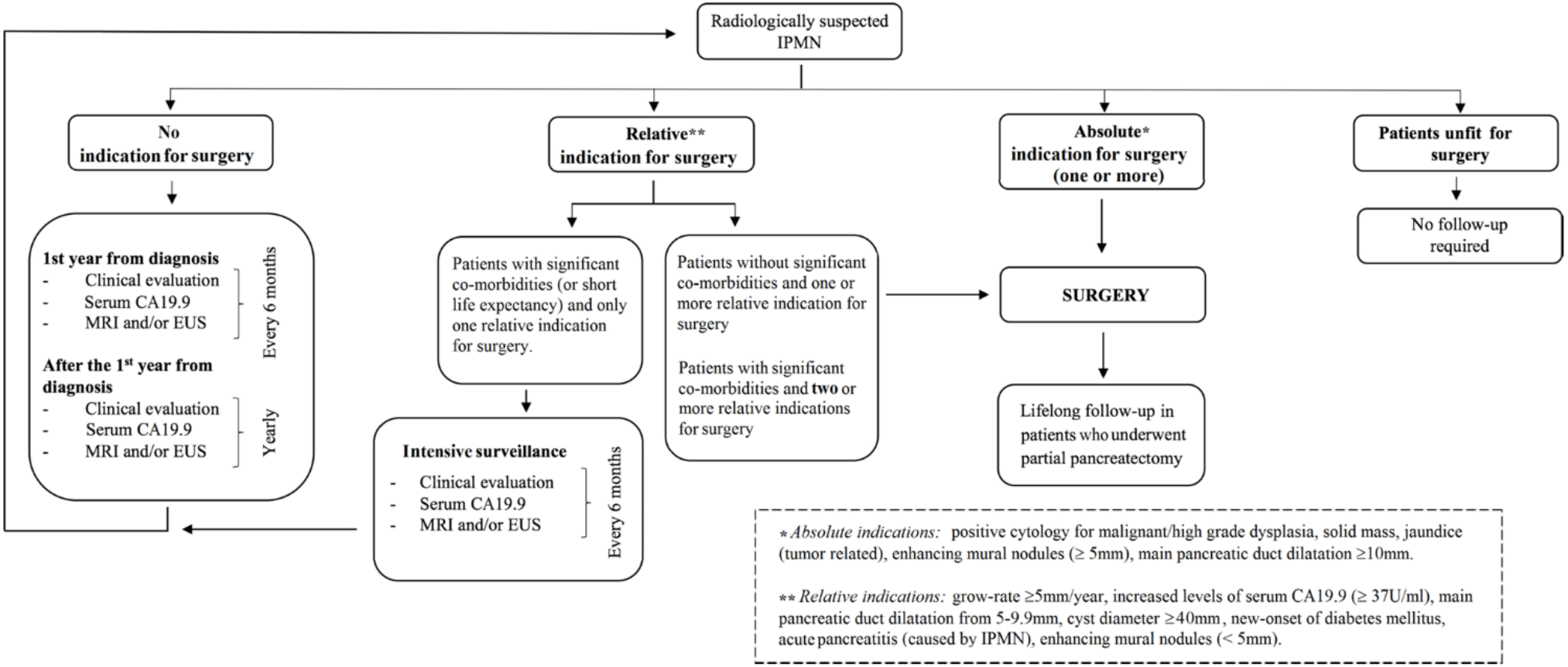
C. Including b values of 50, 500, and 800 s/mm2.

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

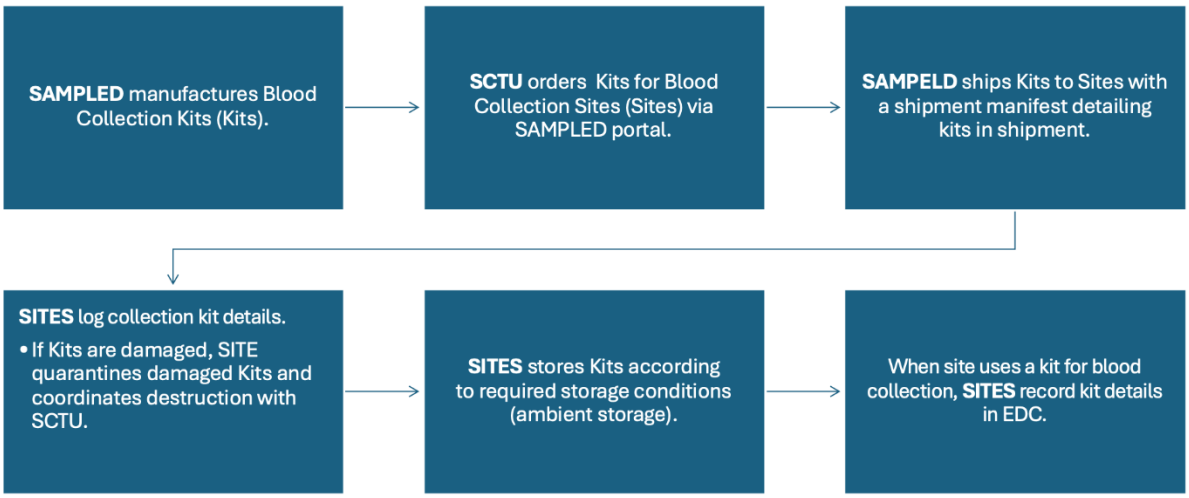
The investigational device for the SAFE-D clinical performance study consists of a laboratory assay (the in vitro diagnostic test) and (for the purposes of the clinical performance study) a blood collection kit (an accessory kit to the IVD device). The laboratory assay does not consist of a kit, but 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 SAMPLED.
Address: 30 Knightsbridge Road, Building 3, Piscataway, NJ 08854, USA
Tel: +1-732273-0699
Email: www.sampled.com

2.2. Number of devices

The number of blood collection kits being manufactured for the purpose of the study is up to 45,000.

2.3. Documentation to be provided by manufacturer

SAMPLED will provide kit quality reports and a shipment manifest to sites 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 SAMPLED to sites

Blood collection kit shipments to blood collection sites will be managed by Southampton Clinical Trial Unit (SCTU). SCTU will order sample collection kits for the sites via SAMPLED portal and SAMPLED will be responsible for the shipment of kits to the sites 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 sites. The number of blood collection kits ordered for each site will be based on recruitment projections. When collection kits need to be replenished, SCTU will place an order via the SAMPLED portal and SAMPLED will send the kits to the blood collection sites.

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 SAMPLED portal.

It is the responsibility of delegated site 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 Site File. It is the site'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 sites in an unsuitable condition, they should be quarantined and kept separate from those that are useable. Unsuitable kits should be destroyed by site as per SOP and documented in the device accountability log.

The SCTU trial team will cross-reference shipment lists and confirmation emails from sites 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 site study staff.

6. Usage and monitoring of medical devices

Kits may be selected at random for use by site staff.

Sites will track which collection kit is assigned to the patient 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 site is the responsibility of the Investigator at each site. However, SCTU will coordinate any process for returns if applicable, and will issue instructions for any actions required at site, including quarantine, return, or disposal of blood collection kits.

9. Warnings / Notes / General Information / Safety

Site investigators retain responsibility for device accountability at their sites. 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