SAFE-D

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

LABORATORY MANUAL

(incl. Device Accountability and Sample Handling & Management)

ISRCTN reference: ISRCTN35242058

Ethics reference number: 25/EM/0016

Sponsor reference number: RHM GSU0292

Chief Investigator: Mr Zaed Hamady

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2. Contact and Mailing Information

For questions regarding this Laboratory Manual, including specimen collection, processing, storage and shipment or the SAFE-D Protocol, please contact*:	
SAFE-D Trial Manager Southampton Clinical Trial Unit (SCTU) MP 131, Centre for Cancer Immunology Southampton General Hospital Southampton, SO16 6YD, UK	**Email:** SAFED@soton.ac.uk **Tel:** 023 8120 5154
*Southampton Clinical Trials Unit (SCTU) opening hours are: Monday to Friday; 9:00am to 5:00pm UK time	
Experimental Cancer Medicine Centre (ECMC) lab shipping address and contact details are as follows**:	
ECMC lab c/o Safe-D Team LF110 Level F, Mailpoint 850 Southampton General Hospital, Tremona Road, Southampton, SO16 6YD	**Email:** SAFEDLAB@soton.ac.uk **Tel:** 02381208136
**ECMC opening hours are: Monday to Friday; 9:00am to 5:00pm UK time	
UK Sponsor	
University Hospital Southampton NHS Foundation Trust Tremona Road, Southampton UK, SO16 6YD	Tel: 023 8120 4989

3. Introduction

SAFE-D is a large prospective, interventional multicentre study for the qualitative detection of the presence or absence of an abnormal 5hmC-based epigenomic and genomic signature in plasma cell-free DNA for the early diagnosis of pancreatic cancer in patients with an elevated HbA1c or new onset type 2 diabetes within the past 200 days.
Following consent, peripheral blood samples will be obtained at up to 3 blood collection visits throughout the study. At each visit the following bloods will be collected;

- 2x10mL Streck tubes for the purpose of early pancreatic cancer detection
- 1x6mL Lithium Heparin tube for metabolomics research

This SAFE-D laboratory manual provides an overview of the process for device accountability and tracking, as well as collecting and posting whole blood samples from SAFE-D Study collection Hubs to the Experimental Cancer Medicine Centre (ECMC) Laboratory in Southampton for processing and onwards shipment to ClearNote Health for on-site storage.

4. Visit Schedule

Study participants will have up to 3 blood collection visits during the study (see Figure 1), T0, T1, and T2. Time point T0 should be within 200 days of type 2 diabetes diagnosis or initial elevated HbA1c. T1 should be 6 months (± 4 weeks) from T0 and T2 at 12 months (±4 weeks) from T0.

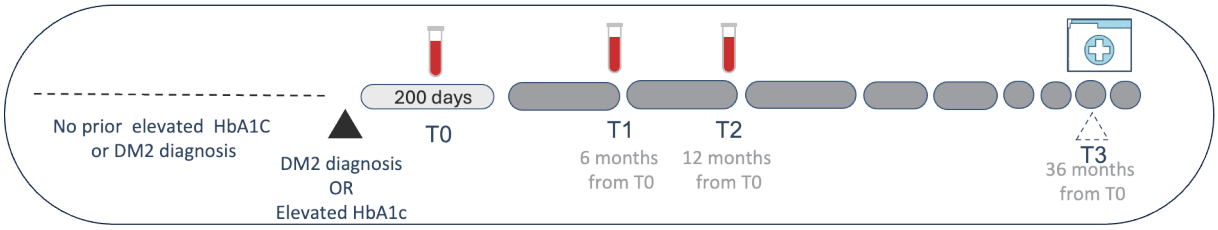


Figure 1 - SAFE-D visit schedule

5. Device Details

The investigational device for the SAFE-D clinical performance study consists of a laboratory assay (the in vitro diagnostic (IVD) 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 (SOP).

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 (Figure 2).

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

Product	Supplier	Catalogue number/identifier
Pre-addressed UN3373 certified posting box	Kaizen Biosciences	Custom bespoke
2 x 10ml Cell-Free DNA BCT Streck blood collection tubes (pre-labelled)	Streck	230244 (x1000) 218997 (x100)
1 Lithium Heparin 6ml blood collection tube (pre-labelled)	BD (fisher scientific)	367885 (x1000) VS367885 (x100)
Biohazard bag	Kaizen Biosciences	Custom bespoke
Absorbent wadding	Kaizen Biosciences	Custom bespoke
Sealable bubble pouch bag	Kaizen Biosciences	Custom bespoke
Security seal sticker	Kaizen Biosciences	Custom bespoke
Test Requisition Form (pre-labelled)	Kaizen Biosciences	Custom bespoke
Duplicate tracking number label	Kaizen Biosciences	Custom bespoke

Figure 2 - Photo of blood collection kit

6. Shipping and Receipt of Medical Devices from Kaizen to Study Locations

6.1 Ordering and Shipping of Blood Collection Kits

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

Study locations should contact the SCTU team at safed@soton.ac.uk to request more Sample Collection kits. Please allow at least two weeks for collection kits to be replenished.

A list of all serial numbers, batch numbers, lot numbers, kit numbers and expiry dates will be included in each shipment packing list (Appendix 15.1) and/or will be available to SCTU via the Kaizen portal.

6.2 Receipt of Blood Collection Kits at Study Locations

It is the responsibility of delegated study location staff to check the shipment, sign and scan the shipment packing list and send to SCTU via SAFE-D email address (at safed@soton.ac.uk). A copy must be retained in the Investigator Location File (ILF).

All expected kits should be added to the local Blood Collection Kit Accountability Log (Appendix 15.2). Any kits that are expected but missing must be recorded on the shipment packing list and the Accountability Log as not received/missing.

If any kits are received in an unsuitable condition, they should be destroyed at the study location as per local policy and documented in the Blood Collection Kit Accountability Log. Also log the damaged/faulty kits on the Device Deficiency Log (Appendix 15.3) and add the DD number to the kit Accountability Log. These steps are also outlined in the top part of the kit lifecycle overview (Figure 3) in Section 8.

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

The SCTU will request for copies of the completed Kit Accountability Log (Appendix 15.2) and the Device Deficiency Log (Appendix 15.3). Please send completed copies to safed@soton.ac.uk when requested to support device accountability monitoring.

7. Storage of Medical Devices

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

8. Usage and Monitoring of Blood Collection Kits

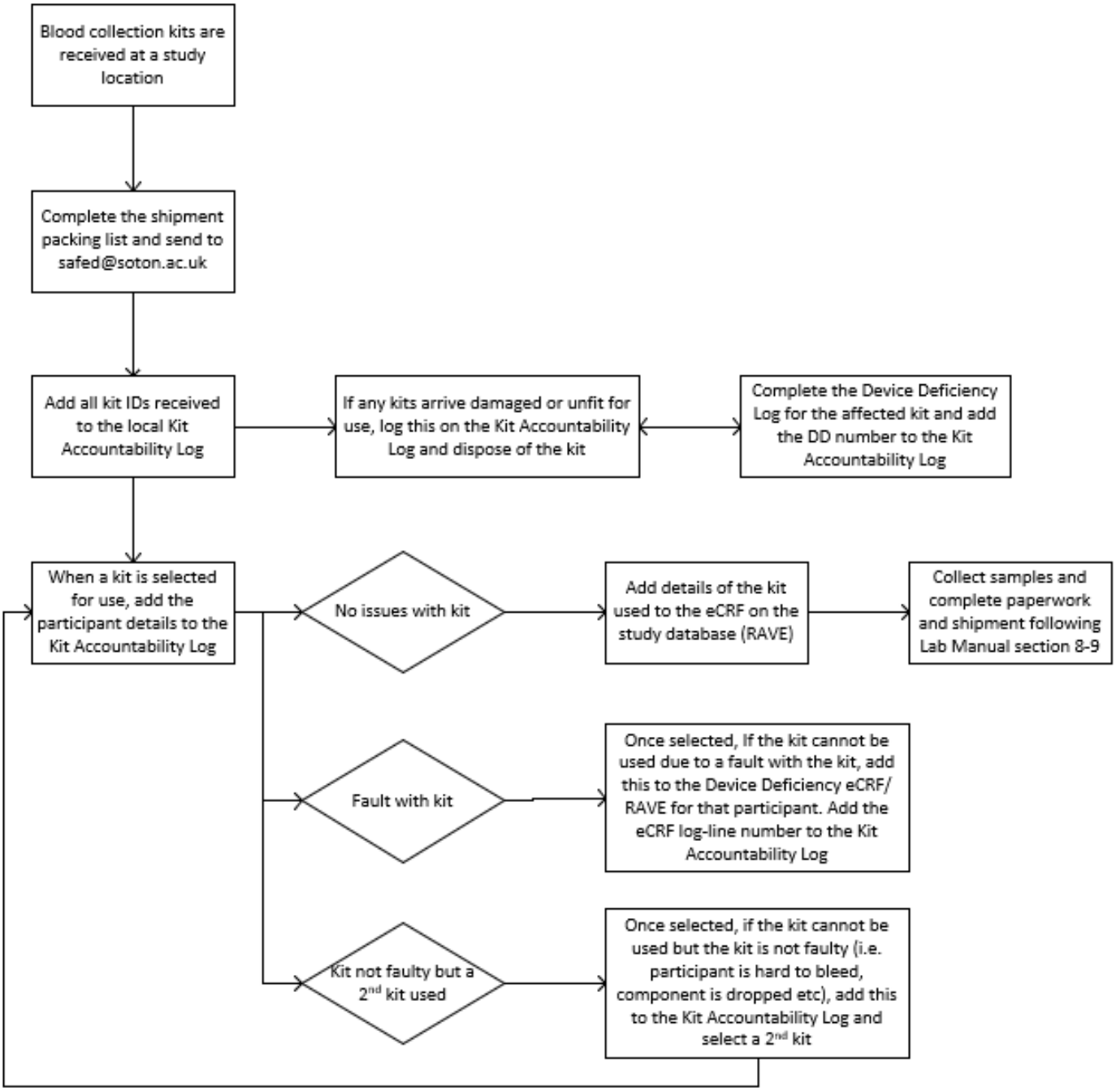


Figure 3 - Overview of blood collection kit lifecycle and documentation

8.1 Participant Registration

At the time of the initial study visit T0 and only after informed consent is obtained, register the participant in RAVE and obtain a participant ID (referred to as patient ID in RAVE and subject ID on the Test Requisition Form (TRF), Appendix 15.4). Write the participant ID in the indicated box on the TRF.

For subsequent follow up visits T1 and T2, use the participant ID assigned at T0.

8.2 Tracking Blood Collection Kits During a Participant Visit

The below described steps are outlined the bottom part of the kit lifecycle overview (Figure 3).

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

Once a kit is selected for use for a specific participant, the participant details and timepoint should be added to the local Device Accountability Log.

One kit must be used per collection. Tubes from multiple kits must not be mixed and matched from different individual kits. If one component of a kit is faulty, or a replacement component is required, the entire collection kit must be discarded and a new collection kit must be used.

If a fault with the kit discovered at the time of the visit (e.g. cracked sample tube, missing component, issue with blood tube vacuum etc.), record this on the Device Deficiency form in eCRF/RAVE. Add the device deficiency number to the Device Accountability Log.

If there is no fault with the kit, but a second kit is required (e.g. a participant is hard to bleed and requires a second attempt, a component is dropped by the user etc.), this does not need recording on the Device Deficiency Log or the eCRF/RAVE form but must be recorded on the Device Accountability Log.
Deficient kits should be disposed of according to local waste policies, ensuring that sharps are correctly disposed of.
Once opened, kits must not be returned to stock.

8.3 Blood Sample Collection

- Blood collection will be performed by qualified personnel who are trained to draw blood according to the institution's requirements and procedures for venepuncture technique.
- Whole blood should be collected Monday through Friday into pre-labelled blood tubes provided in individual sample collection kits (see section 5).
- Collect the sample using a 21- or 22-gauge needle unless deemed unsuitable for the participant in question.
- **Collect both Streck tubes first followed by the Lithium Heparin tube**, this may be contrary to local guidance.
- Ensure each tube is fully filled (10mL for Streck tubes and 6mL for Lithium Heparin tubes) before progressing to the next tube/disconnecting final tube.
- Following collection gently invert the tubes x10 to ensure sufficient mixing of tube additives.
- If an estimated combined volume of less than 8mL blood is collected into the two Streck tubes from one kit, it is permitted to attempt a second venepuncture using a new needle and a new kit as long as the participant agrees and only tubes from one new kit are subsequently used. Please send the tubes from the kit with the highest combined Streck blood volume to the ECMC lab (even if less than 8mL combined). Discard the kit with the lowest combined Streck blood volume as per local procedures. Do not mix tubes from two kits. As all kits need to be accounted for, please log both kits according to instructions in section 8.1-8.2.

Note: the SAFE-D team will inform Hub staff if insufficient plasma was collected after processing and will then request for an optional rebleed to be performed.

8.4 Labelling of Blood Samples

Please see the tables below which detail the specifics of the blood tubes (Table 2), the labelling format (Table 3) and examples of the labels (Figure 4).

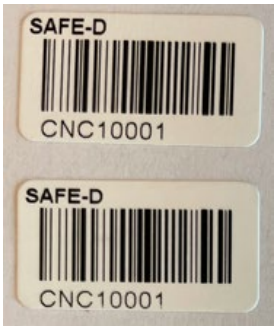
Table 2 - Tube specifications

Sample Type	Tube Type	Max Volume Collected	No. of Tubes	Transport Conditions	Max Time to Processing	Fraction Isolated
Anticoagulated whole blood	Streck	20mL	2 x 10mL	Ambient temperature	7 days	Plasma for cfDNA
Anticoagulated whole blood	Lithium Heparin	6mL	1 x 6mL	Ambient temperature	Not specified	Plasma for metabolomics

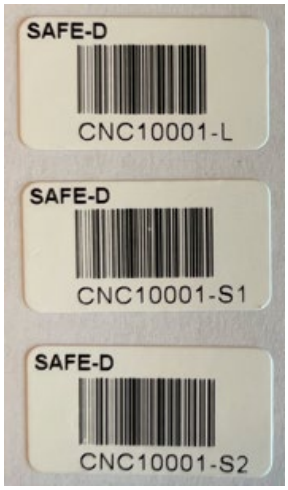
Table 3 - Blood collection kit and labelling format

ID	Format	Example
Study ID	Safe-D	Safe-D
Subject ID	SFD-####-#####	SFD-0001-01234
Sample Collection Kit ID (i.e. TRF ID)	CNC#####	CNC10001
Sample Collection Kit Box Exterior	CNC##### (Same as TRF ID)	CNC10001
Blood Sample ID (Tube ID)	CNC#####-L CNC#####-S1 CNC#####-S2	CNC10001-L CNC10001-S1 CNC10001-S2

Box and TRF labels



Blood Collection Tube Labels



Blood Collection Tube ID suffixes: L = lithium heparin, S1 = Streck Tube 1, S2 = Streck Tube 2

Figure 4 - Example of Box and TRF labels, and Blood Collection Tube labels

9. Blood Sample Packing, Posting and Logging

Once the sample is collected, blood tubes are no longer tracked as a device, but as a study sample. Following this point, the Device Accountability Log does not need completing. However,

the Device Deficiency Log may need to be completed if a fault occurs with the blood tubes (e.g. the tubes crack due to a fault with the packaging)

9.1 Sample Packing and Posting

- When all blood samples have been collected, pack the sample tubes in the UN3373 certified sample box (only include one participant's samples per box) as per instructions on the TRF (Appendix 15.4).
- Complete the TRF and enclose the completed form with the blood samples. ***NOTE: please DO NOT include the consent form***
- Blood tubes will be sent at ambient temperature.
- Post to the ECMC laboratory on same day as collection by using the study location's local posting procedure.

In the event that the address label is missing from the sample box, please address the box to:

ECMC lab c/o Safe-D Team
LF110 Level F, Mailpoint 850
Southampton General Hospital
Tremona Road
Southampton
SO16 6YD

9.2 Sample Tracking

The posted sample can be uniquely tracked once it reaches the sorting office. To enable blood sample shipment tracking, enter the postal tracking number (found on the front of the posting box) into the 'Blood Sample Collection' Form in eCRF/RAVE.

10. Receipt of Whole Blood Specimens at ECMC lab

10.1 Checking Expected Samples

A daily eCRF/RAVE generated report will be sent to the ECMC lab around 7am via email (to safedlab@soton.ac.uk) detailing the subject ID, visit number, sample collection date and tracking ID of posted samples.

The incoming sample report from eCRF/RAVE will inform the lab of what is expected to arrive in the next 24 hours. See Figure 5 for schematic of sample tracking.

eCRF/RAVE will send a follow-up report to the SAFE-D team if the participant's sample has not been marked as received on eCRF/RAVE within 4 days. The follow-up report will trigger an investigation into the sample location which will be initiated by the ECMC lab with SCTU assistance if required.

10.2 ECMC Sample Receipt

Upon receipt of the samples, ECMC lab staff will reconcile samples received against samples expected to be received based on incoming sample reports. ECMC Lab staff will visually assess sample quality before accessioning and logging the samples received. The ECMC lab will transcribe the relevant TRF information into FreezerWorks and file the paper TRF. The ECMC lab

will save all incoming sample tracking reports sent via eCRF/RAVE. All samples from all time-points need to be acknowledged as received in eCRF/RAVE.

If ECMC lab receives samples that were not on the eCRF/RAVE incoming sample report, the ECMC lab team will follow up with SCTU SAFE-D Team who will investigate while the ECMC team proceeds with sample processing as per usual.

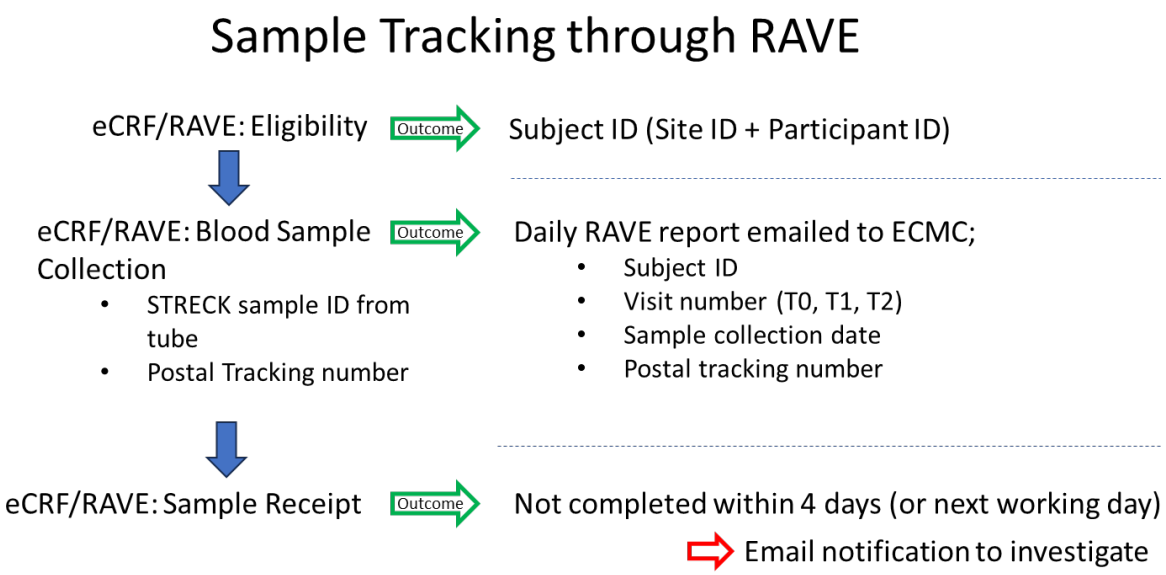


Figure 5 - Schematic showing sample tracking through RAVE

10.3 Device Deficiency upon receipt

If any device deficiency has occurred with the blood tubes (e.g. blood tubes cracked despite packaged correctly, sample spillage due to a seal failure on the blood tube etc.), then this should be recorded by ECMC lab staff on the ECMC Lab Device Deficiency Log.

11. Sample Accessioning, Processing, Storage and Shipment at ECMC Lab

Sample accessioning and processing will be carried out by ECMC lab personnel following CSD/SOP/713 SAFE-D Sample Processing.

Sample shipment to ClearNote Health for Avantect testing will be coordinated by ECMC lab personnel following CSD/SOP/722 SAFE-D Sample Shipment.

12. Deviation Reporting

Any deviations from this laboratory manual must be documented locally (at the Hub, ECMC lab or ClearNote Health lab as applicable). SCTU must be informed via safed@soton.ac.uk as soon as the deviation is known with a list of the affected samples and associated participant ID(s).

Examples of deviations may include but are not limited to:

- Incorrect sample collection (e.g. use of 2 mixed kits, incorrect blood draw order)
- Incorrect storage temperature of samples
- Incorrect processing parameters (e.g. incorrect centrifuge speed)
- Samples collected outside of protocol-defined visit window
- Samples processed beyond time requirements
- Tubes received in ECMC with participant identifiers

13. Emergency Recall of Medical Devices

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

14. Revision History

Date and version	Summary of significant changes
V1.0 04-Apr-2025	Initial approved version.
V2 18-AUG-2026	• Addition of Contacts and Mailing Information section 2 • Changing WISH to ECMC throughout • Added clarification in Section 4 around time frame for visit T1 and T2 (+/- 4 weeks) • Added Device Details section 5, Shipping and receipt of medical devices from Kaizen to study location section 6, Storage of medical devices section 7, Usage and monitoring of blood collection kits section 8 • Clarified the blood collection section (now section 8.3) including preference for needle size (21 or 22 gauge), gentle tube inversion post collection, combined blood level requirement and request for second attempt, clarifications around using one kit per visit and when second attempt being requested. • Removed the requirement to add the postal tracking number to the consent in the sample tracking section. • Removed Randomisation section 9 following study redesign and wording about randomisation throughout. • Addition of more examples of what constitutes a device deficiency in the Deviation Reporting section (now 10). • Removed the withdrawal schematic as withdrawals are managed through RAVE.

	• Removed the withdrawal schematic in previous section 13 as this process is described in the Protocol and documented in RAVE. • Addition of Emergency recall of medical device section 13. Removed the section on "Disposal of blood collection kits" as covered elsewhere. • Updated TRF in the appendix (15.4), addition of Packing List (15.1), Device Accountability Log (15.2), Device Deficiency Log (15.3) and removed Sample box packing and shipping instruction appendix as covered elsewhere.

15. Appendices

15.1 Packing List

Packing List

Order number	
Date	
Shipping address	
Contact	
Packed By	

Check	Kit ID	Kit Lot Number	Kit Sku	Kit Expiry Date	Return Shipment Tracker	Order Details Comments

Please sign and scan a copy of this form back to (EMAIL@) Maintain original for your records.

Received By	
Checked	
Date	

I acknowledge receipt of the items listed above in good condition

Signed	

Comments:

15.2 Blood Collection Kit Accountability Log

Southampton Clinical Trials Unit

BLOOD COLLECTION KIT ACCOUNTABILITY LOG

Study short title:	*SAFE-D*	**REC number:**	25/EM/0016	**Sponsor:**	University Hospital Southampton NHS Foundation Trust
Site name:		**Site number:**		**IRAS:**	326332

KIT ID/ TRF ID	Abnormality: e.g. none/missing/deficient*/state other	Date Used/Abnormality/ Destroyed	Participant ID [SFD-xxxx-xxxxx] or N/A	Visit (T0/1/2 or N/A)	Used by [Name of healthcare provider]	Signature	Kit sent to ECMC (Royal Mail) Date or NA
CNC		DD-MMM-YYYY					DD-MMM-YYYY
CNC		DD-MMM-YYYY					DD-MMM-YYYY
CNC		DD-MMM-YYYY					DD-MMM-YYYY
CNC		DD-MMM-YYYY					DD-MMM-YYYY
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CNC		DD-MMM-YYYY					DD-MMM-YYYY

*when deficient state "deficient" and include RAVE log-line number or DD ref as appropriate

NOTE – when Kit stock reaches a minimum of 5, please contact the SCTU to re-order supply – safed@soton.ac.uk

SAFE-D - Site Blood Collection Kit Accountability Log – v1 15-Apr-2025

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15.3 Device Deficiency Log

Southampton Clinical Trials Unit

BLOOD COLLECTION KIT DEFICIENCY LOG

Study short title:	*SAFE-D*	REC number:	25/EM/0016	Sponsor:	University Hospital Southampton NHS Foundation Trust
Site name:		Site number:		IRAS:	326332

Device Deficiency (DD) Number (sequential)	KIT ID/ TRF ID	Please give a reason for Kit deficiency / not suitable for use	Date	Name	Signature
	CNC		DD-MMM-YYYY		
	CNC		DD-MMM-YYYY		
	CNC		DD-MMM-YYYY		
	CNC		DD-MMM-YYYY		
	CNC		DD-MMM-YYYY		
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15.4 Test Requisition Form