UNIVERSITY OF CAMBRIDGE

NHS Blood and Transplant

NHS National Institute for Health Research

COMPARE

Comparison of NHSBT's current approach with three alternative strategies to assess haemoglobin levels in whole blood donors and creation of a bioresource for future research into donor and public health (COMPARE Study)

Ethics: << 15/EE/0335 >>

ISRCTN: 90871183

Chief Investigators: Dr Emanuele Di Angelantonio and Prof John Danesh

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1. Protocol Summary

Title:	Comparison of NHSBT's current approach with three alternative strategies to assess haemoglobin levels in whole blood donors (COMPARE Study)
Short title:	COMPARE
Sponsor name & reference:	NHS Blood and Transplant
Funder name & reference	NHS Blood and Transplant and National Institute of Health Research
ISRCTN no:	90871183
Design	Multi-site observational study in blood donors in England.
Overall aim:	To evaluate the optimum method to measure haemoglobin levels in potential whole blood donors in advance of each donation in NHSBT's high-throughput context. A further aim is to establish a bioresource of healthy volunteers using samples and data collected during the study to be used in future approved research projects looking at donor and public health. In the future, comparisons to other bioresources related to people with common and rare diseases may also shed light on the causes of diseases.
Primary endpoint:	The primary endpoint will be the proportion of donors in the study who would have been inappropriately bled by each method (ie, the proportion of donors for whom a given method would not identify as having sub-threshold haemoglobin levels [ie, <125g/L for women and <135g/L for men] as measured by a Sysmex haematology analyser).
Secondary endpoints:	1) Differences in the proportion of donors who would have been inappropriately bled when comparing the various newer methods to be studied with one another 2) Differences in the proportion of donors who would have been inappropriately bled when comparing the two non-invasive devices to be studied with each other 3) Feasibility and acceptability of different methods, according to the views of and blood services staff 4) Cost-effectiveness of different methods 5) Variability of the performance of different methods by donors' personal characteristics. 6) Medium and long-term health consequences of inappropriately bleeding at donation. 7) Biological mechanisms of whole blood donation on iron kinetics, iron absorption and iron incorporation in erythrocytes in donors who have particular genetic profiles.
Inclusion & exclusion criteria:	**Inclusion criteria:** 1) age ≥18 years and fulfilling all normal criteria for blood donation with the exception of pre-donation haemoglobin

	levels measured using the current NHSBT methods; 2) willing to undergo additional haemoglobin measurement; 3) willing to donate an extra blood sample to be i) used for measurement of haemoglobin using an automated cell counter and ii) stored for future research 4) willing to come back for a subsequent appointment at standard donation interval (ie 12-wk and 16-wk for men and women respectively) – only relevant for the 18,000 participants to be enrolled in the first stage of recruitment. **Exclusion criteria:** 1) participants who do not have internet access and/or are not willing to provide an email address for study correspondence (as the study will aim to be almost "paper-less" and will involve remote web-based data collection);
Planned number of sites:	10 mobile teams across England.
Summary of haemoglobin measurements:	Haemoglobin levels will be measured using three alternative methods: 1) a "post-donation" method: This method involves using haemoglobin levels obtained from a "gold standard" haematology analyser at the most recent blood donation visit to predict the donor's haemoglobin level at the next visit (ie, typically 12-16 weeks later) 2) a capillary point-of-care test: This method involves taking a drop of capillary blood after a finger-prick and measuring haemoglobin levels using a rapid Hemocue® test. 3) a non-invasive strategy: This method involves either of two hand-held spectrometer devices that estimate haemoglobin levels by shining a light on the skin of a donor's finger.
Duration of recruitment:	Approximately 37 weeks
Translational component	The results from this study will inform national policies that should optimise current haemoglobin screening approach in blood donors across England.
Other related research	Added value will be provided by this study's creation of a bio-resource that will, with separate future funding, enable detailed study of the health of blood donors. More generally, this study should encourage future NHS Blood and Transplant studies that address other relevant service needs.

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1. Abbreviations

AE	Adverse event
AED	Adverse event of donation
NHSBT	NHS Blood and Transplant
DHC	Donor health check form
DIN	Donation identification number
MHRA	Medicines and healthcare regulatory agency
NCC	National call centre
NIHR	National institute for health research
REC	Research ethics committee
SAE	Serious adverse event
SAED	Serious adverse event of donation
SMG	Study management group
SSC	Study steering committee
UoC	University of Cambridge

2. Amendment history

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Amendment No.	Protocol version No.	Date issued	Author(s) of document / changes	Details of changes made
*	**1**	**13/08/15**	**Carmel Moore**	
	2	**12/11/15**	**Emanuele Di Angelantonio**	Additional details on blood sample processing and analysis and future use of stored samples (see Section 13)
	3	**01/12/15**	**Jennifer Sambrook**	The creation of a BioResource has been included as an aim of the study in Sections 1, 3.2.1, and 4.3.2. Additional details have been added on the use of samples / data for approved research studies in Section 13.1
	4	**17/12/15**	**Carmel Moore**	1. New and updated versions of participant documents have been incorporated in the text and annexes. 2. ISRCTN and study sponsor reference number added (front cover and Section 1: Protocol summary) 3. Details of study sites have been added (see Section **4.4.**) 4. Details of collection of an additional 3ml blood in TEMPUS tube (Sections **9.1.3**, **10.4**, **13**, **13.1**).
	5	**01/07/2016**	**Jennifer Sambrook**	1. Addition of questionnaire reminders (partial and non-responders) for Stage 1 participants who have attended two donation sessions and have not completed the baseline questionnaire 2. Removal of the Stage 2 donor copy consent form at the screening booth

* List details of all protocol amendments here whenever a new version of the protocol is produced

3. Introduction

3.1 Background

What is the unmet need? Blood services are mandated to measure the haemoglobin concentration of potential whole blood donors in advance of each donation, both to protect the health of donors (ie, to prevent collection from anaemic donors) and to ensure the quality of blood products. The European legislation on selection criteria of blood donors states that haemoglobin levels should be ≥125g/L for women and ≥135g/L for men to allow blood donation. However, despite such legislation, even within Europe national blood services use varying haemoglobin screening approaches (**Table 1**). This situation reflects a lack of rigorous evidence to support a single optimal policy.

NHS Blood and Transplant (NHSBT) currently use a "copper sulphate finger prick test" on capillary blood to measure pre-donation haemoglobin level, and if this test indicates that the haemoglobin levels are low, donors are asked to provide a sample of venous blood for further testing using the more precise "Hemocue®" test. However, this method has limitations. In an analysis of data from 45,000 donors who gave blood in England during 2012-14, we found that almost 10% were judged to have been inappropriately bled (ie, they had haemoglobin levels below the EU directive cut-off points) when the current NHSBT approach was compared against the "gold standard" haematology analyser.

Table 1. Haemoglobin screening strategies in selected blood services

Organisation	Strategy	Screening procedure		
		Device	Method	Sample
NHSBT*	pre-donation	$CuSO_4$ ± Hemocue	gravimetric/photometry	capillary/venous
Bavarian Red Cross	pre-donation	MBR Haemospect	reflection spectroscopy	non-invasive
Irish Blood Transfusion Service	pre-donation	MBR Haemospect	reflection spectroscopy	non-invasive
Orsola-Malpighi Hospital, Bologna (Italy)	pre-donation	Orsense NMB200	occlusion spectroscopy	non-invasive
Blood Donors in Denmark*	post-donation	Cell counter	spectrophotometry	venous
Etablissement Francais du Sang *	post-donation	Cell counter	spectrophotometry	venous
German Hospital Transfusion Centres **	post-donation	Cell counter	spectrophotometry	venous
Australian Red Cross	pre-donation	Hemocue	photometry	capillary
Canadian Blood Services	pre-donation	DiaSpect	photometry	capillary

*first time donors presenting for a donation undergo a pre-donation screening test using a portable photometer (Hemocue/CompoLab)
****Department of Transfusion Medicine, Eberhard Karls University Tuebingen; Department of Transfusion Medicine, Westfaelische Wilhelms University Muenster; University Medical Centre Schleswig-Holstein.

There are about 1.3 million blood donors each year in England who provide a total of 1.9 million donations. Given NHSBT's duty of care to such a large group of volunteers, there is a fundamental need to determine the optimum method to measure haemoglobin concentration in advance of each donation in order to reduce the number of donors inappropriately bled. An important objective of NHSBT, and a major motivator of the current proposal, is also to move towards a more donor-friendly approach to measure haemoglobin level.

What are the alternatives strategies for haemoglobin measurement? Several national blood services in Western countries use a spectrophotometric test (Hemocue®) on capillary blood obtained by a finger-prick. However, in recent years, alternative approaches to haemoglobin screening have been adopted by blood services in major European countries because of their potential to provide more accurate tests, a more donor-friendly way of testing that saves time at donation sessions, and a reduction in hazardous material for

disposal. Two of the most promising approaches are the use of: (1) a “post-donation” method (this method involves using haemoglobin levels obtained from a “gold standard” haematology analyser at the most recent blood donation visit to predict the donor’s haemoglobin level at the next visit); and (2) a non-invasive strategy (this method involves either of two hand-held spectrometer devices that estimate haemoglobin levels by shining a light on the skin of a donor’s finger). However, the comparative merits of these approaches remain uncertain, as they have been introduced into practice without rigorous scientific evaluation.

Will other studies provide the necessary evidence? To our knowledge, there are no previous (or planned) studies in the UK or elsewhere that aim to compare different strategies to measure haemoglobin levels in blood donors.

3.2 Objectives

3.2.1 Primary objective

The main objective of this study is to provide a robust comparison of the three alternative strategies for haemoglobin testing (ie, a “post-donation” method, capillary blood Hemocue®, and non-invasive spectrometry), comparing each with NHSBT’s current approach and with a “gold standard” haematology analyser. The study’s principal outcome will be the proportion of donors that would have been inappropriately bled with each method.

A further objective is to establish a bioresource of healthy volunteers using samples and data collected during the study to be used in future approved research projects looking at donor and public health. In the future, comparisons to other bioresources related to people with common and rare diseases may also shed light on the causes of diseases.

3.2.2 Secondary objective

Secondary key outcomes will include feasibility and acceptability of the methods for donors and NHSBT staff, cost-effectiveness, and performance of tests in donor subpopulations (ie, study of whether results for different methods vary importantly by age, sex, ethnicity, genetic make-up etc).

4. Study design

4.1 Haemoglobin strategies to be compared

We will compare the following three haemoglobin strategies that are used by various blood services in major Western industrialised countries against the results of a "gold standard" haematology analyser and against the results of the current NHSBT method:

1) a "post-donation" method: This method involves using haemoglobin levels obtained from a "gold standard" haematology analyser at the most recent blood donation visit to predict the donor's haemoglobin level at the next visit (ie, typically 12-16 weeks later)

2) a capillary point-of-care test: This method involves taking a drop of capillary blood after a finger-prick (ie, the same finger-prick used for NHSBT's routine copper sulphate test) and measuring haemoglobin levels using a rapid Hemocue® test. (NB: The point-of-care Hemocue test involves capillary blood, whereas the Hemocue® test currently used by NHSBT involves a venous blood sample). Hemocue® (HemoCue AB, Ängelholm, Sweden) is a point-of-care device tested according to IEC 61010-1 that complies with IVD Medical Device Directive 98/79/EC.

3) a non-invasive strategy: This method involves either of two hand-held spectrometer devices (ie, MBR Haemospect® versus Orsense NMB200®) that estimate haemoglobin levels by shining a light on the skin of a donor's finger.

The MBR Haemeospect® device (produced by MBR Optical Systems GmbH & Co. KG), is a hand-held, point-of-care test that uses transcutaneous reflection spectroscopy to measure haemoglobin level. The device was CE marked in 2008. Using a small probe head directly placed on the finger, the device shines light onto the skin and underlying tissues, then measures the wavelength of the light reflected back. No safety concerns have been reported and it is currently used in the Irish Blood Transfusion Service. The Orsense NMB200® device (produced by OrSense Ltd) is a hand-held, point-of-care test that uses a non-invasive occlusion spectroscopy method to measure haemoglobin level. The device was CE marked in 2009. The device is composed of a ring-shaped sensor probe that fits on the donor's finger, and a portable desktop monitor that calculates and displays the measurement result. No safety concerns have been reported and it is currently used in some transfusion services in Italy.

4.2 Sampling framework

Over a period of about 37 weeks, we will enrol about 31,000 whole blood donors in England. The donors will derive from at least 10 NHSBT "mobile" blood donation teams that operate on a regular basis at the same locations. We estimate that about 120 whole blood donors will attend each of these sessions daily. Assuming 25% of donors at these centres agree to participate in this study (an expectation based on prior experience), we anticipate recruitment of 30 donors / day per mobile centre (ie, a total of 300 participants / day across the 10 centres). Hence, we estimate the recruitment of 1,500 participants / week, assuming recruitment 5 days per week. In the event of slower-than-anticipated recruitment, we plan to extend the duration of the recruitment and/or involve >10 mobile donation teams.

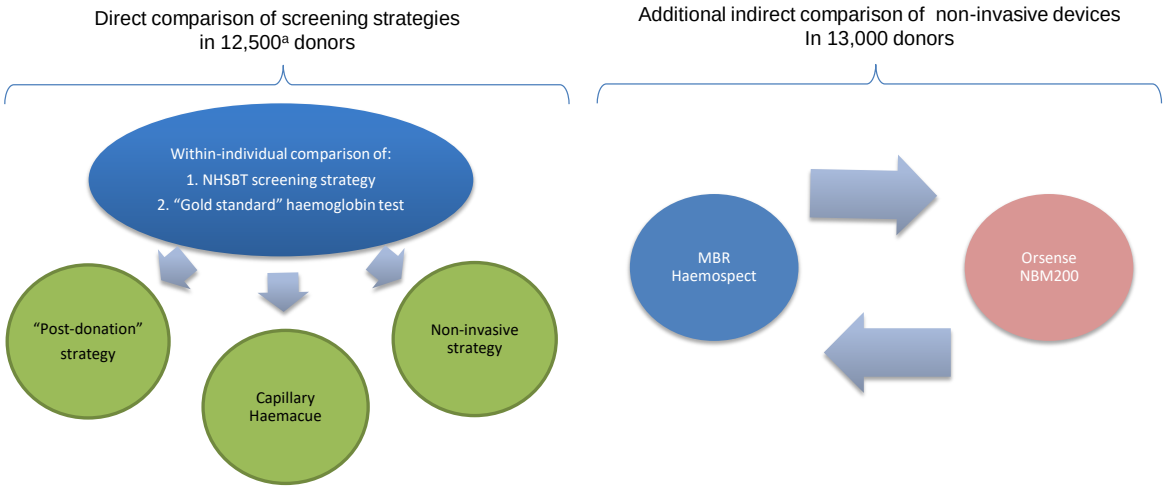
The study will involve two stages of recruitment (**Figure 1**).

Stage 1: will involve head-to-head comparison in a common set of about 12,500 participants of the three new methods (described above) and NHSBT's current method for haemoglobin testing (copper sulphate test with or without venous Hemocue®). Samples will also be sent for testing on the "gold standard" haematology analyser to support the "post-donation" strategy.

The post-donation method requires Stage 1 participants to attend two successive blood donation visits. At the first visit, participants will consent and provide a research sample for testing on the "gold standard" haematology analyser. Prior to donating at this visit, participants' haemoglobin levels will be tested via NHSBT's routine methods only. At the second visit participants will receive measurements of their haemoglobin levels via standard NHSBT methods and also by i) capillary point of care Hemocue® and ii) one of the two non-invasive tests (ie, either MBR Haemospect®or Orsense NMB200®). In addition a sample collected at this 2nd visit will be sent for testing on the "Gold Standard" haematology analyser). We will enrol about 18,000 donors at the first visit in order to yield an anticipated 12,500 participants who attend two successive visits, assuming a non-attendance rate of 30% at the second visit.

Stage 2: One of the new methods to be evaluated (ie, non-invasive spectrometry) involves a choice between two commercially-available devices. It would be ideal to conduct a head-to-head comparison of these two devices in the same set of participants as the other methods are to be compared in. Unfortunately such an approach would likely be too time-consuming and disruptive to NHSBT's high-throughput service. Hence, we plan a second stage of recruitment that will involve enrolment of a further approximately 13,000 participants, focusing on the comparison of two different non-invasive spectrometry devices. During the second stage of recruitment, selection of mobile donation centres will be done in a way to over-sample donors of non-European ancestry (eg, those of African, Middle Eastern, and South Asian ancestry). The rationale is that the performance of non-invasive spectrometry devices is known to differ in people with different skin colour and tone.

Figure 1: Study design



[a] assuming ~30% drop-out rate 18,000 donors need to be recruited at the previous donation visit.

4.3 Primary and secondary endpoints

4.3.1 Primary endpoint

The primary endpoint will be the proportion of donors in the study who would have been inappropriately bled by each method, ie, the proportion of donors for whom a given method would not identify as having sub-threshold haemoglobin levels [ie, <125g/L for women and <135g/L for men] as measured by a "gold standard" haematology analyser. The principal assessment will compare the current NHSBT screening method with each of the three other

alternative methods (ie, three pair-wise comparisons). We hypothesise that the current NHSBT method will involve a higher proportion of donors inappropriately bled than the other newer methods. The null hypothesis is that there are no differences across methods in the numbers of donors who would have been inappropriately bled.

4.3.2 Secondary endpoint

We will study the following important and pre-specified secondary endpoints:

1) differences in the proportion of donors who would have been inappropriately bled when comparing the various newer methods to be studied with one another

2) differences in the proportion of donors who would have been inappropriately bled when comparing the two non-invasive devices to be studied with each other

3) feasibility and acceptability of different methods, according to the views of blood donors and blood services staff

4) cost-effectiveness of different methods

5) variability of the performance of different methods by donors' personal characteristics. Examples of key characteristics include: donor status (repeat versus first-time blood donor), sex, menopausal status (for women), skin colour tone, biological profile (such as measurement of genetic variants [eg, HFE, TMPRSS6, TFR2], soluble biomarkers [eg, ferritin, hepcidin] known to be related to iron or red blood cell metabolism and other DNA and blood-based biomarkers that could define relevant subpopulations)

6) medium and long-term health consequences of inappropriately bleeding at donation via, for example, linking participants' study information with a variety of electronic health records (such as those available through the Health and Social Care Information Centre)

Participants who enrol in COMPARE will also be part of a bioresource of healthy volunteers, and samples and data will be used in future approved research projects looking at donor and public health.

4.4 Study sites

Recruitment will be carried out by 10 mobile teams that operate on a regular basis at the same location in England. Mobile teams will be selected to ensure a maximum representativeness of NHSBT's donor population (including Black, Asian, and other minority ethnic groups).The selected teams, their associated NHSBT codes are details below:

Team Code	TEAM
CLW	Leeds
DSN	Sheffield North
TOL	Oxford
JH1	South Anglia
WHE	Herts
MNL	Lancaster
JHU	Huntingdon
NET	Teesside
HCO	Coventry
JNO	Norwich

4.5 Participant eligibility

4.5.1 Inclusion criteria

1) age ≥18 years and fulfilling all normal criteria for blood donation with the exception of pre-donation haemoglobin levels measured using the current NHSBT methods;
2) willing to undergo additional haemoglobin measurement;
3) willing to donate an extra blood sample to be i) used for measurement of haemoglobin using an automated cell counter and ii) stored for future research
4) willing to come back for a subsequent appointment at standard donation interval (ie 12-wk and 16-wk for men and women respectively) – only relevant for the 18,000 participants to be enrolled in the first stage of recruitment.

4.5.2 Exclusion criteria

1) participants who do not have internet access and/or are not willing to provide an email address for study correspondence (as the study will aim to be almost “paper-less” and will involve remote web-based data collection)

5. Oversight committees

5.1 Study Management Group (SMG)

The SMG will include the chief and co-investigators, scientific study coordinators, chief information officer, NHSBT operational change manager and NHSBT project manager. The SMG will be responsible for overseeing the study. The group will meet or participate in alternate face to face / conference calls at weekly intervals during the recruitment phase of the study.

The SMG will agree protocol amendments prior to submission to the research ethics committee (REC). All study sites will be informed of substantial amendments through the NHSBT operational change manager, following notification by the scientific study coordinator.

5.2 Study Steering Committee (SSC)

The SSC will include an independent Chair, independent members, the chief and principal investigators, scientific study coordinators, chief information officer, NHSBT operational change manager and NHSBT project manager. The role of the SSC is to safeguard the well-being of participants and monitor overall conduct of this study. It will also provide advice (through its independent Chair) to the SMG and the funding body (NHSBT) on all aspects of the study. The SSC will be responsible for making executive decisions about the study. The committee will meet 3 times during the study period.

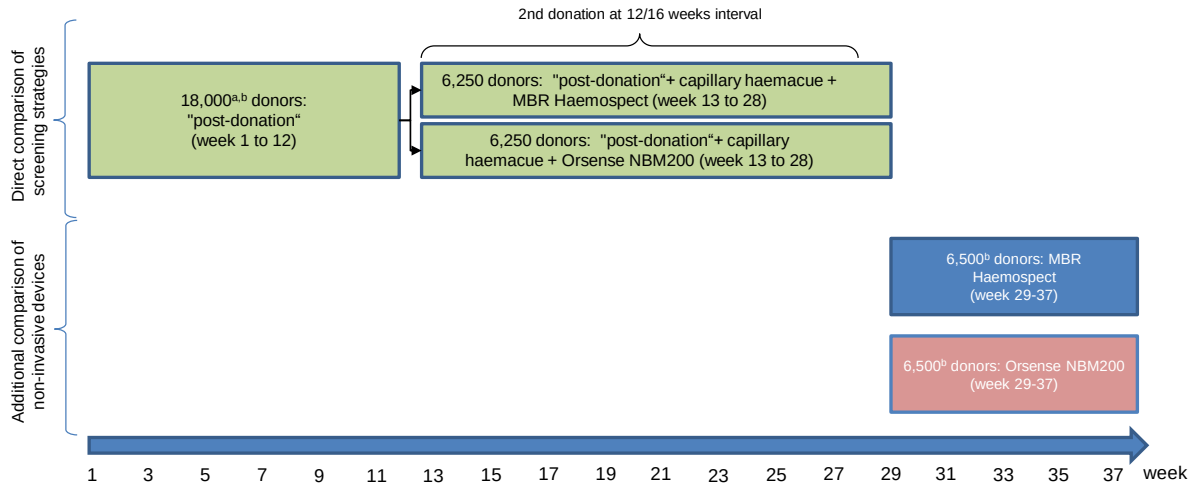
6. Study timeline

6.1 Overall study timeline

The study will involve two stages of recruitment (**Figure 2**). Stage 1 will involve head-to-head comparison in a common set of about 12,500 participants of the three new methods (see **Section 4.1**) and NHSBT's current method for haemoglobin testing (and "gold standard" haematology analyser). One of the new methods to be compared (ie, the post-donation method: see **Section 4.1**) requires participants to attend two successive blood donation visits. Hence, we will enrol about 18,000 donors over a period of approximately 12 weeks at an initial donation visit in order to yield an anticipated 12,500 participants who attend two successive visits, assuming a non-attendance rate of 30% at the second visit.

Stage 2 will involve a further recruitment of approximately 13,000 participants over a period of about 9 weeks, focusing on the comparison of two different non-invasive spectrometry devices.

Figure 2: Study timeline



[a] assuming ~30% drop-out rate 12,500 donors will attend second donation
[b] total of 31,000 unique donors recruited at baseline

6.2 Definition of end of study

The study will extend beyond the recruitment of the last subject as some elements of this observational study (eg, study of long-term health consequences of blood donation) will extend beyond the recruitment phase. For the key secondary study endpoint related to the study of health consequences of inappropriately bleeding of donors, participants will be linked with electronic health records for years after enrolment. For the key secondary study endpoint related to the study of variability in newer haemoglobin test methods by donor characteristics, the biological samples of participants will continue to be used for years after enrolment. The study will also result in the creation of a bioresource of biological samples and data which will continue to be used for years after enrolment.

7. Set up of study teams and sites

7.1 Study Teams and Sites

Recruitment of participants and sample collection will be carried out by 10 NHSBT mobile donation teams. Each mobile team operates from a central base, visiting different donation venues or 'sites' each day, which are re-visited on a regular basis. Donation venues are usually public properties, e.g. village halls, and are not owned by NHSBT but comply with all NHSBT and Medicines and Healthcare Regulatory Agency (MHRA) guidelines.

7.2 Donation venue requirements

Donation venues must be able to comply with:

- All requirements of the study protocol. Most importantly, mobile teams must return to a donation venue 12 or 16 weeks after the previous visit, in order to fulfil the requirements of the post-donation strategy.
- Requirements of the Research Governance Framework (Department of Health, 2005)
- Data collection requirements

7.3 Mobile team staff

Each mobile team will have an operational lead, which for the purposes of this study will be a health-care professional authorised by NHSBT to supervise the work of the study on behalf of the team. The mobile donation teams will consist of trained nurses and donor carers who have experience in all blood donation procedures.

Operational leads will report to the NHSBT Operational Change Manager who in turn will report to the Senior Scientific Coordinator.

All mobile donation team staff must be appropriately qualified (by training and experience) to perform the study-related duties allocated to them and to be aware of the requirements of the Research Governance Framework.

7.4 Mobile team training

Training will be given to all staff, in post, prior to site initiation.

1. Mobile team operational leads: A training session will be held for each operational lead of the 10 mobile donation teams to explain the objectives of the study and walk through the end-to-end operational processes (see **Annex 1**).

2. Mobile team training event: An on-site training event will be organised by each of the mobile team's operational leads, four weeks in advance of the go-live date. This will be attended by all mobile team staff. Where possible a project team member either from NHSBT or the University of Cambridge will be present at each of these training events to give support as necessary.

3. Prior to the go-live date an operational lead from each of the mobile donation sessions will complete a checklist to confirm that the team has received the necessary training to carry out the research protocols and has access to all study documentation and equipment. On receipt of this information the team will receive an 'activated' status i.e. enrolment of participants may take place by this team in the week following the off-site training.

7.5 Recruitment targets

We estimate that about 120 whole blood donors will attend each of these sessions daily. Assuming 25% of donors at these centres agree to participate in this study (an expectation based on prior experience), we anticipate recruitment of 30 donors / day per mobile centre

(ie, a total of 300 participants / day across the 10 centres). Hence, we estimate the recruitment of 1,500 participants / week, assuming recruitment 5 days per week. The study aims to recruit 18,000 participants in Stage 1 within the first 12 weeks of the study period and to further recruit 13,000 participants in Stage 2 within the last 9 weeks of the study. In the event of slower-than-anticipated recruitment, we plan to extend the duration of the recruitment and/or involve >10 mobile donation teams.

7.6. Set up of COMPARE study helpdesk

A COMPARE study helpdesk will be established at the academic coordinating centre, at the University of Cambridge (UoC), prior to the start-up of the study. A training programme will be delivered to the helpdesk which will cover all aspects of the team's responsibilities during the study, which will be to:

1. Deal with donor queries regarding their participation in the study.
2. Deal with and action donor requests to withdraw from the study.
3. Deal with queries from UoC regarding non-reconciliation of consent forms or samples to donors registered on the study.

8. Summary of study procedures

A summary of study procedures is show in **Table 2** below.

Table 2: Study procedures in Stage 1 and Stage 2 participants (at-and post-session)

Study Procedures	**Stage 1** Head-to-head comparison of 3 new methods and NHSBT's current method for Hb testing. One of the new methods - the post-donation method - requires participants to attend two successive blood donation visits.				**Stage 2** Head-to-head comparison of two different non-invasive spectrometry devices.	
	Visit 1		**Visit 2**			
	At session	Post-session	At session	Post-session	At session	Post-session
Invitation & consent	●				●	
Hb screening (per participant)						
Standard NHSBT	●		●		●	
Post donation[a]	●		●			
Capillary Hemocue®			●			
Non-invasive (one of two)			●		●	
Research samples[b]	●		●		●	
Health / lifestyle questionnaire		●				●
Hb screening questionnaire				●		●

[a] This method requires Hb measurement using "glod standard" haematology analyser.

[b] Research samples include 4ml EDTA, 6ml EDTA and 6ml serum tubes The 4ml EDTA will be used to perform Full Blood Count on "Gold Standard" haematology analyser.

9. Stage 1 study procedures

9.1 Donation visit 1

9.1.1 Invitation

Regular whole blood donors attending their donation appointment, who typically have about a 20-minute waiting period prior to the start of donation proceedings, will be invited at the Donation Centre reception (or “Welcome”) desk to take part in the study. If the donor is interested the NHSBT “Welcomer” will confirm or update the donor’s email address and telephone number and, also, check that they meet the broad criteria for joining the study. They will then provide the donor with a study information leaflet (see **Annex 2.1** COMPARE participant information leaflet (Stage 1) V5 21.12.2015).

9.1.2 Donor screening and informed consent

After reading the information leaflet in the waiting area, the donor will be invited by a NHSBT Donor Carer to a private booth in the health screening area of the mobile session. If, after completing the routine donation health check[1] (but before routine haemoglobin screening), there are no reasons to defer the donor, the donor carer will check that the donor remains interested in joining the study and will re-assess if they meet the eligibility criteria for enrolment (See **Section 4.5**). The donor will have an opportunity to ask the donor carer questions about the research study. If donors require more time to consider their participation, they will be able to join at a subsequent donation visit, provided that the visit falls within the study recruitment period.

Eligible donors will be asked to complete both copies of the consent form (see **Annex 2.2 and 2.3** COMPARE consent Stage 1 (donor copy) V3 04.11.2015 and COMPARE consent Stage 1 (study copy) V2 20.10.2015). Once completed, the donor carer will sign and retain the 'study copy' of the consent form and hand the other copy to the donor.

For those donors who, after the routine donation health check, do not meet criteria to donate, reasons for non-eligibility (with the exception for low haemoglobin assessed using the current NHSBT screening method), and thus to take part in the study, will be recorded on the donor health check form (DHC) to be subsequently added to the donor's electronic record.

Once the consent forms have been completed, the donor carer next carries out routine pre-donation haemoglobin measurements, which consist of an initial copper sulphate gravimetric test using capillary blood obtained by a finger-prick, followed (when this initial test fails) by a spectrophotometric test (Hemocue®) using a venous blood sample. If the donor fails the venous Hemocue® test they are not eligible to donate blood and will be deferred from donating for a period of time. Consented donors who fail NHSBT’s routine haemoglobin measurements will be able to remain in the study. However for donors whose haemoglobin level is <114g/L (for women) and <124/L (for men), the deferral period will be longer than 16 weeks and 12 weeks respectively. As such these participants will not be able to attend their 2nd study visit.

On completing the pre-donation haemoglobin screening, the Donor Carer will place the DHC and consent form, of enrolled COMPARE donors, into study-specific (red) wallet.

[1] NHSBT medical screening is carried out which is based on the Blood Supply Quality Regulations and regulated by the MHRA

9.1.3. Research sample collection

Donors who have consented to participate in the study will provide 19ml of blood for research (ie, 1 x 4ml EDTA plasma, 1 x 6ml EDTA plasma, 1 x 6ml serum and 1 x TEMPUS tube requiring 3ml blood).

For donors who pass NHSBT's pre-donation test, the 19ml research sample will be collected in standard tubes from surplus blood routinely collected in the satellite pouch that forms part of the blood collection unit (ie, a separate venepuncture will *not* be required).

The procedures for research sample collection are described below:

1. At the donation pack table research sample tubes will be added to the donation baskets of donors containing a red study-specific wallet. These will be placed in a study-specific sample container. The additional sample tubes will consist of:

4ml EDTA tube (purple top)
6ml EDTA tube (purple top)
6ml serum tube (red top) – top to be ringed with black marker pen
TEMPUS tube (blue top)

2. At the donation bed the donor carer will attach a donation identification number (DIN) label to each of the research sample tubes; this should be placed so that it covers the existing label on the sample tube. The DIN labels should only be attached to research sample tubes after the DHC, NHSBT mandatory sample tubes and blood bag have been labelled. If, for any reason, there are insufficient labels for the research sample tubes the DIN should be hand written on the existing label.

3. Completely fill the satellite blood pouch.

4. Take the research samples, once all NHSBT mandatory samples have been collected, in the following order: 4ml EDTA (purple top); 6ml EDTA (purple top); 6ml Serum (red top); TEMPUS tube (blue top)

5. Invert the filled EDTA and serum research sample tubes three times as soon as the blood is added to the tube and vigorously shake the Tempus™ tube for 10 sec, as soon as the blood is added to the tube

6. Place research sample tubes in the donation basket together with packs, mandatory sample tubes and DHC and take this to the reconciliation table (Important: all research sample tubes are placed in donation pack for donors whether filled, partially-filled or unfilled).

7. Note in the 'staff use only' box of the DHC that the three research samples have been collected.

For donors who fail the standard copper sulphate NHSBT haemoglobin test the 16ml of blood will be collected from the venepuncture used for the standard secondary (venous HemoCue®) haemoglobin screening test (ie, once again, an additional venepuncture will *not* be required).

Donor carers will follow the same steps for sample collection, as described above, other than those which relate to aspects of the routine donation.

The research samples collected donors who subsequently pass venous Haemocue® remain with the DHC (and consent) and go to bedside in donation basket.

9.1.4 Participant booking of 2nd appointments

After donating and/or providing research samples, participants will be directed to the tea table for refreshments and to book their 2nd donation visit i.e. participants will go to the tea table either directly from the screening booth (if they do not pass haemoglobin screening) or from the donation bed if they are eligible to donate blood.

At the tea table, the donor carer books the second donation appointment on PULSE in 12 weeks (for men) and 16 weeks (for women) and writes the appointment date and time on the study-specific donor appointment card (see **Annex 2.4)**. If not already registered, the donor carer encourages the donor to sign up to the 'NHSBT donor portal' to enable donors to change appointments online if necessary. If donors do not wish to book an appointment at session and / or register on the 'donor portal' they will be able to book / change appointments by calling the NHSBT National Call Centre (NCC) or via the donor portal.

9.1.5 Reconciliation of consent forms and research samples

The donor carer at the reconciliation table will:

1. Separate the research sample tubes and the study wallets (containing the consent forms and DHC) from the donation packs
2. Reconcile the number of research samples and consent forms on a study-specific checklist and investigate reasons for non-reconciliation and report these on the checklist
3. Update PULSE donor records with 'outcome of donation' and add the communication code (**CP1**) on the donor record
4. Write a note on the DHC to prompt the Donor Records Team to add a temporary message to the donor record. The temporary message will appear on the donor's DHC, which they take with them to each blood donation, and will indicate to the mobile team staff that a research sample must be taken
5. Separate the DHC and the consent form
6. Post consent forms and reconciliation checklists to the NHSBT administration team. NB: If no donors have been recruited, the donor carer will send an email to UK BioCentre, cc'd to the admin team and UoC
7. Post the DHCs to the Donor Records Team
8. Complete a session delivery note and place research sample tubes in appropriate research-specific transport boxes for collection by routine transport staff
9. Pack samples in transport boxes from bottom left backwards then bottom right backwards.

9.1.6. Transport of Samples

Research blood samples will be transported from the point of collection to UK BioCentre (Stockport, UK or Milton Keynes, UK) within approximately 24 hours. This will be a three-stage process i.e:

1. Samples will be collected each day (Monday – Friday) from the mobile sessions by the routine NHSBT transport systems and taken to NHSBT stockholding units (in Manchester, Bristol (Filton) and London (Colindale)).

2. Samples which are not transported directly to Manchester, Filton or Colindale will be forwarded to these sites through usual NHSBT transport routes. On arrival the session delivery note will be checked against the number of samples received and the samples will be kept in a designated holding area for collection by UK BioCentre transport.

3. UK BioCentre will collect the research samples from NHSBT sites at Manchester, Filton and Colindale and transport to their repository (at Stockport, UK or Milton Keynes, UK) . UK BioCentre transport staff will collect samples early morning Tuesday – Saturday. A despatch note will be signed and copies retained by both NHSBT staff and UK BioCentre couriers as a record of the number of sample boxes retrieved.

From the point of collection to NHSBT stockholding sites the samples will be transported at room temperature (i.e. held at between ~ 20°C and 24°C). Samples will be transported at ambient temperature from the stockholding units to UK BioCentre.

UK BioCentre will supply study-specific sample transport boxes to each of the centres.

9.1.7. Post-donation questionnaire

Within two weeks of attending visit 1, Stage 1 donors will receive an email (see **Annex 2.5** COMPARE Email welcome and questionnaire (Stage 1, Visit 1 and Stage 2) V2 26.10.2015) from the UoC Data Manager with an online (URL) link to a study questionnaire. The URL-link will contain a unique custom tag which will be used to anonymously track questionnaire completion and to verify that it has been completed by the intended recipient. The participant will also receive a separate email with the questionnaire password (see **Annex 2.6** COMPARE Email_questionnaire key_V1 13.08.2015). If the participant does not provide their responses to the questionnaire they will be sent an email reminder after 7 days (see **Annex 2.7** COMPARE Email_questionnaire reminder 1 (Stage 1, visit 1 and Stage 2) V2 26.10.2015). A second email reminder will be sent after a further 14 days (see **Annex 2.8** COMPARE Email_questionnaire reminder 2 (Stage 1, visit 1 and Stage 2) V2 26.10.2015). If the questionnaire has not been completed 7 days after reminder 2, then a text reminder will be sent (see **Annex 2.9** COMPARE questionnaire text reminder (Stage 1 and Stage 2) V1 17.12.2015) The questionnaire will include the following questions; more details can be found in **Annex 2.10** COMPARE study questionnaire V3 15.12.2015:

<u>Section 1</u>
Questions about the general demographic characteristics of the participant.

<u>Section 2</u>
The validated Fitzpatrick questionnaire for skin type assessment.

<u>Section 4</u>
Questions regarding the symptoms of iron deficiency.

<u>Section 5</u>
The validated Medical Outcomes Survey SF-36 version 2 for general health and wellbeing.

<u>Section 6</u>
Questions regarding general adverse blood donation outcomes, e.g. breathlessness and fainting, including the validated short-form Blood Donors Reaction Inventory (BDRI).

<u>Section 7</u>
Questions regarding the lifestyle habits of donors, e.g. smoking, alcohol intake, dietary intake in general and of iron-containing foods in particular, and physical activity.

Completion of the study questionnaire is not essential to remain part of the study, however a maximum of two reminder emails will be sent to participants who do not complete it (see above).

On completion of the questionnaire participants will be sent a thank you email which will be tailored to donors who: have made their next (study visit 2) appointment (see **Annex 2.11** Thank you email Stage 1, Visit 1 – appointment made V1 17.12.2015), have not made an appointment (see **Annex 2.12** Thank you email Stage 1, Visit 1 – appointment not made V1 17.12.2015), or have been deferred for a period greater than the standard donation interval for men (12 weeks) and women (16 weeks) (see **Annex 2.13** Thank you email Stage 1, Visit 1 – deferred at first visit V1 17.12.2015).

9.2 Donation visit 2

9.2.1 Prior to 2nd donation visit

Prior to the second donation visit, participants will receive a courtesy reminder email 7 days before the appointment (see **Annex 2.14** COMPARE Stage 1 2nd visit reminder V1 13.08.2015). The email will reiterate the date of the booked appointment and will provide details of how to make or change appointments and how to contact the study helpdesk with any queries.

9.2.2 Arrival at the mobile donation session

On arrival at the mobile session, the donor carer checks the donor DHC for a temporary message indicating whether a research sample should be collected. The DHC is then placed in the study-specific wallet ready for collection by the screening donor carer.

9.2.3 Donor screening

The screening donor carer collects the study-specific wallet from the welcome desk and checks the DHC for a temporary message.

If the DHC has a temporary message, indicating that a research sample should be taken, the donor carer will:

1. Conduct pre-donation medical screening; if a participant is deferred for reasons other than for low haemoglobin, they will not provide any samples or measurements for the research and their participation in the study will end here
2. Perform a copper sulphate finger prick test (with or without a subsequent venous sample for HemoCue®) in those donors who pass the pre-donation medical screening
3. Perform a haemoglobin measurement on a capillary sample with the HemoCue®. This will be performed at the same time as the copper sulphate test to avoid additional finger pricks
4. Perform a haemoglobin measurement using a non-invasive device (i.e. either the Haemospect® or Orsense NMB200®, whichever is in current use by the mobile team)
5. Collect a research sample if the participant fails the copper sulphate test (if the participant passes the copper sulphate test, the donor will provide the research samples at the donation bed as part of their normal blood donation).

9.2.4 Research Sample Collection

Donors will provide a 4ml EDTA plasma sample

For donors who pass NHSBT's pre-donation test, the 4ml research sample will be collected in from surplus blood routinely collected in the satellite pouch that forms part of the blood collection unit (ie, a separate venepuncture will *not* be required).

The procedures for research sample collection are as described in **Section 9.1.3** however only one 4ml EDTA tube (purple top) will be collected. Thus, in the 'staff use only' box of the DHC the donor carer will indicate that one research sample has been collected.

For donors who fail the standard copper sulphate NHSBT haemoglobin test, the 4ml of blood will be collected from the venepuncture used for the standard secondary (venous HemoCue®) haemoglobin screening test (ie, once again, an additional venepuncture will *not* be required.

9.2.5 Reconciliation of research samples

The donor carer at the reconciliation table will:

1. Separate the research sample tubes and the study wallets (containing the DHC) from the donation packs.
2. Reconcile the number of research samples and DHC forms on a study specific checklist and investigate reasons for non-reconciliation and report these on the checklist.
3. Update PULSE donor records with 'outcome of donation'
   Post reconciliation checklists to the NHSBT administration team. NB: If no donors have been recruited, the donor carer will send an email to UK BioCentre, cc'd to the admin team and UoC.
4. Complete a session delivery note and place research sample tubes in appropriate research-specific transport boxes for collection by routine transport staff.
5. Pack samples in transport boxes filled from bottom left backwards then bottom right backwards.

9.2.6 Transport of Samples

The protocol for the transport of research samples from the second donation will be identical to the processes described in **Section 10.1.6**

9.2.7. Post-donation questionnaire

Within two weeks of attending visit 2, Stage 1 donors will receive an email from the UoC Study Data Manager (see **Annex 2.15** COMPARE Email questionnaire (Stage 1, Visit 2) V1 26.10.2015) with an online (URL) link to a study questionnaire. The URL-link will contain a unique custom tag which will be used to anonymously track questionnaire completion and to verify that it has been completed by the intended recipient. The participant will also receive a separate email with the questionnaire password (see **Annex 2.6** COMPARE Email_questionnaire key_V1 13.08.2015). If the participant does not provide their responses to the questionnaire they will be sent an email reminder after 7 days (see **Annex 2.16** COMPARE Email_questionnaire reminder 1 (Stage 1, Visit 2) V1 26.10.2015). A second email reminder will be sent after a further 14 days (see **Annex 2.17** COMPARE Email_questionnaire reminder 2 (Stage 1, visit 2) V1 26.10.2015). If the questionnaire has not been completed 7 days after reminder 2, then a text reminder will be sent (see **Annex 2.9** COMPARE questionnaire text reminder (Stage 1 and Stage 2) V1 17.12.2015)

This very brief questionnaire, which will take no more than 5 minutes to complete will ask the questions contained in Section 3 of the questionnaire shown in **Annex 2.10** COMPARE study questionnaire V3 15.12.2015.

On completion of the questionnaire the participant will be taken to a 'thank you' web page.

For participants who have attended both donation visits, and have completed the questionnaire following visit 2 but have not responded to visit 1 questionnaire, they will receive an email with a URL-link (the password will be sent separately) see **Annex 2.24**, COMPARE Email_questionniare (Part 1 re-invite, Stage 1) V1 05.07.2016.

For participants who have not completed the questionnaire following either visit but have attended both donation visits, an email invite with a request to complete the baseline questionnaire will be sent – see **Annex 2.25**, COMPARE Email_questionniare (Part 1 & 2, Stage 1) V1 05.07.2016.

10. Stage 2 study procedures

10.1 Invitation

The invitation process will be the same as that described for Stage 1 participants in **Section 9.1.1.** However, Stage 2 participants will receive a modified version of the participant information leaflet (see **Annex 2.18** COMPARE participant information leaflet (Stage 2) V5 21.12.2015).

10.2 Donor screening and informed consent

The donor screening and informed consent process will be the same format as that described for Stage 1 participants in **Section 9.1.2** (however any statements relating to attendance of a 2nd visit are irrelevant). For Stage 2, only the 'study copy' will be completed by the participant and the donor carer. An example 'donor copy' Stage 2 consent form will be provided in the information leaflet that participants receive before joining and can keep for future reference. Stage 2 participants will receive modified versions of the consent forms which refer to the different version of the participant information leaflet (described above) (see **Annex 2.20** COMPARE consent Stage 2 (study copy) V2 20.10.2015) and **Annex 2.18** COMPARE participant information leaflet (Stage 2) V5 21.12.2015) for a donor copy..

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10.3 Non-invasive haemoglobin measurement

Following screening, consent process and the standard NHSBT haemoglobin measurements, enrolled donors will have their haemoglobin level re-measured using a non-invasive device. This will be done using either of two hand-held spectrometer devices (ie, MBR Haemospect® versus Orsense NMB200®).

10.4. Research sample collection

The process for the collection of the research samples will be the same as described in **Section 9.1.3**. Donors who have consented to participate in the study will provide 19ml of blood for research (ie, 1 x 4ml EDTA plasma, 1 x 6ml EDTA plasma, 1 x 6ml serum and 1 x TEMPUS tube, requiring 3ml blood).

10.5. Reconciliation of consent forms and research samples

These processes will be the same as those described in **9.1.5.** However the communication code **CP2** (rather than CP1) will be added to the donor record, together with the study outcome. Update PULSE donor records with 'outcome of donation' and add the communication code (**CP1**) on the donor record. Furthermore it will not be necessary to write a note on the DHC to prompt the Donor Records Team to add a temporary message to the donor record indicating that a research sample must be taken at the next visit.

10.6. Transport of Samples

The process for the transport of samples will be the same as that described in **Section 9.1.6**.

10.7 Post-donation questionnaire

Within two weeks of enrolling on the study donors will receive an email from the UoC Study Data Manager (see **Annex 2.5** COMPARE Email welcome and questionnaire (Stage 1, Visit 1 and Stage 2) V2 26.10.2015) with an online (URL) link to a study questionnaire. The URL-link will contain a unique custom tag which will be used to anonymously track questionnaire completion and to verify that it has been completed by the intended recipient. The participant

will also receive a separate email with the questionnaire password (see **Annex 2.6** COMPARE Email_questionnaire key_V1 13.08.2015). If the participant does not provide their responses to the questionnaire they will be sent an email reminder after 7 days (see **Annex 2.7** COMPARE Email_questionnaire reminder 1 (Stage 1, visit 1 and Stage 2) V2 26.10.2015). A second email reminder will be sent after a further 14 days (see **Annex 2.8** COMPARE Email_questionnaire reminder 2 (Stage 1, visit 1 and Stage 2) V2 26.10.2015). If the questionnaire has not been completed 7 days after reminder 2, then a text reminder will be sent (see **Annex 2.9** COMPARE questionnaire text reminder (Stage 1 and Stage 2) V1 17.12.2015)

The questionnaire will include:

Section 1
Questions about the general demographic characteristics of the participant

Section 2
The validated Fitzpatrick questionnaire for skin type assessment

Section 3
Questions about participants' experiences and preference of current and alternative methods for pre-donation haemoglobin measurements

Section 4
Questions regarding the symptoms of iron deficiency

Section 5
The validated Medical Outcomes Survey SF-36 version 2 for general health and wellbeing

Section 6
Questions regarding general adverse blood donation outcomes, e.g. breathlessness and fainting, including the validated short-form Blood Donors Reaction Inventory (BDRI)

Section 7
Questions regarding the lifestyle habits of donors, e.g. smoking, alcohol intake, dietary intake in general and of iron-containing foods in particular, and physical activity

Completion of the study questionnaire is not essential to remain part of the study, however a maximum of two reminder emails will be sent to participants who do not complete it (see above).

On completion of the questionnaire the participant will be taken to a 'thank you' web page.

11. Data management

11.1 Data management processes at mobile sessions

11.1.1 Donor record management

Mobile session staff will place a communication code (**CP1** or **CP2)** on the records of donors who enrol on Stage 1 or Stage 2 of the study respectively. This communication code will flag a donor's participation in the study and result in daily business objects (BoBs) reports being generated by NHSBT from their national database, PULSE. These BoBs reports (described in more detail in **Section 11.3.1**) will include data on enrolled donors and will be sent to the UoC COMPARE Data Manager for the purposes of managing the study protocols, tracking study participation and populating the research database in an efficient and secure way.

Mobile session staff will also write a note on Stage 1 participants' DHCs to prompt the Donor Records Team to add a temporary message to the donor record. The temporary message will appear on the donor's DHC, which they take with their 2nd study blood donation visit, and will indicate to the mobile team staff that a research sample must be taken.

11.1.2 Electronic transfer of data from non-invasive measurements

At the end of the day, members of the mobile team will upload any data collected from the non-invasive devices to a secure NHSBT server site that can be viewed by study staff with NHSBT honorary contracts. The data will consist of the haemoglobin measurement(s), a time and date stamp and the Donor Number. The data will, therefore, consist of minimal personal identifiable detail. Once the data have been uploaded, the mobile team will send an email of notification to the UoC Helpdesk and Data Manager.

11.1.3 Transfer of consent forms

At the end of the day, members of the mobile team will post consent forms and reconciliation checklists to the NHSBT administration team. NB: If no donors have been recruited, the donor carer will send an email to UK BioCentre, cc'd to the admin team and UoC.

11.2 Data management process at NHSBT Administration Team

On receipt of consent forms and reconciliation checklists from NHSBT mobile teams, the administration team will cross-check the number of consent forms with the information on the study-specific reconciliation checklist. Consent forms and checklists will then be scanned and placed onto a server drive that can be viewed by study staff with NHSBT honorary contracts. Consent forms and checklists will be organised on the server drive both by mobile team and by date. Paper copies will be kept in a secure place until the end of the study when they will be sent to UoC Study Team for long-term storage.

Every day, the UoC Data Manager will receive a BoBs report (see above) generated from PULSE which will include the number of donors who have consented to the study. Once donor numbers have been reconciled between the BoBs report and consent forms, the Data Manager will generate a unique study ID for each donor and email the online study questionnaire. If donor numbers cannot be reconciled, the Data Manager will investigate the audit trail for a possible explanation and solution. The actions to be taken in the event of non-reconciliation are documented in **Annex 1: Flowchart 4.**

11.3 Data management processes at University of Cambridge

11.3.1. Population and management of research database

The UoC Data Manager will receive a set of PULSE Business Objects reports (**BoBs#1 - #6**) from NHSBT containing data for the purposes of managing the study protocols, tracking

study participation and population of the research database in an efficient and secure way. The data to be exchanged are fully described in **Annex 2.21** (URS COMPARE Business Objects Reports V1 13.08.2015). The reports will be in .csv format, to be saved as a zipped file with encryption known only by certain members of the UoC Research Study Team, and emailed to a nominated email address at UoC.

11.3.2. Reconciliation of research samples

The UoC Data Manager will receive a daily list from UK BioCentre containing the donation identification numbers (DINs)[2] retrieved from research sample tubes and the date of samples received. This report will be created in .csv format, saved as a zipped file with encryption known only by certain members of the UoC Research Study Team, and emailed to a nominated email address at UoC. The Data Manager will reconcile the number of DINs from the UK BioCentre report with the number of DINs from the PULSE reports (**BoBs#1 and #2** see **Annex 3**). The actions to be taken in the event of non-reconciliation are documented in **Annex 1**: **Flowchart 4**.

11.3.3 Transferring non-invasive measurement data to research database

Once the helpdesk receives notification from the mobile teams of non-invasive and HemoCue® data on the NHSBT server site, they will securely transfer it to the UoC Study Data Manager for secure storage on the COMPARE study research database.

11.4 Privacy and confidentiality of participant data Steps taken to protect participants'' privacy and confidentiality include:

1. Personal information (including name and address) will be directly provided by study participants through the study online questionnaire. This information will be used to communicate with participants and will be held in a secure location, separately from the study data.

2. At the blood donation session, consent to take part in the study will be recorded on a form that will include identifiers including participant name. Scanned copies of consent forms, collected at the donation visit, will be transferred to the study coordinating centre at the University of Cambridge. This transfer will involve the use of NHSBT secure systems. The forms will be stored in a secure location, separately from the study data; in the long-term these data will be stored using an off-site storage facility (eg, Iron Mountain).

3. Limited personal information will be accessed and retrieved from the national NHSBT database (PULSE). This will include email address and telephone number for the purposes of study communication only. In addition we will retrieve participants' Donor Number and NHS number. These personal data will be stored in a secure location, separately to the study database. Access to this information will be password-protected and restricted to designated members of staff working under the direct supervision of the senior investigators.

4. Samples and data collected during the study will be stored using a unique, anonymous study identification number.

[2] The Donation Identification Number is unique to each donation and donor.

5. A table linking participants' anonymous study identification number to their Donor Number and NHS number will be stored on a separate password protected location which may be accessed by the Study Data Manager only. This link table, which may be accessed with the explicit approval of senior investigators, will be used to retrieve relevant health information from participants medical and other health-related records. The retrieved information will be pseudo-anonymised as any personal identifying details will have been removed and replaced by the unique anonymous study identification number. The applicants received ethical approval to retrieve electronic health records data, in the same way, in previous studies of blood donors, eg, the INTERVAL study [REC 11/EE/0538], Cambridge CardioResource (REC 09/H0304/42), and the donor-EHR study (REC 14/EE/0182).

6. All study data will be stored in restricted-access, study databases. This 'study database' will not be connected to the NHSBT database containing participants' personal details. The study data will be linked to the study identification number. Access to the study database will be password-protected and will be used only by named researchers working on this study under the direct supervision of the senior scientific investigators.

12. Future data collection

Participant data will be linked to various existing health records using the NHS number which will be included in the Business Object report (**BoBs#**1) received by UoC Data Manager from NHSBT. This will allow tracking of participants' health in the future and will provide relevant information to NHSBT on the long-term health consequences of blood donation. It will also offer wider scope to look at determinants of future health outcomes in the general population e.g. genetic variants and lifestyle factors.

13. Blood sample processing and analysis

Research blood samples collected at blood donation sessions will be transported to a purpose-built bio-repository, UK BioCentre (Milton Keynes and Stockport). This facility provides a proven service to academic and industrial partners conducting biomedical studies (most notably UK Biobank -a study in 500,000 people to study the causes of common diseases http://www.ukbiobank.ac.uk/ and the INTERVAL study - a study in 50,000 blood donors to determine whether the interval between blood donations in England can be safely and acceptably decreased http://www.interval.org.uk/).

UK BioCentre holds a Human Tissue Authority License and complies with ISO 9001:2008 (Quality Management accreditation of services provision) and ISO 27001:2005 (Information Security Management accreditation of service provision – accreditation held at Stockport and pending at Milton Keynes).

UK BioCentre will support the study's processing and assay requirements. Blood samples will be collected at the registration visit and at the second visit for Stage 1 participants only. At each of these time-points UK BioCentre will:

1. Generate lists of samples received by scanning the DIN on sample labels and email these sample lists to the study centre in Cambridge. This will enable consolidation of the number of samples and number of consent forms retrieved (see **Section 11.3.2** above).
2. Use whole blood from the 4ml EDTA sample to generate an extended haematological profile of blood cell indices using a Sysmex Full Blood Count analyser. Aliquots of whole blood will be stored at -80^{o}C for future use.
3. Sub-aliquot the 6ml serum sample into 2 x 0.8ml serum aliquots. These will be labelled with a unique study identifier linked to the DIN and stored at - 80°C for future research, including measurement of soluble biomarkers (e.g. ferritin, hepcidin) known to be related to iron or red cell metabolism
4. Sub-aliquot the 6ml EDTA sample into 2 x 0.8 ml plasma aliquots and buffy coat. The plasma will be stored at -80^{o}C for future use. DNA will be extracted from the buffy coat. Extensive genotyping and/or sequencing will be done, including for genetic variants relevant to iron homeostasis and blood cell indices (e.g. variants in *HFE*, *TMPRSS6*, *TFR2*). DNA will be stored. These will be labelled with a unique study identifier linked to the DIN.
5. Storage of TEMPUS tubes at -80^{o}C for future research
6. Store samples in an anonymised form. Access to the tables linking study identification numbers to a participant's identity will be stored on a separate password-protected system which may be accessed only with the explicit approval of senior investigators. A Data Access Committee will review written proposals for the use of samples and assess their scientific excellence. Stored samples will be labelled with the study identification number only therefore researchers using the samples will never know the identity of the person who donated the sample. The release of samples to other organisations and researchers will be regulated by a material transfer agreement.

13.1 Future use of stored samples

As stated above, we plan to collect 19ml of whole blood for research in four sample tubes i.e. 4ml EDTA, 6ml EDTA and 6ml serum sample and TEMPUS tubes. These will be collected at baseline study visits. Participants enrolled in the first stage of recruitment will also be asked to give research sample (4 ml) with their second routine donations.

The stored samples will provide an epidemiological bioresource that will, enable detailed study of the health of blood donors. More generally, this resource will encourage future

studies in NHSBT that address other relevant service needs. These subsidiary studies could help advance scientific understanding and public health, addressing existing and unanticipated hypotheses which the current applicants may carry out with other academic and/or industrial collaborators.

Future use of samples will include carrying out biomarker measurements in the stored plasma/serum samples and using current and/or future genotyping or sequencing technologies that assay stored DNA samples. Specifically, samples will be used for:

1. Analysis, amplification and storage of DNA extracted from blood: including tests that will look at DNA sequence variation e.g. genotyping tests, genomic hybridization arrays and sequencing of a part or the whole genome, and the analysis of RNA by sequencing or expression arrays.

2. Analysis and storage (indefinitely) of blood cells, blood components or derivatives for future use in research: including the isolation and storage of any type of cell (e.g. red blood cells) and other components found in plasma and serum such as proteins, carbohydrates and lipids and performing biochemical and chemical tests on these.

Biological materials and derivatives will be exchanged with collaborating research and NHS/private sector laboratories in the UK and abroad. In the case of exchange of materials with non-named study collaborators, a material transfer agreement will be used to regulate the transfer of materials and to regulate adherence to the principles of good guardianship. Collaborating partners will also have a range of laboratory tests that include, but are not restricted to studying cellular and biochemical parameters and analysis of DNA and RNA as stated above. This may include genome wide analysis of SNPs and/or re-sequencing of genes and testing serum/plasma factors.

Samples and data which will include a participant's full DNA (genetic) code may be used in a number of approved research projects. The results of these projects may not be known for several years. As sample measurements are not performed in the same way or to the same laboratory standards as clinical tests, participants will not be informed of any incidental findings. Researchers using these samples will only be provided with anonymised data which ensures they cannot link the sample or data to a participant by name.

14 Safety reporting

14.1 Donation deferrals

NHSBT will run a daily automated PULSE query to provide the UoC Data Manager with a report detailing deferrals in study participants (see **Annex 2.21**: **BoBs#3)**. This report will include Donor ID (Donor Number), deferral date and deferral code. These data will be emailed as an encrypted csv file to a study-specific UoC email address. These data will be reported to the Study Steering Committee at intervals to be specified by this committee.

14.2 Adverse events of donation (AEDs)

AEDs during the donation visit (e.g. faints) will be dealt with using NHSBT systems which are currently in operation i.e. the event will initially be recorded on the DHC and later uploaded to the PULSE database.

AEDs occurring after the donation visit and reported to NHSBT will be referred to the Clinical Support Team. Events will be recorded on the PULSE database.

NHSBT will run an automated PULSE query to provide UoC Data Manager with a report detailing adverse events AEDs (see **Annex 2.21: BoBs#4**). This report will include AEs occurring during or after the donation visit (e.g. faints) and recorded by NHSBT on PULSE. This report will include Donor ID (donor number), AE date and AE code.

These data will be reported to the Study Steering Committee at intervals to be specified by this committee.

14.3 Serious adverse events

14.3.1 Definition of a serious adverse event (SAE)

An adverse even on any treatment that:
1. Results in death
2. Is life threatening (the term “life-threatening” refers to an event in which the participant was at risk of death at the time of the event. It does not refer to an event that hypothetically might have caused death if it was more severe)
3. Requires patient hospitalisation
4. Results in persistent or significant disability/incapacity

14.3.2 Death

NHSBT will provide the UoC Data Manager with a report (see **Annex 2.21: BoBs#5**) which will include the donor numbers of any participants who die during the study and details on cause of death (if available). Deaths will be reported to the Study Steering Group who will monitor the rate and causes (if available) of death.

14.3.3 Serious adverse events of donation (SAEDs)

Any SAEDs are recorded by NHSBT and will be reported to UoC, on a case-by-case basis, by the NHSBT Operational Change Manager. These incidents will be reported to the Study Steering Committee.

For further details of reporting procedures for serious adverse events, see **Annex 1: Flowcharts 8b – 8d.**

15. Withdrawals

15.1 Identifying level of withdrawal

All requests from donors to withdraw from the study will be directed to the research study team

A participant is free to withdraw their consent from the study, at any time, without giving a reason. Participants will be able to choose their desired level of withdrawal after discussion with the study team; there are two options:

15.2 No further contact

This will mean that the participant will no longer be contacted by the study team but will continue to give their permission to retain and use information and samples provided previously and to obtain and use further information from health records. Participants will be required to complete a form indicating these wishes (see **Annex 2.22** COMPARE withdrawal (no further contact) V1 13.08.15)

15.3 No further use

This will mean that the participant withdraws their permission:
1. to be contacted by the study team
2. for further information about them to be collected
3. for previously collected information and samples to be made available to researchers

If a participant requests no further use it will not be possible to remove results of any tests already obtained from samples from the study database, but we will prevent records from being used in any future research. Blood samples will be removed from the central study repository after receiving written notification of withdrawal. However it will not be possible to remove small volumes of samples which already have been distributed to research laboratories but results which are generated after withdrawal will not be uploaded to the study database. Participants will be required to complete a form indicating these wishes (see **Annex 2.23** COMPARE withdrawal (no further use) V1 13.08.15).

15.4 Positive microbiology

The University of Cambridge will be notified by NHSBT of any donors who test positive for routine microbiology tests conducted by the blood service. These donors will no longer be eligible to donate blood and therefore will be withdrawn from the project.

15.5 Recording withdrawals

The UoC Study Data Manager will place a flag on the research database to ensure appropriate use of data and will notify the helpdesk of withdrawal. The helpdesk will add a communications code (**CP3**) to the PULSE database to indicate the donor is no longer taking part in the study, and change the donor procedure code back to WHB (whole blood) and move the donor to an appropriate subpanel to ensure their next appointment at the standard donation interval.

University of Cambridge research staff will instruct UK BioCentre to remove all archive samples from the bio-repository for donors who have requested no further use and for participants who have been withdrawn from the study due a positive microbiology result.

Signed withdrawal forms will be kept as a record of the participant's wishes.

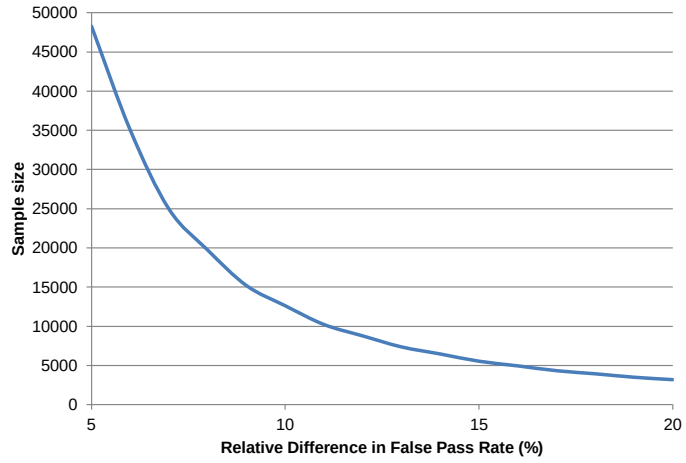
16. Sample size and statistical analysis plan

16.1 Sample size

The overall study sample size has been determined on the basis of the following (partially overlapping) considerations: (i) the need to generate evidence sufficiently compelling to influence regulators and policy-makers; (ii) NHSBT's duty of care to 1.3 million blood donors per year, making it vital for the service to evaluate even subtle changes in the proportion of donors that are bleed with an haemoglobin levels below the recommended threshold; (iii) NHSBT's objective to move toward a more donor-friendly way of haemoglobin testing, that can improve donor's experience and optimise donor session flow.

Our power calculation is based on having 80% power to detect a 10% relative difference in false pass rate between the current NHSBT screening method and either: (i) Hemocue® on capillary blood; (ii) a "post-donation" screening strategy, or (iii) a non-invasive strategy to measure pre-donation haemoglobin concentration. The sample size calculations are based on a direct (ie, within person) comparison using a McNemar's paired test. Using information on a previous study and on INTERVAL data, we assumed a prevalence of "true" low haemoglobin of 10%, a sensitivity of the current NHSBT screening method of 55%, and a correlation coefficient between current method and any alternative novel strategies of 0.70 (**Figure 3**). Similar sample size will be required for the indirect (ie, between person) comparison of non-invasive devices (MBR Haemospect® vs Orsense NBM 200®), assuming that the sensitivity of non-invasive devices is about 20% (as reported by previous publications).

Figure 3. Sample size required for a within-person pairwise comparison to detect relative differences in false pass rate for low haemoglobin between screening strategies with 80% power



16.2 Statistical analysis plan

For comparison of alternative novel strategies versus the current NHSBT screening strategy, analyses will involve only within-person comparisons. Differences in sensitivity (Se) and specificity (Spe) (measured against the gold standard) of the novel screening methods versus the current methods will be calculated. In order to clarify the impact of a given difference in sensitivity and specificity between devices in terms of donor screening, difference in false pass rate (FPR) will also be calculated (**Box 1**). Further within-person (direct) comparisons will be conducted to assess differences in sensitivity and specificity in the novel screening methods amongst individuals that have both novel screening methods of

interest assessed. In comparison of non-invasive devices (MBR Haemospect® vs Orsense NBM 200®), analyses will involve between-person comparisons. To assess the performance of the Sysmex auto-analyser as a “gold standard” haemoglobin measurement, we will test 10% of samples in duplicates.

Box 1. Definitions of key statistical metrics used for analysis

	Sysmex auto-analyser (“gold standard”)	
Screening strategy	Positive (Low Hb)	Negative (Sufficient Hb)
Positive test result (Low Hb)	True Positive (TP)	False Positive (FP)
Negative test result (Sufficient Hb)	False Negative (FN)	True Negative (TN)

Hb, haemoglobin

Sensitivity = probability of detecting low Hb given the donor truly has low Hb

= probability of testing positive given the donor is true positive (has low Hb)

= TP / (TP+FN)

Specificity = probability of detecting sufficient Hb given the donor truly has sufficient Hb

= probability of testing negative given the donor is true negative (Sufficient Hb)

= TN / (TN+FP)

False Pass Rate = probability of inappropriately bleeding a donor

= FN / (TP+FP+TN+FN)

17. Finance and insurance arrangements

17.1 Finance

Funding for the study is from NHSBT and the University of Cambridge (NIHR) Blood and Transplant Research Unit.

17.2 Insurance

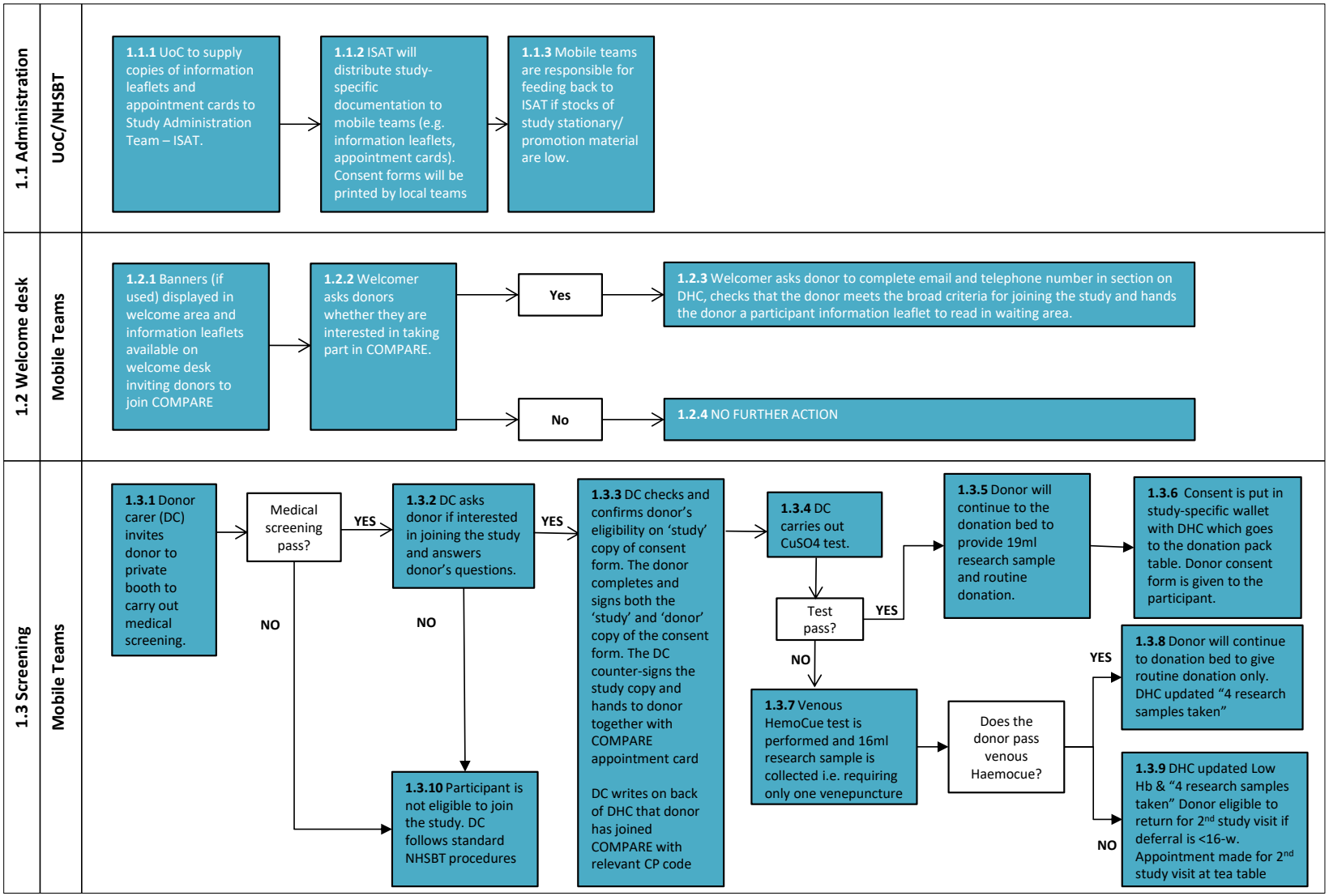
An NHSBT indemnity scheme will apply. NHSBT is a Special Health Authority which is a member of the NHS Litigation Authority risk pooling schemes for clinical negligence and liabilities to third parties.

18. Publication policy

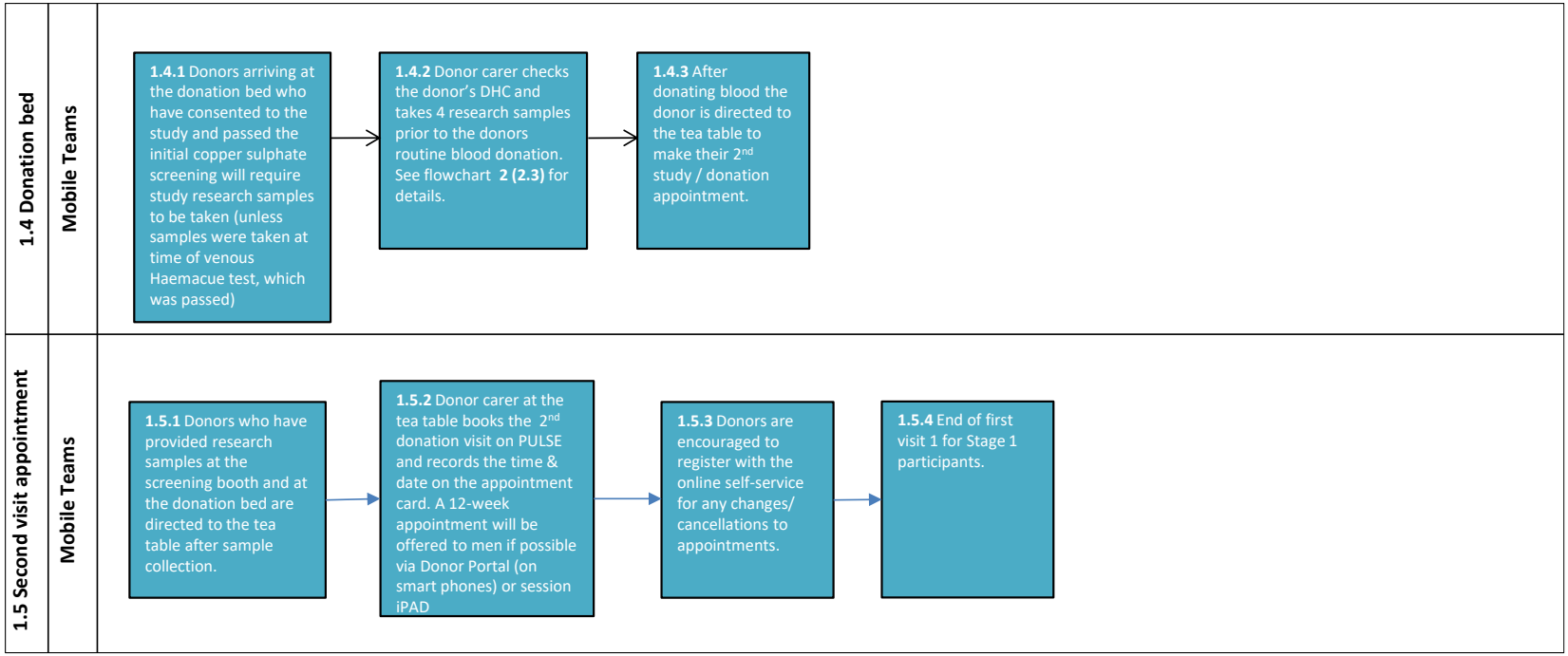
The publication policy for this study will be addressed in a separate document drafted by the TMG.

ANNEXE 1: End-to-end operational processes

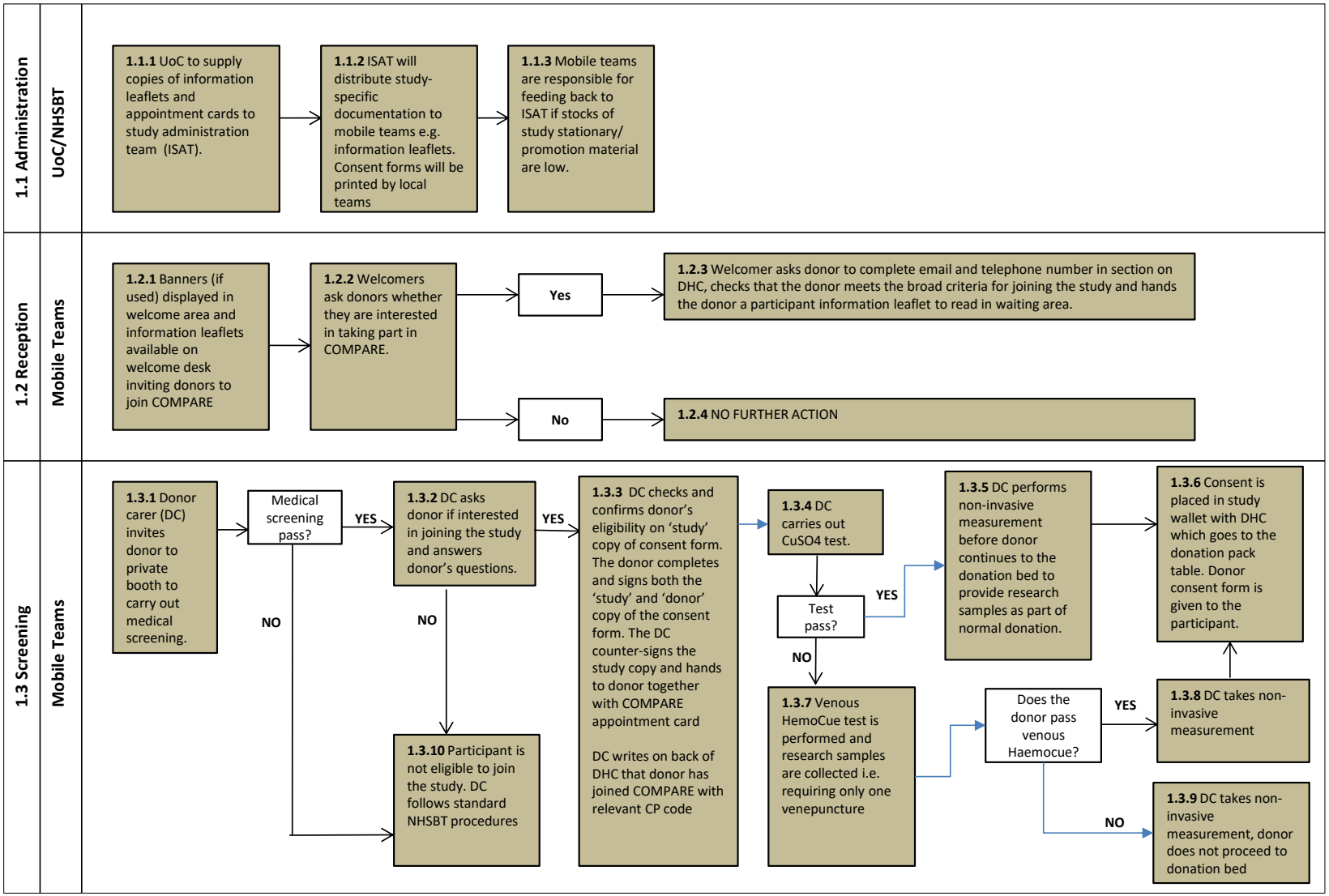
Flowchart 1a: Stage 1, visit 1 (Donor screening and consent)



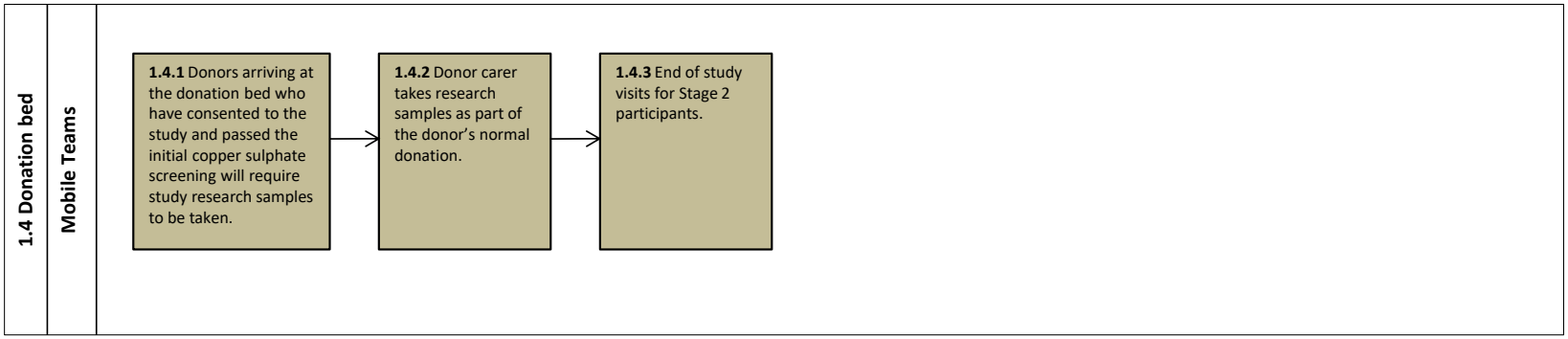
Flowchart 1a: Stage 1, visit 1 (Blood donation and booking 2nd study visit)



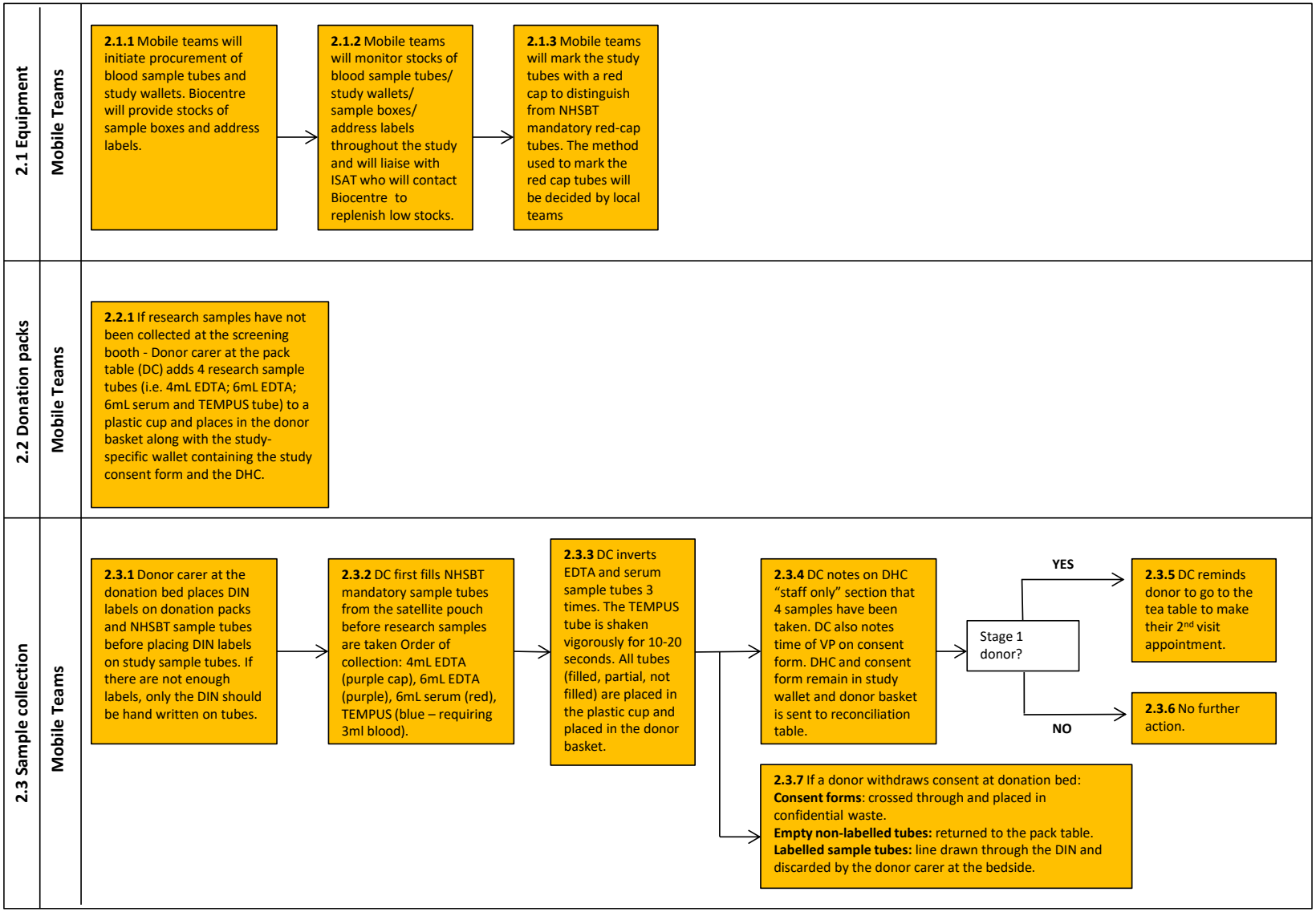
Flowchart 1b. Stage 2 (Donor screening and consent)



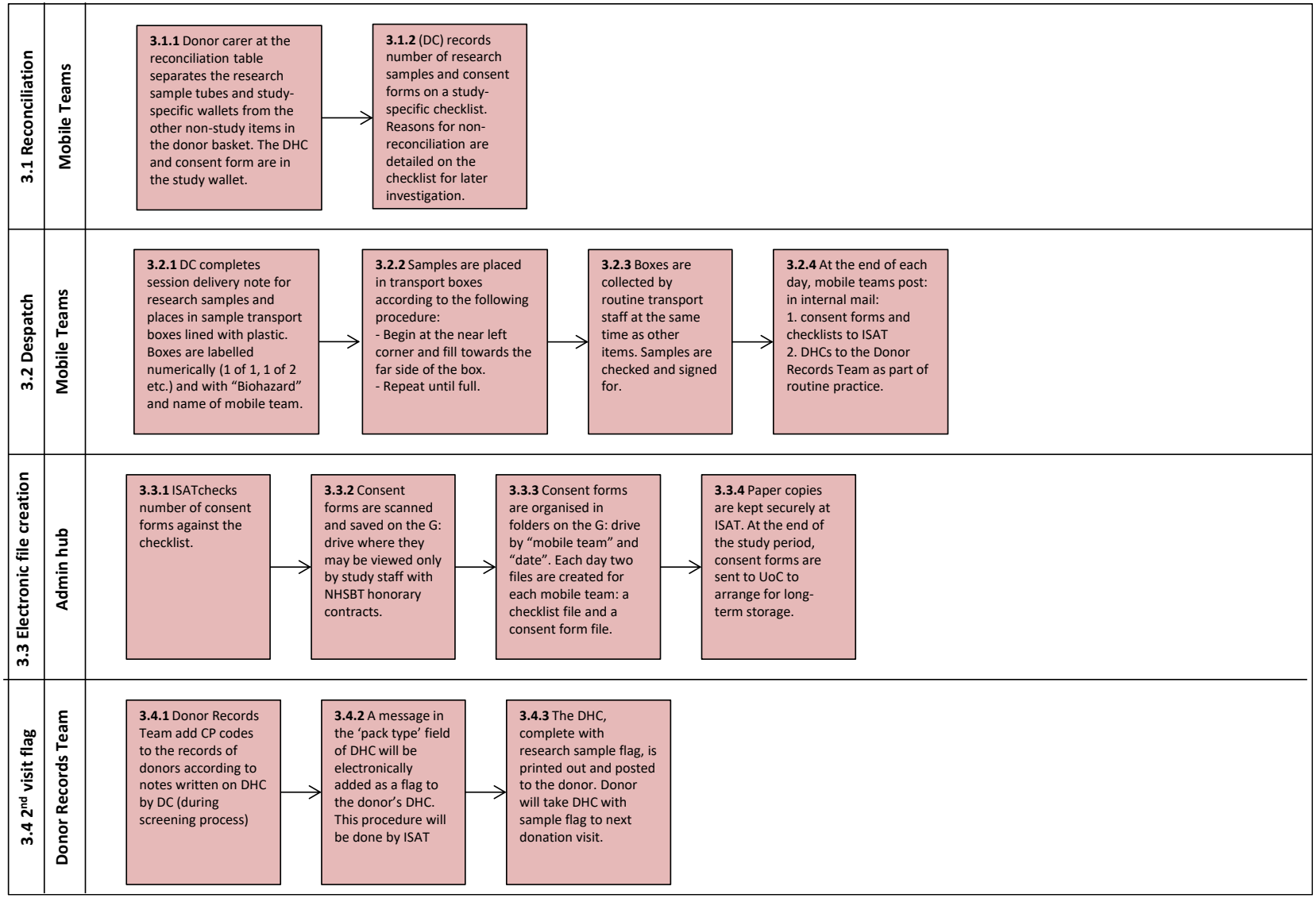
Flowchart 1b: Stage 2 Donor registration protocol – non-invasive strategy



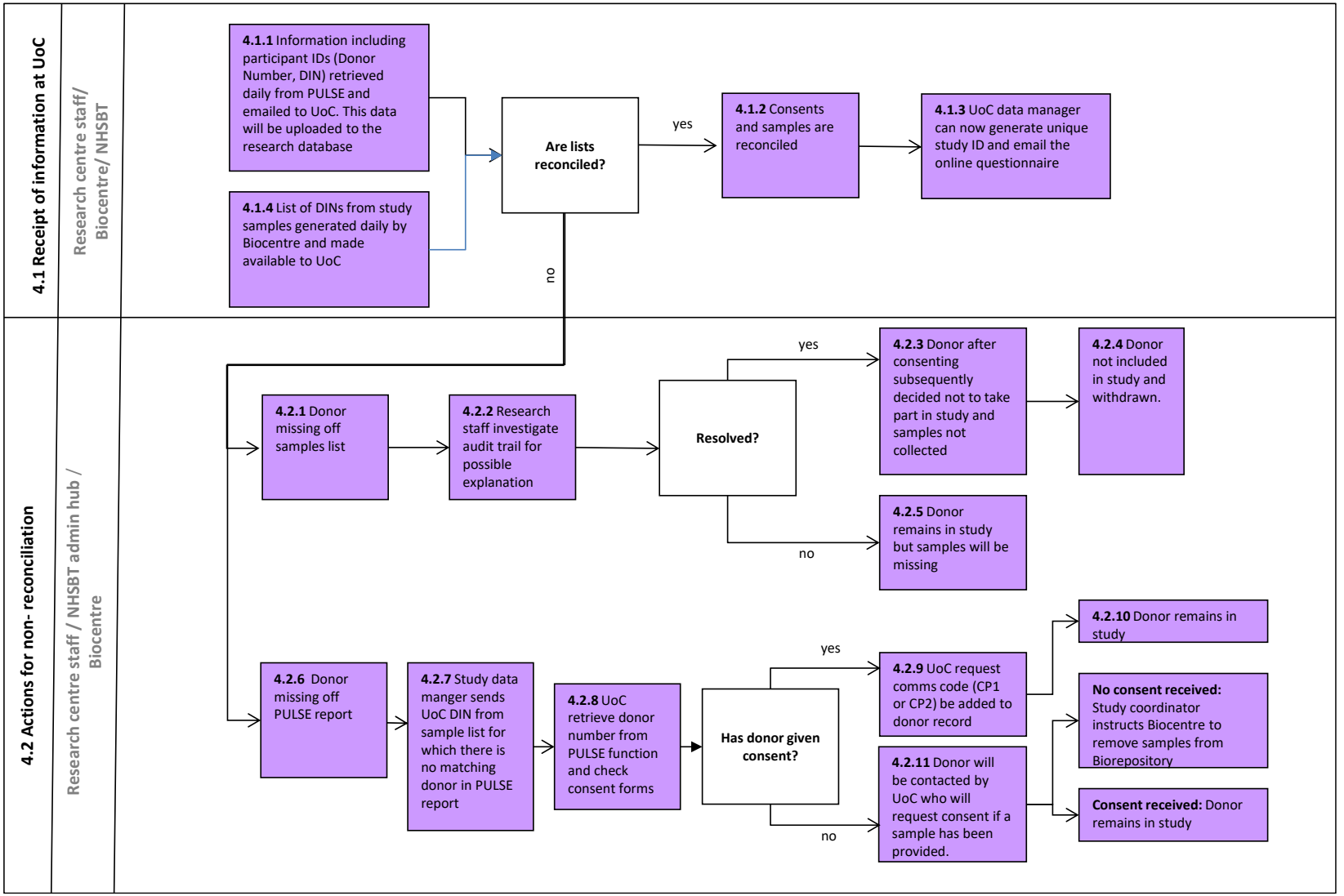
Flowchart 2: Research sample collection protocol



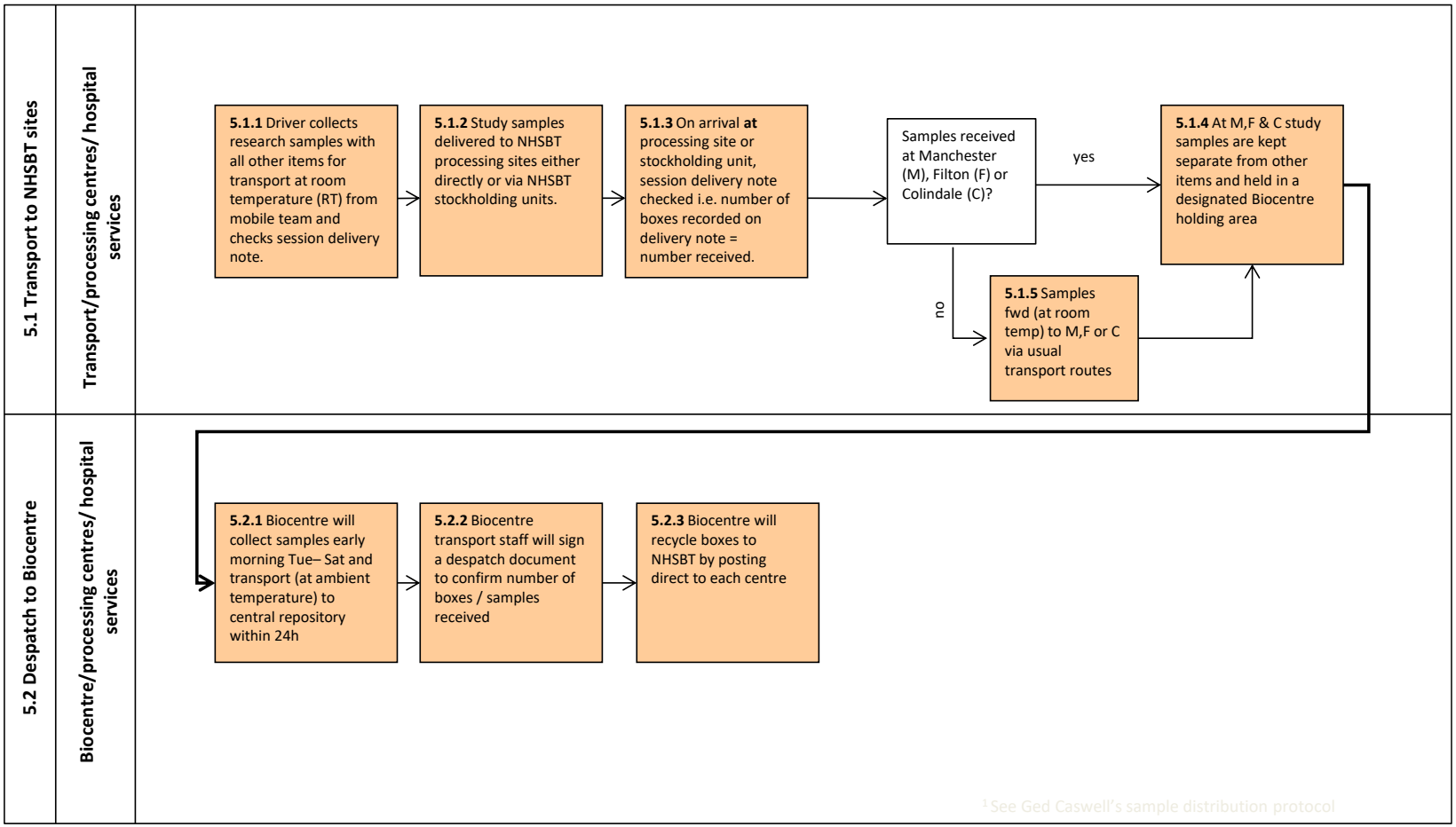
Flowchart 3: Sample, consent and DHC reconciliation protocol



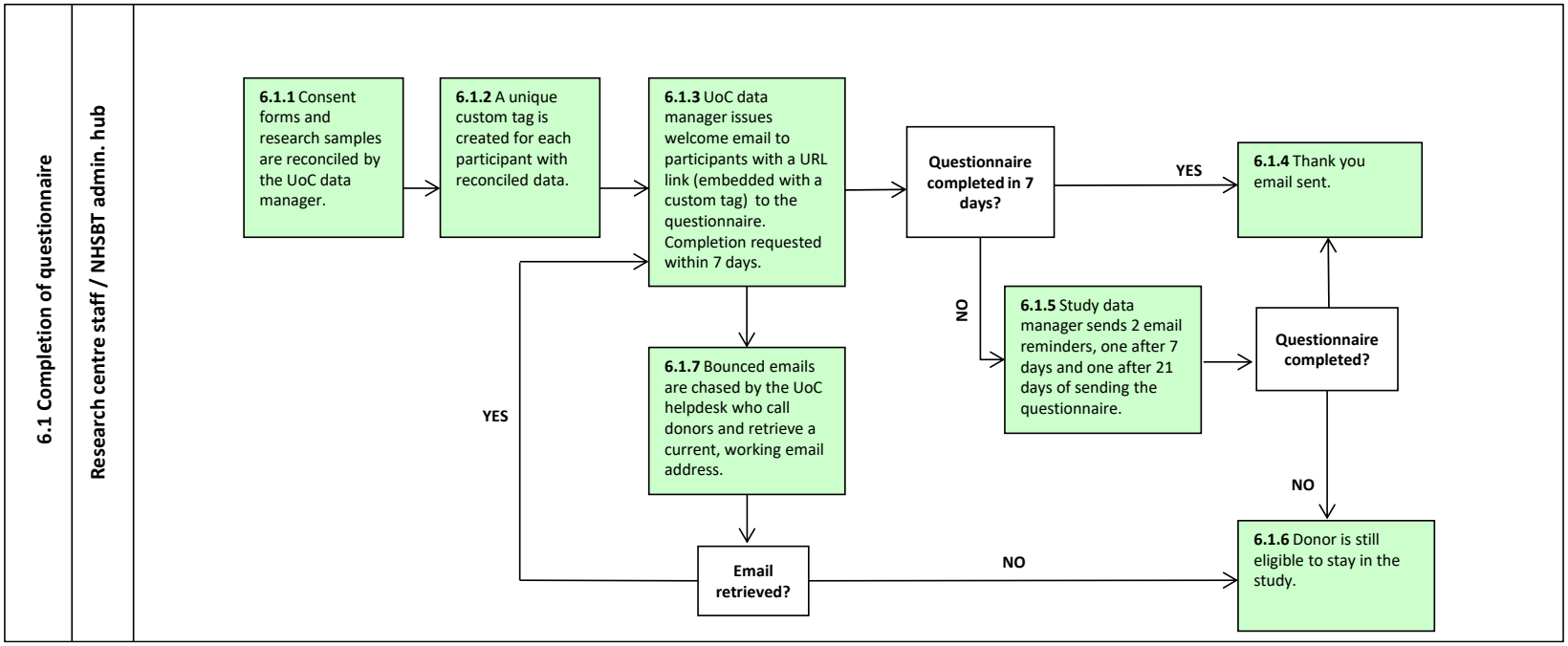
Flowchart 4: Research centre reconciliation protocol



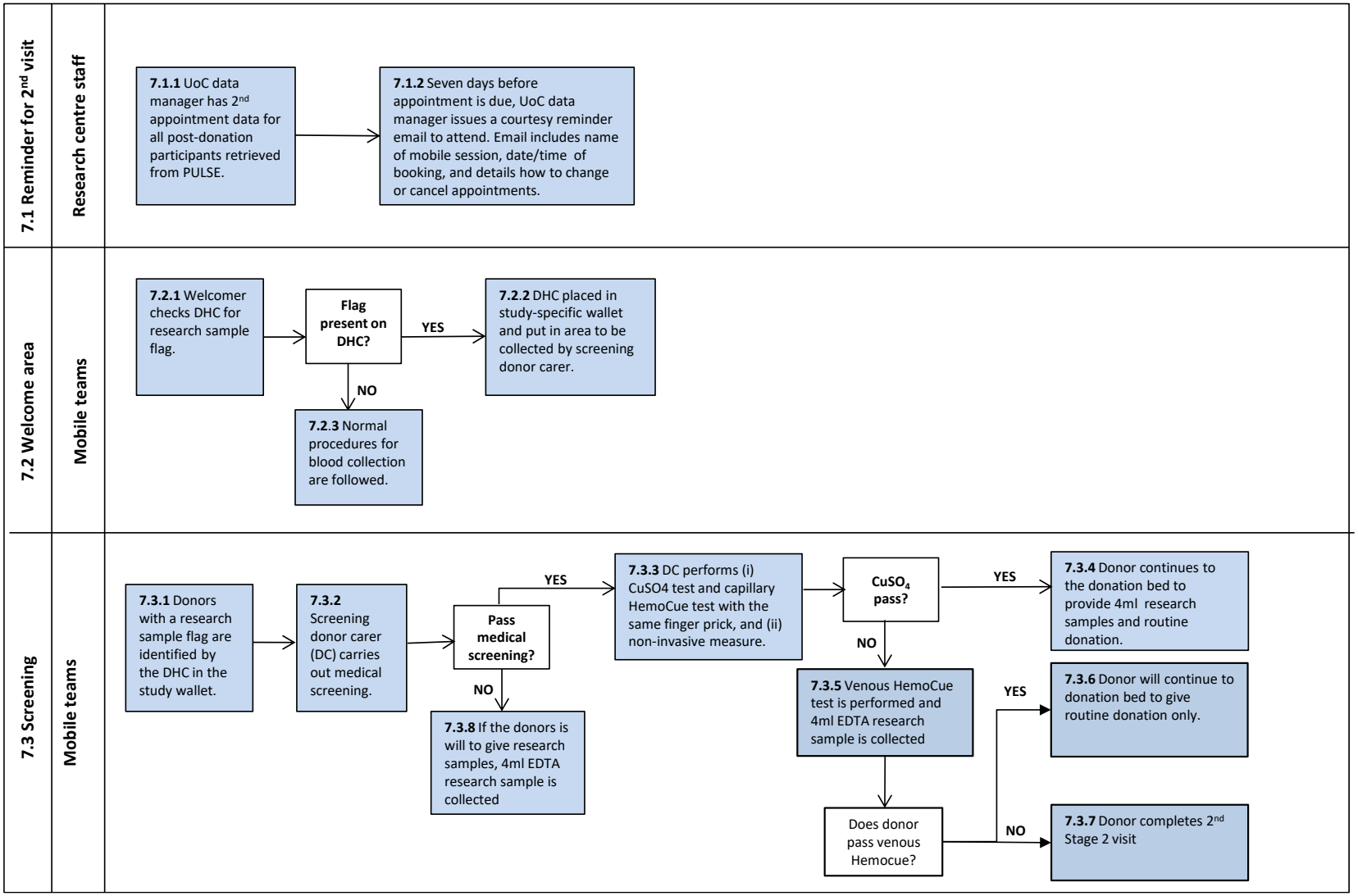
Flowchart 5. Research sample transport protocol



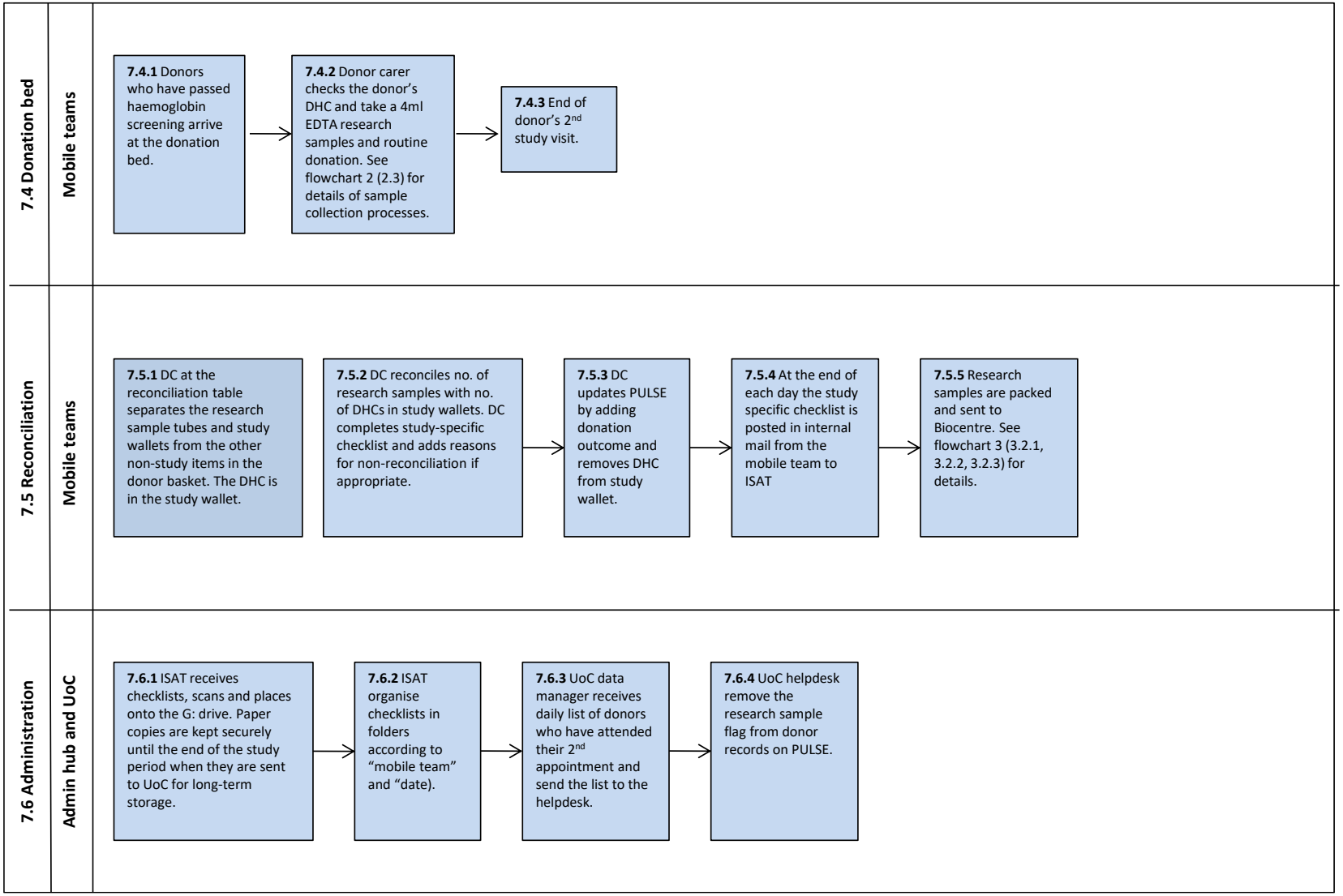
Flowchart 6. Online questionnaire protocol



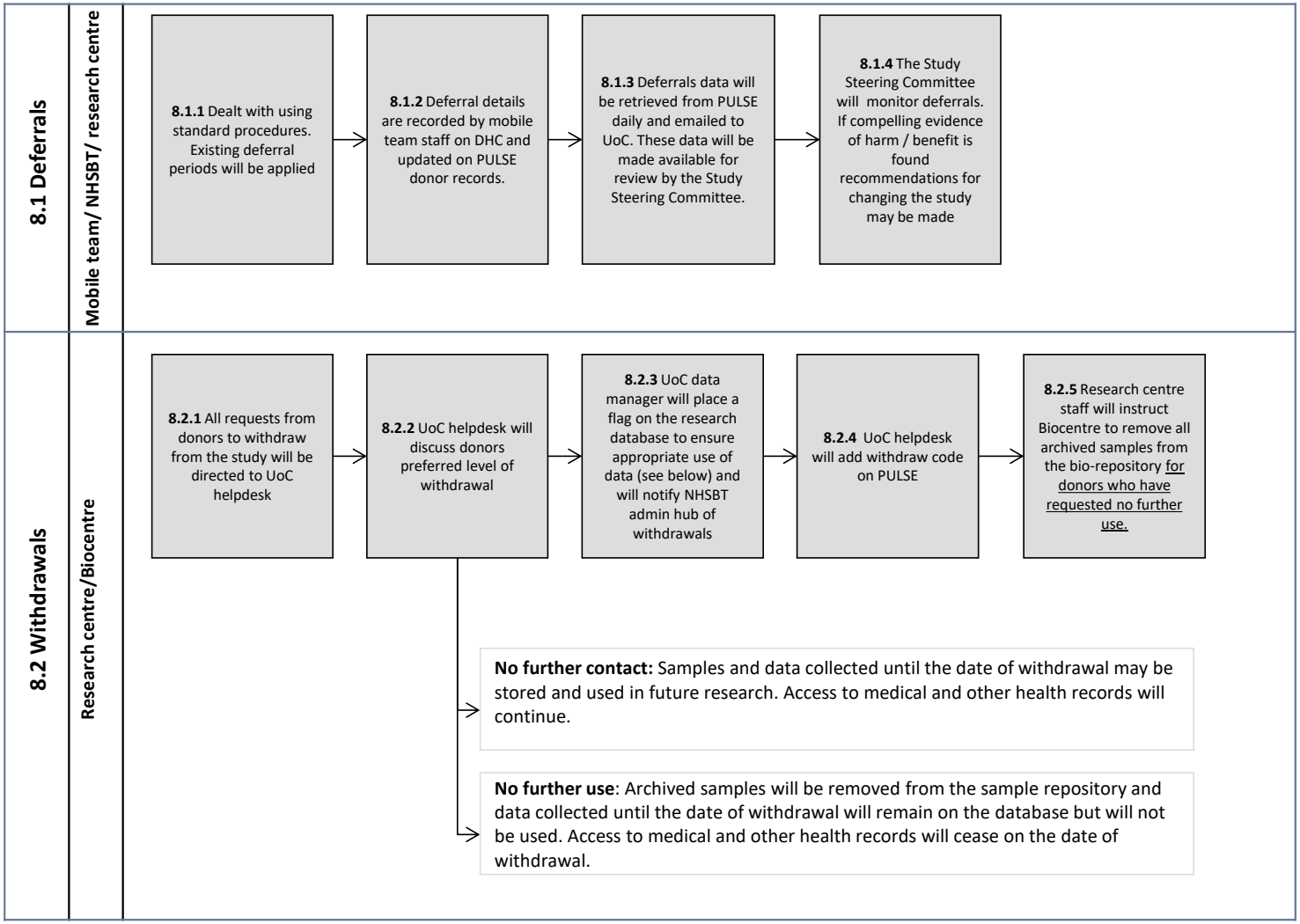
Flowchart 7. Stage 1, 2nd attendance protocol



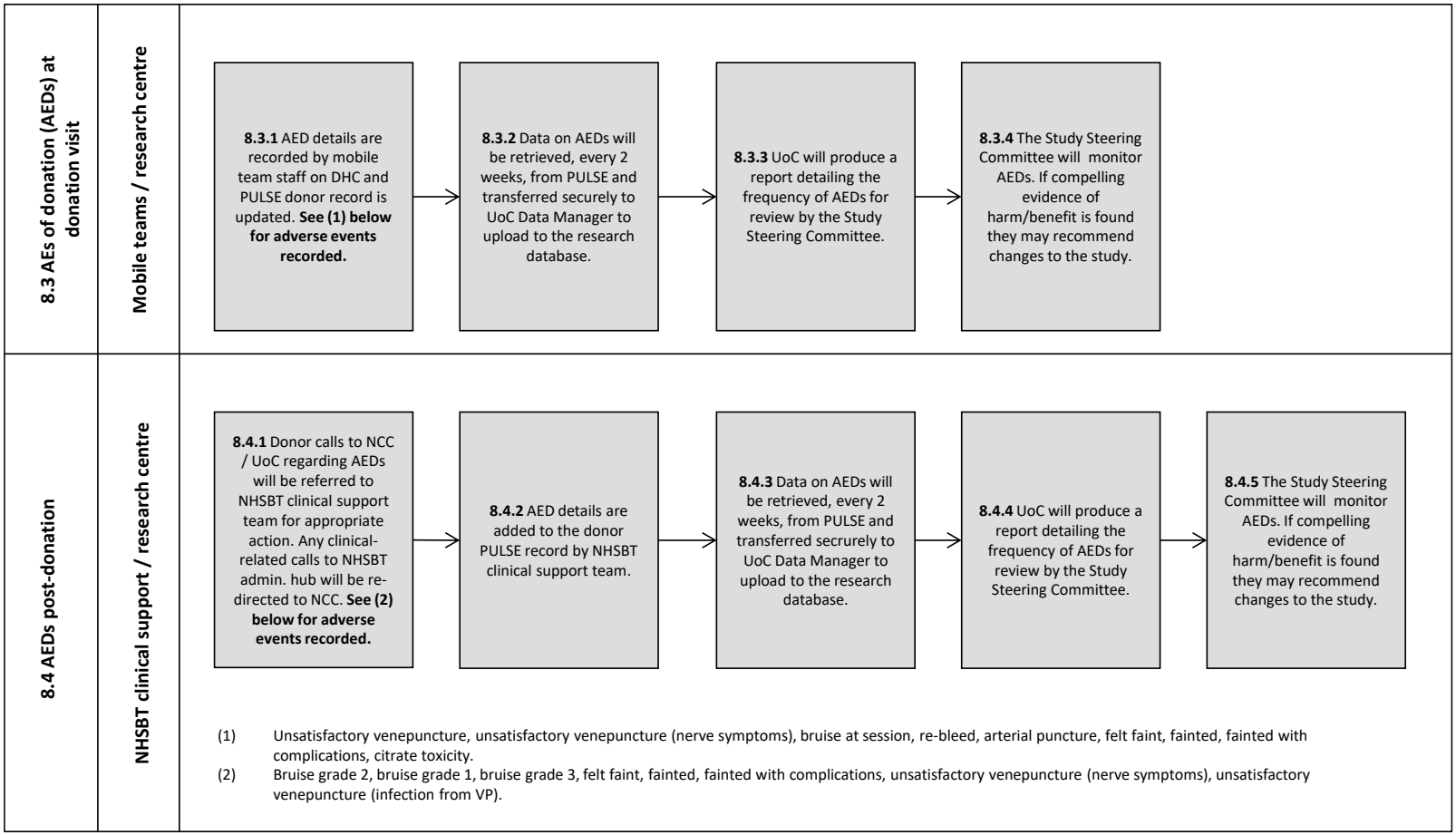
Flowchart 7. Stage 1, 2nd attendance protocol



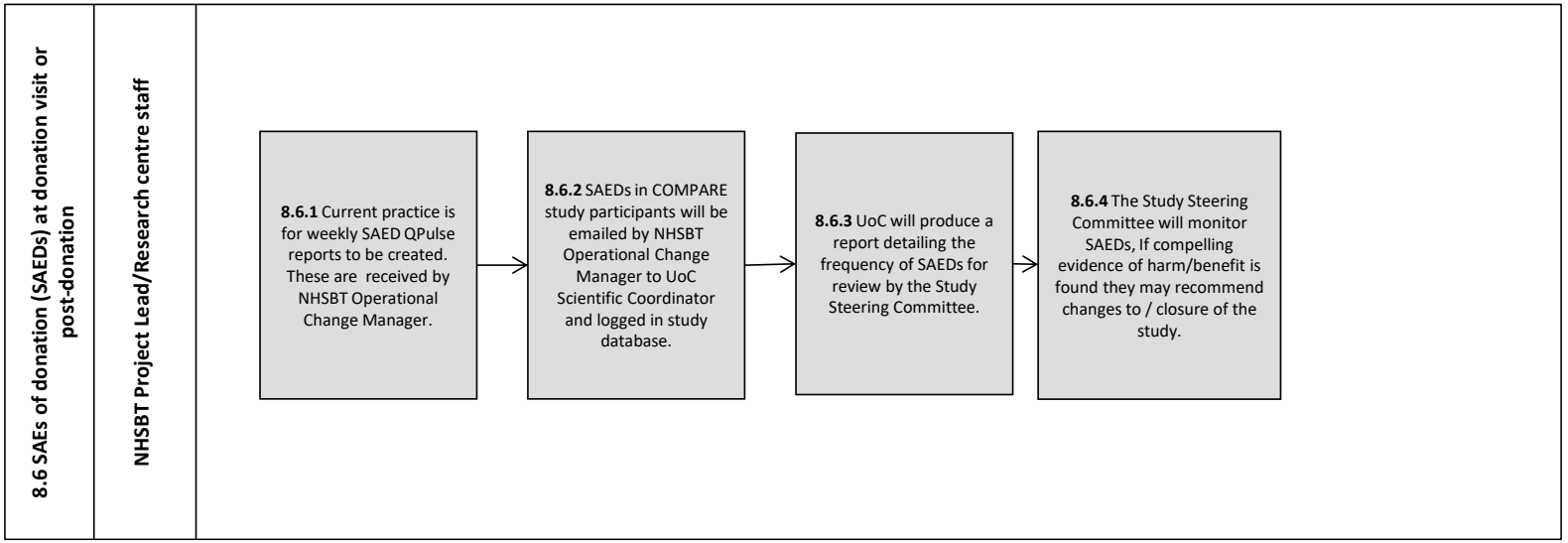
Flowchart 8a. Donor management protocols – deferrals and withdrawals



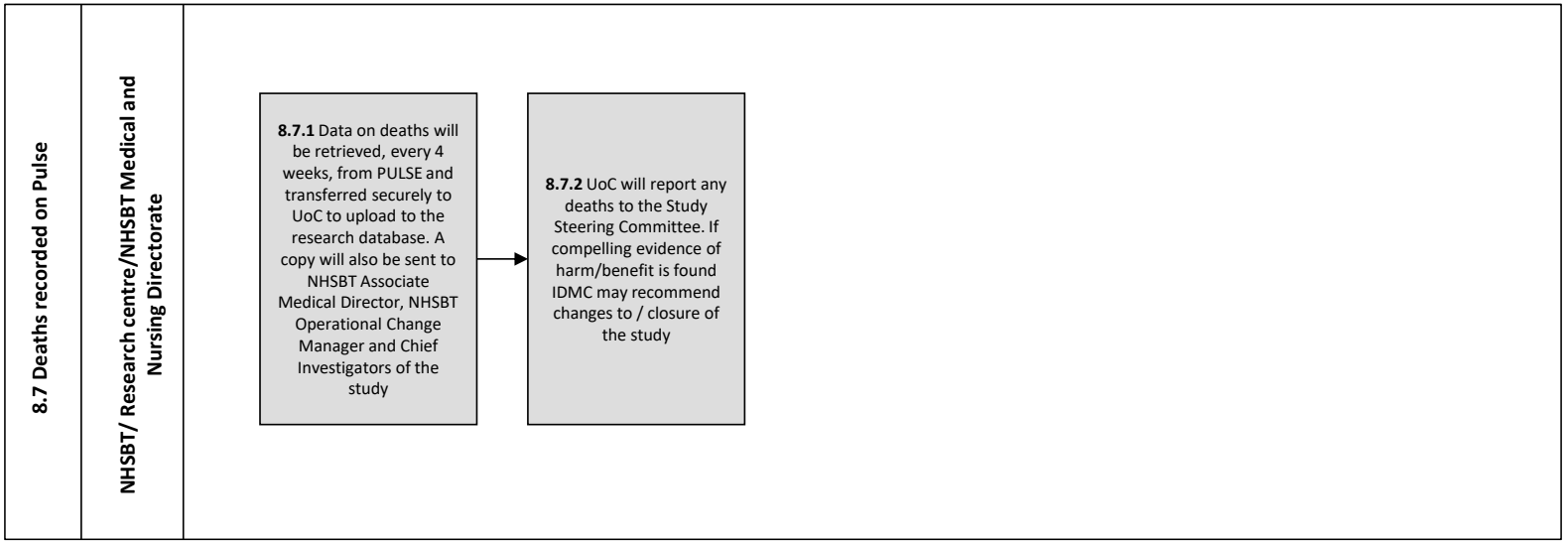
Flowchart 8b. Donor management protocols – adverse events (AEs)



Flowchart 8c. Donor management protocols – serious adverse events (SAEs)



Flowchart 8d. Donor management protocols – deaths



ANNEX 2: STUDY DOCUMENTATION

Annex 2.1:

COMPARE: a study of haemoglobin testing methods and to create a bioresource for future research into donor and public health

INFORMATION LEAFLET

We would like to invite you to join the COMPARE study which is led by doctors and scientists at the University of Cambridge, NHS Blood and Transplant (NHSBT) and National Institute for Health Research (NIHR).

To help protect the health of blood donors, it's a requirement to find out whether a donor's blood haemoglobin levels are adequate. However, it's not clear what the best method is for rapidly measuring haemoglobin levels. So, this study of 31,000 blood donors aims to provide a clear answer.

The study is comparing the method of haemoglobin testing used by NHSBT with three promising and newer approaches used by blood services in Europe and the USA. The results should help safeguard the well-being of future blood donors and define best practice for England's blood service. A further objective is to create a bioresource of healthy volunteers using samples and data collected during the study to be used in future approved research projects looking at donor and public health.

Before you decide whether to participate, it's important for you to understand why the study is being done and what is involved. Please take the time to read the following information carefully, and discuss it with others if you wish.

If anything is not clear, or if you would like more information, please call the freephone number on 0800 XXX XXXX (Monday to Friday: 0900h - 1700h) to talk to a member of our study team or email helpdesk@comparestudy.org.uk.

Many thanks for taking the time to consider taking part in the COMPARE study.

Dr Emanuele Di Angelantonio	Dr Gail Miflin	Prof John Danesh
NHSBT & University of Cambridge	**NHSBT**	**University of Cambridge**

The COMPARE Study

University of Cambridge, Department of Public Health and Primary Care

Wort's Causeway, Cambridge CB1 8RN

Email: helpdesk@comparestudy.org.uk

Freephone: 0800 XXX XXXX

Website: www.comparestudy.org.uk

Why is the study needed?

To help protect the health of donors, it's a requirement to find out whether a donor's blood haemoglobin levels are adequate. The blood service in England screens potential donors with an initial finger prick ("copper sulphate") test. For people suspected of having inadequate haemoglobin levels, a more precise ("HemoCue") test is then immediately done using a venous blood sample. However, blood services in different countries use different screening approaches. We are leading a study of 31,000 donors to compare different methods. The goal is to help safeguard the well-being of future blood donors and define best practice for NHSBT.

What haemoglobin tests are being compared?

This study is comparing the method used by NHSBT with three promising and newer approaches:

- a version of the "HemoCue" test that requires only a blood drop from a finger prick
- a non-invasive light-shining device ("spectrometer") placed over a finger for about one minute, which avoids taking a blood sample altogether
- a method that involves predicting current haemoglobin levels from venous blood tested at the previous donation visit, using a "gold standard haematology analyser".

What will I be asked to do if I participate?

You will be asked to do the following **today**:

- complete a consent form agreeing to participate in this study
- provide a sample of your blood (~16mL, equivalent to about 3 teaspoons) for research. This sample will be obtained from the same venepuncture used in your routine donation
- book a further donation appointment, at the same mobile session, to attend in about 12 weeks if you are a man, or in about 16 weeks if you are a woman. However, if today you are deferred from giving blood for a prolonged duration (>12 weeks for men; >16 weeks for women), then we will not ask you to book a further donation.

About one week from today, you will receive an email message asking you to complete a brief (15 minute) online questionnaire about your personal details, health, and lifestyle. We will also ask about your individual characteristics that are associated with skin tone (e.g. eye and hair colour) to evaluate variability in the performance of the non-invasive devices according to skin tone.

At your next appointment, you will need to do the following:

- provide an extra drop of blood for research from the same finger prick used in routine donation
- provide ~16mL of your blood for research from the venepuncture used in your routine donation
- wear a clip device around your finger for about one minute for a non-invasive haemoglobin test
- complete a brief (5 minute) questionnaire on your haemoglobin testing experience that day.

Who is eligible for the study?

We are inviting all blood donors who usually give blood at one of about 10 selected mobile donation sessions. You **are eligible** to take part in the study if you are:

- aged 18 years or older.
- willing to return in ~12 weeks if you are a man, or in ~16 weeks if you are a woman.
- willing to undergo additional haemoglobin measurements
- willing to provide a small sample of blood for research, even if your haemoglobin levels are slightly below the threshold for donating blood.
- willing to complete an online questionnaire at home (and, thus, provide your email address).

Do I have to take part?

No, it is completely up to you. If you decide to take part you will be asked to sign a consent form (see the end of this leaflet for a sample copy). You are free to withdraw at any time, without giving a reason. Your decision will have no influence on your blood donation now or in the future.

What should I do if I want to take part?

If you would like to join the study, then all you need to do is let your donor carer know. Your carer will take you through the consent form and answer any questions you might have.

How will my blood samples be used?

Research samples will be measured within one day of collection for a "gold standard" full blood count and then frozen. Stored samples of separate blood components (e.g., plasma, serum, DNA) will be:

- kept securely at a central laboratory, labelled only with a unique study number
- used for medical and health-related studies that have relevant scientific and ethics approval
- used to measure blood substances ("biomarkers") that reflect health status (e.g., iron levels)
- used to study your DNA and related substances to find out, for example, how genes regulate blood cells and haemoglobin levels. Genes are made up of DNA and you have two copies, one from your mother and the other from your father. Researchers can now read a large fraction or the entire genetic code within days to really understand the role of genes in health and disease. We will test for many genes and determine the sequence of part of or your entire genetic code.
- in addition to this initial study, your samples and data on your full DNA (genetic) code will be used in a number of future approved research projects investigating donor and public health. The results may not be known for several years. As they are not performed in the same way or to the same laboratory standard as clinical tests you will not be informed of any incidental findings. Researchers using your sample will only be provided with anonymised data which ensures they cannot link the sample or data to you by name.

How will my study information be used?

Your study information will be used to compare different haemoglobin testing methods, and serve as a resource to help answer wider health questions in approved studies. We are asking for your permission to access your medical and other health-related records, and for the long-term confidential storage and use of this data for future health-related research purposes with relevant approvals. We are asking for your permission to invite you to further studies, which you will be able to accept or decline on a case-by-case basis.

Are there any benefits for me in joining the study?

You will not receive an immediate benefit. However, the study's findings should help safeguard the well-being of future blood donors and define best practice for England's blood service.

Are there any additional risks for me in joining the study?

No. Your safety will be looked after by NHSBT in the usual way. That is, you will receive the **usual** screening test for haemoglobin levels and you will need to be within the safe range to be eligible to donate. If your haemoglobin levels are not adequate, you will not be allowed to donate blood.

However, you will be asked to give a small research blood sample (~16mL) because it's important to compare the different screening methods in people with lower haemoglobin levels.

How will information about me be kept confidential?

We will protect your privacy and ensure confidentiality through several measures:

● At the donation session, your consent to take part in the study will be recorded on a form that will contain your name. The form will be stored in a secure location, separately from the study data.

● Limited personal information will be accessed and retrieved from the national NHSBT database (PULSE). This will include your email address and telephone number for study communication only. In addition we will retrieve your Donor Number and NHS number. These personal data will be stored in a secure location, separately to the study database.

● Your samples will **not** include any personal identifying details and will be stored using a unique, anonymous study identification number.

● A single table linking your study identification number to your NHSBT Donor Number and your NHS number will be stored on a separate password-protected location which may be accessed only by scientists given the specific approval of the senior study investigators.

● The link table will be used to retrieve relevant health information from your medical and other health-related records. Personal identifying details will have been removed and replaced by the unique anonymous study identification number.

● Study data will be stored in a restricted-access database not connected to the NHSBT database containing your personal details. The study data will be linked to your study identification number. Access to the study database will be password-protected and will be used only by named researchers working on this study under the direct supervision of the senior investigators.

● Your study data will include results from laboratory measurements using your blood sample; this will include data on the sequence of your entire genetic code. Because this code is unique to you, it is, in principle, possible for someone to identify you from these data. However, the risk of this happening in practice is small. This is because such an occurrence would require that a researcher not only has your anonymised genetic sequence data from the COMPARE study but also has a) comparable data on your genetic sequence from another source which identifies you and b) the computing systems to match the two sequences. While this is technically possible, the risk of identification is remote due to the safeguards described above.

● Your personal details provided during the study will be stored in a secure location, separately from the study database and used for the purpose of study communication. Personal information will only be linked to the study database with the permission of the senior investigators.

What will be stored on the study database?

Confidential information that will be stored on the database (i.e., information that can be linked to your personal identifiers only with the permission of the senior investigators) will include:

● Relevant information from your NHSBT donor record, such as sex, month and year of birth, details of your donation history and blood group

● Data from the study's online questionnaire

● Results from laboratory measurements using your blood sample, including DNA

● Information on health outcomes collected from routine medical and other health-related records.

How do I withdraw if I want to do so?

You can withdraw from the study at any time and without giving a reason. However, the benefits of the study will be increased if few people withdraw from it, so please discuss any concerns with us in advance. To discuss withdrawing from the study, please call freephone 0800 XXX XXXX (Monday to Friday 0900h - 1700h) or write to helpdesk@comparestudy.org.uk or our postal address. In the unlikely event of you losing capacity (including death) to decide on continued participation in the study, the blood samples and personal data collected will continue to be used confidentially in connection with the purposes for which consent has been granted.

Who will be able to use my information and samples?

Your information and samples will be available only to researchers who have relevant approvals for their planned research. This could include researchers who are working in other countries (including outside the EEC) and in commercial companies who are looking for new treatments or laboratory tests. Insurance companies and employers will not be given any individual's information, samples or test results, and we will not allow access to the police, security services, relatives or lawyers, unless forced to do so by the courts.

There will be a requirement to publish the results of any research arising out of the samples and data collected during the study to ensure others can benefit from it. Our website will include a list of reports arising from the study. The website will not contain any personal information.

We generally do not plan to provide feedback of results. However, we would communicate results to you that would have an immediate impact on your healthcare (such as finding cells in your blood that may suggest a significant health problem e.g. leukaemia). In this case, we will inform an NHSBT medical professional about the nature of the problem, and about who you are. An NHSBT medical professional would then use the routine procedures applicable in the NHS to get in touch with you and offer advice, which may involve contacting your GP.

Who is organising and funding the study?

The University of Cambridge, NHS Blood and Transplant and National Institute for Health Research.

Who has approved the study?

Research in the NHS is reviewed by independent groups of people ("Research Ethics Committee") to protect your safety, rights, wellbeing and dignity. This project has been reviewed and was given a favourable review by the << to be added>> Research Ethics Committee.

What will happen if an invention is made using my sample?

You are giving your sample as an absolute gift, i.e., without receiving a payment and without attaching conditions. This study is operating on a non-commercial basis, meaning it does not sell your sample to make a profit and will not allow anyone else who is working with the sample to do so either. However, if samples are made available to other research institutions or to private-sector research partners, a fee may be charged to cover the operational costs.

In the future, your sample may help researchers in the public and private sector to make an invention, e.g., to develop a new product to diagnose, prevent or treat disease. If an invention results from the research undertaken with your sample you will not receive any compensation or

payment. The study investigators may work together with commercial companies to develop inventions for the benefit of patient and donor care; and we hope that such products are brought into use by the NHS to improve health care in the future.

What happens if something goes wrong?

The risk of participants suffering harm as a result of taking part is minimal. Nevertheless, insurance is in place to provide compensation for any negligent harm caused by participation.

Who do I contact if I have any concerns?

If you have any concerns or complaints about anything to do with the COMPARE study then you can telephone the freephone number on 0800 XXX XXXX (Monday to Friday 0900h - 1700h) to speak to a member of the study team or email us at helpdesk@comparestudy.org.uk. Alternatively, if you would like to write to us, please send your letter to the COMPARE study coordinator, University of Cambridge, Department of Public Health and Primary Care, Wort's Causeway, Cambridge CB18RN.

COMPARE STUDY CONSENT FORM ('DONOR COPY')

Chief Investigators: Dr Emanuele Di Angelantonio and Professor John Danesh

University of Cambridge and NHS Blood and Transplant

Blood Donor ID number:

You need to tick <u>all boxes from 1 to 9</u> to be eligible to take part in the study

1. I confirm that I have read and understood the COMPARE participant information leaflet (Stage 1) dated XX.XX.XX (version X) for the above study. I have had the opportunity to ask questions, and these have been answered fully.	☐
2. I understand that my participation is voluntary and that I am free to withdraw at any time without giving any reason.	☐
3. I understand and grant permission for relevant sections of my blood donation records to be retrieved and used by the study team.	☐
4. I give permission for long-term, anonymised storage of my blood samples (including DNA) for health-related research purposes (even after my incapacity or death), and relinquish all rights to these samples which I am donating to the study.	☐
5. I understand that information held by the NHS and records maintained by the NHS Information Centre and the NHS Central Register may be used to provide information about my health status and I give permission for long-term anonymised storage and use of this and other information about me, for health-related research purposes (even after my incapacity or death).	☐
6. I agree to provide an email address and for my contact phone details to be given to members of the study team, to send me communications about the study. I will maintain the email address provided or, if necessary, supply a new one in the future.	☐
7. I understand that none of my results (other than those which have an immediate impact on my health care) will be given to me and that I will not benefit financially from taking part (e.g. if research leads to commercial development of a new treatment or blood test).	☐
8. I understand I may be contacted by the COMPARE study team about further studies, which I will be able to accept or decline on a case-by-case basis.	☐
9. I confirm that I am 18 years or over.	☐
10. I agree to take part in the above study.	☐

Participant name:	Signature:	Date:

Annex 2.2

COMPARE STUDY CONSENT FORM ('DONOR COPY')

Chief Investigators: Dr Emanuele Di Angelantonio and Professor John Danesh

University of Cambridge and NHS Blood and Transplant

Blood Donor ID number:

You need to tick <u>all boxes from 1 to 9</u> to be eligible to take part in the study

1. I confirm that I have read and understood the COMPARE participant information leaflet (Stage 1) dated XX.XX.XX (version X) for the above study. I have had the opportunity to ask questions, and these have been answered fully.	☐
2. I understand that my participation is voluntary and that I am free to withdraw at any time without giving any reason.	☐
3. I understand and grant permission for relevant sections of my blood donation records to be retrieved and used by the study team.	☐
4. I give permission for long-term, anonymised storage of my blood samples (including DNA) for health-related research purposes (even after my incapacity or death), and relinquish all rights to these samples which I am donating to the study.	☐
5. I understand that information held by the NHS and records maintained by the NHS Information Centre and the NHS Central Register may be used to provide information about my health status and I give permission for long-term anonymised storage and use of this and other information about me, for health-related research purposes (even after my incapacity or death).	☐
6. I agree to provide an email address and for my contact phone details to be given to members of the study team, to send me communications about the study. I will maintain the email address provided or, if necessary, supply a new one in the future.	☐
7. I understand that none of my results (other than those which have an immediate impact on my health care) will be given to me and that I will not benefit financially from taking part (e.g. if research leads to commercial development of a new treatment or blood test).	☐
8. I understand I may be contacted by the COMPARE study team about further studies, which I will be able to accept or decline on a case-by-case basis.	☐
9. I confirm that I am 18 years or over.	☐
10. I agree to take part in the above study.	☐

Participant name:	Signature:	Date:

Time samples collected (*using 24 hour clock*)	☐☐ : ☐☐

Annex 2.3

COMPARE STUDY CONSENT FORM ('STUDY COPY')

Chief Investigators: Dr Emanuele Di Angelantonio and Professor John Danesh

University of Cambridge and NHS Blood and Transplant

Blood Donor ID number:

You need to tick <u>all boxes from 1 to 9</u> to be eligible to take part in the study

1. I confirm that I have read and understood the COMPARE participant information leaflet (Stage 1) dated XX.XX.XX (version X) for the above study. I have had the opportunity to ask questions, and these have been answered fully.	☐
2. I understand that my participation is voluntary and that I am free to withdraw at any time without giving any reason.	☐
3. I understand and grant permission for relevant sections of my blood donation records to be retrieved and used by the study team.	☐
4. I give permission for long-term, anonymised storage of my blood samples (including DNA) for health-related research purposes (even after my incapacity or death), and relinquish all rights to these samples which I am donating to the study.	☐
5. I understand that information held by the NHS and records maintained by the NHS Information Centre and the NHS Central Register may be used to provide information about my health status and I give permission for long-term anonymised storage and use of this and other information about me, for health-related research purposes (even after my incapacity or death).	☐
6. I agree to provide an email address and for my contact phone details to be given to members of the study team, to send me communications about the study. I will maintain the email address provided or, if necessary, supply a new one in the future.	☐
7. I understand that none of my results (other than those which have an immediate impact on my health care) will be given to me and that I will not benefit financially from taking part (e.g. if research leads to commercial development of a new treatment or blood test).	☐
8. I understand I may be contacted by the COMPARE study team about further studies, which I will be able to accept or decline on a case-by-case basis.	☐
9. I confirm that I am 18 years or over.	☐
10. I agree to take part in the above study.	☐

Participant name:	Signature:	Date:
Staff member name:	Signature:	Date:

Office use only. For completion by NHSBT staff.	
Blood donor ID number:	
Please confirm that the donor is (i) aged at least 18 years, (ii) committed to returning in 12 or 16 weeks, and (iii) willing to provide an email address for study correspondence:	**YES** ☐ **NO** ☐

ANNEX 2.4

COMPARE Study – donor appointment card for post-donation strategy participants

FRONT

The COMPARE Study

COMPARE

Your second visit is DATE _ _ / _ _ / _ _ _ _
TIME _ _ : _ _

To cancel or rearrange: go to blood.co.uk
or call 0300 123 23 23

Please put this email in your contacts:
donotreply@comparestudy.org.uk

NHS Blood and Transplant

UNIVERSITY OF CAMBRIDGE

BACK

The COMPARE Study
A Quick Summary for donors

AFTER 1ST VISIT

Complete online questionnaire

Return for 2nd visit:
- In 12 weeks for men
- In 16 weeks for women

2nd VISIT

Follow usual donation procedures +

- Provide a capillary sample from your finger
- Have a clip placed over your finger/thumb for 30-90 seconds for a haemoglobin measurement
- Provide a small venous blood sample

AFTER 2nd VISIT

Complete online questionnaire

ANNEX 2.5

Dear Donor,

Thank you very much for taking part in the COMPARE Study. Your support is very important to the success of this research and is helping to safeguard the wellbeing of all blood donors in the future.

As part of your involvement in COMPARE, you kindly agreed to complete a study questionnaire for us. This <<first part>> of the questionnaire will ask you questions about your general health and lifestyle as well as questions related to being a blood donor. It should take approximately 15 minutes <<10 minutes >> to complete. ***Please do your best to answer every question.***

The password required to begin the questionnaire will arrive in a separate email entitled "**COMPARE Key**" Once you have the password, please return to this email and click on the link below to access the questionnaire:

LINK

If you are unable to access the questionnaire with the link above, please copy and paste the following into a new window in your internet browser: fulllinktoquestionnairehere.com

Thank you very much for taking the time to complete the questionnaire. Your answers will be treated as strictly confidential and will only be used for medical research. If you have any questions please contact the COMPARE team using the details below.

Many thanks,

The COMPARE team.

Freephone: 0800 021 7182 (Mon-Fri: 09:00 to 17:00)

E-mail: helpdesk@comparestudy.org.uk

Annex 2.6

SUBJECT LINE: COMPARE Key

Dear Donor,

Thank you for taking part in the COMPARE Study. Separately from this email you will have already received an email containing a link to the online COMPARE questionnaire. The password required to begin is:

PASSWORDGOESHERE

The COMPARE team would like to thank you for taking the time to complete the questionnaire and assure you that all answers will be treated in the strictest confidence.

Many thanks,

The COMPARE team

Freephone: 0800 021 7182 (Mon-Fri: 09:00 – 17:00)

Email: helpdesk@comparestudy.org.uk

Annex 2.7

SUBJECT LINE: COMPARE study – questionnaire reminder

Dear Donor,

Thank you once again for taking part in the COMPARE Study. One week ago we emailed you a link to the <<first part of the >> COMPARE study online questionnaire. If you have completed the questionnaire in the last 24 hours please discard this reminder. If not, we would be very grateful if you could complete the questionnaire – it takes about 15 minutes << 10 minutes >>. Please click the link below to access the questionnaire:

LINK

The password to begin the questionnaire was sent to you one week ago in an email entitled "**COMPARE Key"**. If you have any trouble finding the password please contact the helpdesk using the details below.

If you are unable to access the questionnaire with the link above, please copy and paste the following into a new window in your internet browser: fulllinktoquestionnairehere.com

Thank you very much for taking the time to complete the questionnaire. Your answers will be treated as strictly confidential and will only be used for medical research. If you have any questions please contact the COMPARE team using the details below.

Many thanks,

The COMPARE team.

Freephone: 0800 021 7182 (Mon-Fri: 9:00 to 17:00)

E-mail: helpdesk@comparestudy.org.uk

ANNEX 2.8

SUBJECT LINE: COMPARE study – questionnaire reminder

Dear Donor,

Thank you once again for taking part in the COMPARE Study. Three weeks ago we emailed you a link to the <<first part of the>> COMPARE study online questionnaire. If you have completed the questionnaire in the last 24 hours please discard this reminder. If not, we would be very grateful if you could complete the questionnaire - it takes about 15 minutes << 10 minutes >>. Please click the link below to access the questionnaire:

LINK

The password to begin the questionnaire was sent to you three weeks ago in an email entitled "**COMPARE Key"**. If you have any trouble finding the password please contact the helpdesk using the details below.

If you are unable to access the questionnaire with the link above, please copy and paste the following into a new window in your internet browser: fulllinktoquestionnairehere.com

Thank you very much for taking the time to complete the questionnaire. Your answers will be treated as strictly confidential and will only be used for medical research. If you have any questions please contact the COMPARE team using the details below.

Many thanks,

The COMPARE team.

Freephone: 0800 021 7182 (Mon-Fri: 9:00 to 17:00)

E-mail: helpdesk@comparestudy.org.uk

ANNEX 2.9

From COMPARE address (Stage 1, Visit 1 and Stage 2)

There's still time to answer the blood donor study's short questionnaire, this is critical to our research! Call 0800 021 7182 if you'd like it re-sent. Thanks [159 characters]

From COMPARE address: (Stage 1, Visit 2)

There's still time to answer the donor study's 2nd short questionnaire, this is critical to our research! Call 0800 021 7182 if you'd like it re-sent. Thanks [157 characters]

ANNEX 2.10

WELCOME TO THE COMPARE STUDY QUESTIONNAIRE

The COMPARE Study is a collaboration between the University of Cambridge, NHS Blood and Transplant and National Institute for Health Research (NIHR). It compares the method of haemoglobin screening used by NHSBT with three newer approaches used by blood services in Europe and the USA.

The results of this study should help safeguard the wellbeing of future blood donors and define best practice for England's blood service. By completing this questionnaire you are helping us to answer this important question.

The questionnaire is split into 8 main sections. Please allow yourself approximately 15 minutes for completion of the questionnaire and please also do your best to answer every question.

You can exit the questionnaire at any time by simply closing the website. You do not need to save the answers that you have already completed as this will be done automatically for you.

The bar at the top of the page will indicate how far through the questionnaire you are.

To enter the questionnaire we will ask for your correct month/year of birth and gender.

Thank you very much in advance for completing the COMPARE Study questionnaire. If you have any questions at any point, please contact the helpdesk on 0800 021 7182 or email helpdesk@comparestudy.org.uk

Variable name	Question asked	Response codes and descriptions
Gender	Please enter your gender	1 = male 2 = female
dob_m	When were you born? : month	1 - 12 = January - December
dob_y	When were you born? : year	

SECTION 1: GENERAL QUESTIONS ABOUT YOU		
Ht_Wt_M	How would you prefer to enter your height and weight?	1= Feet/inches and stones/pounds 2 = Feet/inches and kilograms 3 = Metres/centimetres and kilograms 4 = Metres/centimetres and stones/pounds
Ht	What is your height (without shoes)?	**If ft/in**: 4ft 0 – 7ft 11 as given **If m/cm**: 0 - 2.99 as given
Wt	What is your weight (without shoes/heavy clothing?	**If st/lbs**: 6st 0 – 30st 13 as given; 777 > 30st 13 **If kg**: 38 - 190 as given; 777 > 190kg
Ethnic	How would you describe your ethnicity?	1 = White - British 2 = White - Irish 3 = White - Other 4 = Mixed - White and Black Caribbean 5 = Mixed - White and Black African 6 = Mixed - White and Asian 7 = Mixed - Other 8 = Asian - Indian 9 = Asian - Pakistani 10 = Asian - Bangladeshi 11 = Asian - Other

		12 = Black - Caribbean 13 = Black - African 14 = Black - Other 15 = Chinese 16 = Other 999 = Don't know/prefer not to answer
Occupation	Which of the following best describes your current situation	1 = In full-time employment (paid or unpaid) 2 = In part-time employment (paid or unpaid) 3 = Do not work (e.g. retired, unemployed, student) 999 = don't know / prefer not to answer

SECTION 2: YOUR SKIN COLOURING		
The following set of 9 questions will ask you about your individual characteristics that are associated with skin tone (e.g. eye and hair colour). Your answers will help researchers assess the variability in the performance of the non-invasive ('light-shining') haemoglobin devices depending on skin tone.		
fitzEyes	**Which of the following best describes your natural eye colour? Please choose one that matches you most.**	**0 = Light blue, light grey or light green 1 = Blue, grey or green 2 = Hazel or light brown 3 = Dark brown 4 = Brownish black 5 = Don't know / prefer not to answer**
fitzHair	**Which of the following best describes your natural hair colour? Please choose one that matches you the most.**	**0 = Red or light blond 1 = Blond 2 = Dark blond or light brown 3 = Dark brown 4 = Brownish black 5 = Don't know / prefer not to answer**
fitzSkin	**Which of the following best describes your natural skin colour before sun exposure? Please choose one that matches you the most.**	**0 = Ivory white or reddish 1 = Fair or pale 2 = Fair to beige, with golden undertone 3 = Olive or light brown 4 = Dark brown or black 5 = Don't know / prefer not to answer**
fitzFreckle	**How many freckles do you have on unexposed areas of your skin? Please choose one that matches you the most.**	**0 = Many 1 = Several 2 = A few 3 = Very few 4 = None 5 = Don't know / prefer not to answer**
fitzBurn	**How does your skin respond to spending too long in the sun? Please choose one that matches you the most.**	**0 = Always burns, blisters and peels 1 = Often burns, blisters and peels 2 = Burns moderately 3 = Burn rarely, if at all 4 = Never burns 5 = Don't know / prefer not to answer**
fitzTan1	**To what degree does your skin tan? Please choose one that matches you the most.**	**0 = Never, I always burn 1 = I seldom tan 2 = I sometimes tan 3 = I often tan 4 = I always tan 5 = Don't know / prefer not to answer**
fitzTan2	**Do you tan within several hours after sun exposure? Please choose one that matches you the**	**0 = Never 1 = Seldom 2 = Sometimes**

	most.	3 = Often 4 = Always 5 = Don't know / prefer not to answer
fitzFace	How sensitive is your face to the sun? Please choose one that matches you the most.	0 = Very sensitive 1 = Sensitive 2 = Normal 3 = Resistant 4 = Very resistant / never had a problem 5 = Don't know / prefer not to answer
fitzExpose	When did you last expose your body to sun (or artificial sunlamp / tanning cream)?	0 = More than 3 months ago 1 = 2-3 months ago 2 = 1-2 months ago 3 = Less than a month ago 4 = less than 2 weeks ago 5 = Don't know / prefer not to answer

SECTION 3: MEASURING YOUR HAEMOGLOBIN LEVELS		
Cuso41	Thinking about the finger prick test performed before you donate blood, please indicate how much you agree or disagree with the following statements. It reliably measures my haemoglobin levels.	1 = Strongly disagree 2 = Disagree 3 = Somewhat disagree 4 = Neither agree nor disagree 5 = Somewhat agree 6 = Agree 7 = Strongly agree
Cuso42	It is quick to do	1 = Strongly disagree 2 = Disagree 3 = Somewhat disagree 4 = Neither agree nor disagree 5 = Somewhat agree 6 = Agree 7 = Strongly agree
Cuso43	It does not hurt	1 = Strongly disagree 2 = Disagree 3 = Somewhat disagree 4 = Neither agree nor disagree 5 = Somewhat agree 6 = Agree 7 = Strongly agree
Cuso45	Overall it is a good test to measure haemoglobin levels	1 = Strongly disagree 2 = Disagree 3 = Somewhat disagree 4 = Neither agree nor disagree 5 = Somewhat agree 6 = Agree 7 = Strongly agree
Importance1	We would like to know what is important to you with regards to checking your haemoglobin levels before donation. Please rank each statement in order of importance from 1 (most important) to 5 (least important). The blood test should accurately measure my haemoglobin levels.	1 = most important 2 = 2nd most important 3 = 3rd most important 4 = 4th most important 5 = least important
Importance2	The blood test should cause minimal pain and discomfort.	1 = most important 2 = 2nd most important 3 = 3rd most important 4 = 4th most important 5 = least important
Importance3	The blood test should take as	1 = most important

	little time as possible.	2 = 2nd most important 3 = 3rd most important 4 = 4th most important 5 = least important
Importance4	The blood test should cost as little as possible to the blood service.	1 = most important 2 = 2nd most important 3 = 3rd most important 4 = 4th most important 5 = least important
Importance5	The blood test should provide me with a value of my haemoglobin level.	1 = most important 2 = 2nd most important 3 = 3rd most important 4 = 4th most important 5 = least important
Preference1	Based on your experience at your last donation as part of the COMPARE study, please rank by order of preference each of the following methods for haemoglobin screening. Method A: Finger-prick test: Before donation, a sterilised pin is used to puncture your finger and obtain a drop of blood.	1 = most preferred 2 = 2nd most preferred 3 = least preferred
Preference2	Method B: Non-invasive test: Before donation, a clip is placed on your finger for approximately 30-90 seconds.	1 = most preferred 2 = 2nd most preferred 3 = least preferred
Preference3	Method C: Post-donation test: A small amount of the blood from your previous donation is used to screen haemoglobin levels.	1 = most preferred 2 = 2nd most preferred 3 = least preferred

SECTION 4: YOUR HAEMOGLOBIN AND IRON LEVELS AND RELATED SYMPTOMS		
Fellow	In the last 6 months, has a GP or hospital doctor told you that you have low iron levels or anaemia?	1 = yes 2 = no 999 = don't know / prefer not to answer
haemLow	In the last 6 months, has a member of NHS Blood and Transplant told you that you have low haemoglobin levels?	1 = yes 2 = no 999 = don't know / prefer not to answer
Headache	In the last 6 months, have you experienced headaches more frequently than usual?	1 = yes 2 = no
sleepDisturbed	In the last 6 months, have you experienced sleep disturbance more frequently than usual?	1 = yes 2 = no
irritable	In the last 6 months, have you experienced irritability more frequently than usual?	1 = yes 2 = no
notConcentrate	In the last 6 months, have you experienced reduced ability to concentrate more frequently than usual?	1 = yes 2 = no
notRelax	In the last 6 months, have you experienced restlessness / inability to relax more frequently than usual?	1 = yes 2 = no

Pica_1 – Pica_7	In the last 6 months, have you craved and regularly eaten or chewed any of the following non-nutritional substances. Please tick all that apply.	Pica_1 = 1 → Ice Pica_2 = 1 → Clay Pica_3 = 1 → Dirt Pica_4 = 1 → Raw pasta Pica_5 = 1 → Chalk Pica_6 = 1 → Coal Pica_7 = 1 → None
feSuppPres	In the last 6 months, have you been prescribed iron supplements by your GP or a hospital doctor?	1 = yes 2 = no 999 = don't know / prefer not to answer
feSuppFreq1	How regularly have you been taking the iron supplements prescribed to you?	1 = all of the time 2 = most of the time 3 = some of the time 4 = a little of the time 5 = none of the time 998 = not applicable
feSuppMulti	Do you currently take over-the-counter iron supplements that are contained within multivitamins / other supplements	1 = yes 2 = no 999 = don't know / prefer not to answer
feSuppFreq2	How regularly do you take the over-the-counter iron supplements that are contained within multivitamins / other supplements?	1 = all of the time 2 = most of the time 3 = some of the time 4 = a little of the time 5 = none of the time 998 = not applicable
feSuppOnly	Do you currently take over-the-counter iron supplements that are iron only supplements?	1 = yes 2 = no 999 = don't know / prefer not to answer
feSuppFreq3	How regularly do you take over-the-counter supplements that are iron only?	1 = all of the time 2 = most of the time 3 = some of the time 4 = a little of the time 5 = none of the time 998 = not applicable
rls_1	Do you have, or have you had, recurrent uncomfortable feelings or sensations in your legs while you are sitting or lying down?	1 = yes 2 = no
rls_2	Do you, or have you had, a recurrent need or urge to move your legs while you were sitting or lying down?	1 = yes 2 = no
rls_3	Are you more likely to have these feelings when you are resting (either sitting or lying down) or when you are physically active?	1 = resting 2 = active 998 = not applicable
rls_4	Do these feelings usually start when you are resting (either sitting or lying down)?	1 = yes 2 = no 998 = not applicable
rls_5	If you get up or move around when you have these feelings do these feelings get any better while you keep moving?	1 = yes 2 = no 998 = not applicable 999 = don't know
rls_6a – rls_6g	Which times of day are these feelings in your legs most likely to occur? (more than one option)	rls_6a = 1 → Morning rls_6b = 1 → Mid-day rls_6c = 1 → Afternoon

		rls_6d = 1 → Evening rls_6e = 1 → Night rls_6f = 1 → About equal at all times rls_6g = 1 → = not applicable
rls_7a – rls_7g	Which times of day are these feelings in your legs least likely to occur?	rls_7a = 1 → Morning rls_7b = 1 → Mid-day rls_7c = 1 → Afternoon rls_7d = 1 → Evening rls_7e = 1 → Night rls_7f = 1 → About equal at all times rls_7g = 1 → = not applicable
rls_8	Will simply changing leg position by itself once without continuing to move usually relieve these feelings?	1 = Usually relieves 2 = Does not usually relieve 998 = not applicable 999 = Don't know
rls_9a	Are these feelings ever due to muscle cramps?	1 = yes 2 = no 998 = not applicable 999 = don't know
rls_9b	If so, are they always due to muscle cramps?	1 = yes 2 = no 998 = not applicable 999 = don't know
rls_10	Do these feelings occur only when sitting or only when lying down?	1 = Neither 2 = Only when sitting 3 = Only when lying down 4 = Both when sitting & when lying down 998 = not applicable
rls_11	When you actually experience the feelings in your legs, how distressing are they?	1 = Not at all distressing 2 = A little bit 3 = Moderately 4 = Extremely distressing 998 = not applicable
rls_12	In the past 12 months, how often did you experience these feelings in your legs?	1 = Every day 2 = 4-5 days per wk 3 = 2-3 days per wk 4 = 1 day per wk 5 = 2 days per month 6 = 1 day per month or less 7 = Never 998 = not applicable
rls_13	Approximately how old were you when you first noticed these feelings in your legs?	1 = less than 10 years old 10 - 75 = age 777 = more than 75 years old 998 = not applicable

SECTION 5: YOUR GENERAL WELLBEING		
SF-36v2™ Health survey © Date by Health Assessment Lab, Medical Outcomes Trust and QualityMetric Incorporated. All rights reserved.		
health1	In general, would you say your health is:	1 = excellent 2 = very good 3 = good 4 = fair 5 = poor 999 = don't know / prefer not to answer
yearAgo	Compared to one year ago, how would you rate your health in	1 = much better now 2 = somewhat better now

	general now?	3 = about the same 4 = somewhat worse now 5 = much worse now 999 = don't know / prefer not to answer
vig	Does your health now limit you in the following activity: vigorous activities (e.g. running, lifting heavy objects, strenuous sport)	1 = yes, limited a lot 2 = yes, limited a little 3 = no, not limited at all 999 = don't know / prefer not to answer
mod	Does your health now limit you in the following activity: moderate activities (e.g. housework, golf)	1 = yes, limited a lot 2 = yes, limited a little 3 = no, not limited at all 999 = don't know / prefer not to answer
lift	Does your health now limit you in the following activity: lifting / carrying groceries	1 = yes, limited a lot 2 = yes, limited a little 3 = no, not limited at all 999 = don't know / prefer not to answer
stairA	Does your health now limit you in the following activity: climbing several flights of stairs	1 = yes, limited a lot 2 = yes, limited a little 3 = no, not limited at all 999 = don't know / prefer not to answer
stairB	Does your health now limit you in the following activity: climbing one flight of stairs	1 = yes, limited a lot 2 = yes, limited a little 3 = no, not limited at all 999 = don't know / prefer not to answer
bend	Does your health now limit you in the following activity: bending, kneeling, or stooping	1 = yes, limited a lot 2 = yes, limited a little 3 = no, not limited at all 999 = don't know / prefer not to answer
mile	Does your health now limit you in the following activity: walking more than one mile	1 = yes, limited a lot 2 = yes, limited a little 3 = no, not limited at all 999 = don't know / prefer not to answer
halfmile	Does your health now limit you in the following activity: walking several hundred yards	1 = yes, limited a lot 2 = yes, limited a little 3 = no, not limited at all 999 = don't know / prefer not to answer
walk	Does your health now limit you in the following activity: walking one hundred yards	1 = yes, limited a lot 2 = yes, limited a little 3 = no, not limited at all 999 = don't know / prefer not to answer
bath	Does your health now limit you in the following activity: bathing / dressing	1 = yes, limited a lot 2 = yes, limited a little 3 = no, not limited at all 999 = don't know / prefer not to answer
phys_time	During the past 4 weeks, have you had to cut down on the time spent at work / on activities due to physical health	1 = all of the time 2 = most of the time 3 = some of the time 4 = a little of the time 5 = none of the time 999 = Don't know / prefer not to answer
phys_less	During the past 4 weeks, have you accomplished less at work / on other regular daily activities due to physical health:	1 = all of the time 2 = most of the time 3 = some of the time 4 = a little of the time 5 = none of the time 999 = Don't know / prefer not to answer
phys_kind	During the past 4 weeks, have you been limited in the kind of work / regular daily activities due to physical health:	1 = all of the time 2 = most of the time 3 = some of the time 4 = a little of the time 5 = none of the time 999 = Don't know / prefer not to answer

phys_diff	During the past 4 weeks, have you had difficulty in performing the work / regular daily activities due to physical health:	1 = all of the time 2 = most of the time 3 = some of the time 4 = a little of the time 5 = none of the time 999 = Don't know / prefer not to answer
emo_time	During the past 4 weeks, have you had to cut down on the time spent at work / on activities due to emotional problems:	1 = all of the time 2 = most of the time 3 = some of the time 4 = a little of the time 5 = none of the time 999 = Don't know / prefer not to answer
emo_less	During the past 4 weeks, have you accomplished less at work / on other regular daily activities due to emotional problems:	1 = all of the time 2 = most of the time 3 = some of the time 4 = a little of the time 5 = none of the time 999 = Don't know / prefer not to answer
emo_care	During the past 4 weeks, have you accomplished work / other regular daily activities less carefully due to emotional problems:	1 = all of the time 2 = most of the time 3 = some of the time 4 = a little of the time 5 = none of the time 999 = Don't know / prefer not to answer
social1	During the past 4 weeks, to what extent has your physical health or emotional problems interfered with your normal social activities?	1 = not at all 2 = slightly 3 = moderately 4 = quite a bit 5 = extremely 999 = don't know / prefer not to answer
pain1	During the past 4 weeks, how much bodily pain have you had?	1 = none 2 = very mild 3 = mild 4 = moderate 5 = severe 6 = very severe 999 = don't know / prefer not to answer
pain2	During the past 4 weeks, how much did pain interfere with normal daily activities?	1 = not at all 2 = a little bit 3 = moderately 4 = quite a bit 5 = extremely 999 = don't know / prefer not to answer
getUp	How you feel and how things have been for you during the last 4 weeks: Did you feel full of life?	1 = all the time 2 = most of the time 3 = some of the time 4 = a little of the time 5 = none of the time 999 = don't know / prefer not to answer
nervous	How you feel and how things have been for you during the last 4 weeks: Have you been a very nervous person?	1 = all the time 2 = most of the time 3 = some of the time 4 = a little of the time 5 = none of the time 999 = don't know / prefer not to answer
down	How you feel and how things have been for you during the last 4 weeks: Have you felt so down that nothing could cheer you up?	1 = all the time 2 = most of the time 3 = some of the time 4 = a little of the time 5 = none of the time 999 = don't know / prefer not to answer
calm	How you feel and how things	1 = all the time

	have been for you during the last 4 weeks: Have you felt calm and peaceful?	2 = most of the time 3 = some of the time 4 = a little of the time 5 = none of the time 999 = don't know / prefer not to answer
energy	How you feel and how things have been for you during the last 4 weeks: Did you have a lot of energy?	1 = all the time 2 = most of the time 3 = some of the time 4 = a little of the time 5 = none of the time 999 = don't know / prefer not to answer
sad	How you feel and how things have been for you during the last 4 weeks: Have you felt downhearted and sad?	1 = all the time 2 = most of the time 3 = some of the time 4 = a little of the time 5 = none of the time 999 = don't know / prefer not to answer
worn	How you feel and how things have been for you during the last 4 weeks: Did you feel worn out?	1 = all the time 2 = most of the time 3 = some of the time 4 = a little of the time 5 = none of the time 999 = don't know / prefer not to answer
happy	How you feel and how things have been for you during the last 4 weeks: Have you been a happy person?	1 = all the time 2 = most of the time 3 = some of the time 4 = a little of the time 5 = none of the time 999 = don't know / prefer not to answer
tired	How you feel and how things have been for you during the last 4 weeks: Did you feel tired?	1 = all the time 2 = most of the time 3 = some of the time 4 = a little of the time 5 = none of the time 999 = don't know / prefer not to answer
social2	During the past 4 weeks, how much of the time has your physical health or emotional problems interfered with your social activities?	1 = all the time 2 = most of the time 3 = some of the time 4 = a little of the time 5 = none of the time 999 = don't know / prefer not to answer
sick	I seem to get sick a little easier than other people	1 = definitely true 2 = mostly true 3 = don't know 4 = mostly false 5 = definitely false 999 = don't know / prefer not to answer
others	I am as healthy as anybody I know	1 = definitely true 2 = mostly true 3 = don't know 4 = mostly false 5 = definitely false 999 = don't know / prefer not to answer
worse	I expect my health to get worse	1 = definitely true 2 = mostly true 3 = don't know 4 = mostly false 5 = definitely false 999 = don't know / prefer not to answer
health2	My health is excellent	1 = definitely true 2 = mostly true 3 = don't know

		4 = mostly false 5 = definitely false 999 = don't know / prefer not to answer

SECTION 6: OTHER MEDICAL EVENTS AND SYMPTOMS		
painChest	Do you often have difficulty walking on level ground at the same speed as other people of a similar age due to: Chest pain that goes away within 10 minutes of resting?	1 = yes 2 = no 999 = don't know / prefer not to answer
shortBreath	Shortness of breath that requires you to stop?	1 = yes 2 = no 999 = don't know / prefer not to answer
painCalf	Pain in your calves that goes away on resting?	1 = yes 2 = no 999 = don't know / prefer not to answer
painJoint	Pain in your joints?	1 = yes 2 = no 999 = don't know / prefer not to answer
feel_after	Immediately after giving blood how do you feel physically compared to how you usually feel	1 = Much better 2 = Slightly better 3 = About the same 4 = Slightly worse 5 = Much worse
breathless	Do you ever experience breathlessness?	1 = yes 2 = no 999 = don't know / prefer not to answer
breathless_scale	Please choose a phrase that best describes your breathlessness.	1 = Not troubled by breathlessness except on strenuous exercise 2 = Short of breath when hurrying on the level or walking up a slight hill 3 = Walk slower than most people on the level, stop after a mile or so, or stop after 15 minutes walking at own pace 4 = Stop for breath after walking about 100 yards or after a few minutes on ground level 5 = Too breathless to leave the house, or breathless when undressing 998 = not applicable
BDRI1	Indicate the degree to which you experienced the following sensations at your last blood donation. Faintness (if about to faint or become unconscious).	0 = Not at all 1 = To a slight degree 2 = To a moderate degree 3 = To a strong degree 4 = To a very strong degree 5 = To an extreme degree
BDRI2	Dizziness	0 = Not at all 1 = To a slight degree 2 = To a moderate degree 3 = To a strong degree 4 = To a very strong degree 5 = To an extreme degree
BDRI3	Weakness	0 = Not at all 1 = To a slight degree 2 = To a moderate degree 3 = To a strong degree 4 = To a very strong degree 5 = To an extreme degree
BDRI4	Lightheadedness	0 = Not at all

		1 = To a slight degree 2 = To a moderate degree 3 = To a strong degree 4 = To a very strong degree 5 = To an extreme degree
Faint	In the last 6 months, after donating blood, have you fainted?	1 = yes 2 = no 999 = don't know / prefer not to answer
delayFaint	In the last 6 months, after donating blood, have you fainted AFTER you have left a blood donation?	1 = yes 2 = no 999 = don't know / prefer not to answer

SECTION 7: YOUR GENERAL HEALTH AND LIFESTYLE		
med_gluc	Do you currently take any medications that control your blood sugar?	1 = yes 2 = no 999 = don't know
med_hyperten	Do you currently take any medications that control your blood pressure?	1 = yes 2 = no 999 = don't know
med_lipid	Do you currently take any medications that control your cholesterol?	1 = yes 2 = no 999 = don't know
Qu_female	The next page is relevant for women only. If it is not relevant to you please click "skip section."	1 = continue 2= Skip section
hrt	Do you regularly take hormone replacement therapy medications?	1 = yes 2 = no 999 = don't know / prefer not to answer
pill	Do you regularly take oral contraceptive medications?	1 = yes 2 = no 999 = don't know / prefer not to answer
menopause	Have you had your menopause?	1 = yes 2 = no 3 = not sure – had hysterectomy 4 = not sure – other reason 999 = don't know / prefer not to answer
smEver	Have you ever smoked?	1 = yes 2 = no 999 = don't know / prefer not to answer
smCurr	Do you currently smoke?	1 = yes 2 = no 999 = don't know / prefer not to answer
smStartAge	How old were you when you first started smoking	0.1 = less than 10 years old 10 – 70 = age started 777 = greater than 70 years old
smStopAge	How old were you when you stopped smoking?	0.1 = less than 10 years old 10 – 70 = age started 777 = greater than 70 years old
smFreq	About how often do / did you smoke?	6.5 = 6-7 times / week 4.0 = 3-5 times / week 1.5 = 1-2 times / week 0.5 = 1-3 times / month 0.1 = special occasions only
smCig	How many cigarettes do / did you smoke in a typical day?	0 = don't smoke it 0.1 = less than one per day 1 – 80 =number per day 777 = greater than 80 per day
smCigar	How many cigars do / did you	0 = don't smoke it

	smoke in a typical day?	0.1 = less than one per day 1 – 80 =number per day 777 = greater than 80 per day
smPipe	How many pipes do / did you smoke in a typical day?	0 = don't smoke it 0.1 = less than one per day 1 – 80 =number per day 777 = greater than 80 per day
alcEver	Have you ever drunk alcohol?	1 = yes 2 = no 999 = don't know / prefer not to answer
alcCurr	Do you currently drink alcohol?	1 = yes 2 = no 999 = don't know / prefer not to answer
alcYearsStop	For how many years have you stopped drinking alcohol?	0.1 = less than one month 0.3 = 1-6 months 0.7 = 6-12 months 1-50 = years stopped 777 = greater than 50 years
alcFreq	About how often do / did you drink alcohol?	6.5 = 6-7 times / week 4.0 = 3-5 times / week 1.5 = 1-2 times / week 0.5 = 1-3 times / month 0.1 = special occasions only
alcWhite	In an average WEEK how many glasses of white wine, rose wine or champagne do/did you drink	0 = don't drink it 0.1 = less than one measure per week 1 – 50 = measures per week 777 = greater than 50 measures per week
alcRed	In an average WEEK how many glasses of red wine do/did you drink	0 = don't drink it 0.1 = less than one measure per week 1 – 50 = measures per week 777 = greater than 50 measures per week
alcBeer	In an average WEEK how many pints of beer / cider (include bitter, lager, and Guinness®) do/did you drink	0 = don't drink it 0.1 = less than one measure per week 1 – 50 = measures per week 777 = greater than 50 measures per week
alcSpirit	In an average WEEK how many measures of spirits / liquors (e.g. whisky, gin, rum, vodka, brandy) do/did you drink	0 = don't drink it 0.1 = less than one measure per week 1 – 50 = measures per week 777 = greater than 50 measures per week
alcFwine	In an average WEEK how many glasses of fortified wine (e.g. sherry, port, vermouth) do/did you drink	0 = don't drink it 0.1 = less than one measure per week 1 – 50 = measures per week 777 = greater than 50 measures per week
alcPops	In an average WEEK how many bottles of alcopops (e.g. Bacardi Breezer®, WKD®, Smirnoff Ice®) do/did you drink	0 = don't drink it 0.1 = less than one measure per week 1 – 50 = measures per week 777 = greater than 50 measures per week
meatEater	Do you eat meat or fish?	1 = yes 2 = no 999 = don't know / prefer not to answer
ageVeg	How old were you when you last ate any kind of meat or fish (vegetarians only)?	0 = never eaten meat / fish 1 - 70 = age 777 = more than 70 years old 999 = don't know / prefer not to answer
liver	In an average WEEK how many times do you eat Liver (any type e.g. pigs, chicken, lambs)	0 = do not eat it 0.1 = less than once a week 1 – 20 = times / week 777 = more than 20 times per week
redMeat	In an average WEEK how many times do you eat Red meat (e.g. beef, lamb, pork, bacon, ham, sausages, burgers)	0 = do not eat it 0.1 = less than once a week 1 – 20 = times / week 777 = more than 20 times per week

poultry	In an average WEEK how many times do you eat Poultry (e.g. chicken, turkey)	0 = do not eat it 0.1 = less than once a week 1 – 20 = times / week 777 = more than 20 times per week
whiteFish	In an average WEEK how many times do you eat White fish (e.g. cod, haddock, tinned tuna)	0 = do not eat it 0.1 = less than once a week 1 – 20 = times / week 777 = more than 20 times per week
oilyFish	In an average WEEK how many times do you eat Oily fish (canned or fresh e.g. sardines, mackerel, salmon, trout)	0 = do not eat it 0.1 = less than once a week 1 – 20 = times / week 777 = more than 20 times per week
veg	Please indicate the times during an average day that you consume vegetables (excluding potatoes)	1 = with meals 2 = between meals 3 = with and between meals 4 = never / rarely
fruit	Please indicate the times during an average day that you consume fruit (whole)	1 = with meals 2 = between meals 3 = with and between meals 4 = never / rarely
juice	Please indicate the times during an average day that you consume fruit juice	1 = with meals 2 = between meals 3 = with and between meals 4 = never / rarely
smooth	Please indicate the times during an average day that you consume fruit smoothies	1 = with meals 2 = between meals 3 = with and between meals 4 = never / rarely
tea	Please indicate the times during an average day that you consume tea	1 = with meals 2 = between meals 3 = with and between meals 4 = never / rarely
eatBefore	Thinking about the amount of food you eat in 24 hours BEFORE giving blood, do you eat…	1 = more 2 = less 3 = the same
drinkBefore	Thinking about the amount of non-alcoholic beverages you drink in the 24 hours BEFORE giving blood, do you drink…	1 = more 2 = less 3 = the same
eatAfter	Thinking about the amount of food you eat in the 24 hours AFTER giving blood, do you eat…	1 = more 2 = less 3 = the same
drinkAfter	Thinking about the amount of non-alcoholic beverages you drink in the 24 hours AFTER giving blood, do you drink…	1 = more 2 = less 3 = the same
eatTyp_change	Thinking about your usual diet do you change the types of food you eat as a result of giving blood	1 = yes 2 = no
eatTyp_BefAft	When do you make changes to the types of food you eat as a result of giving blood	1 = In the weeks prior to giving blood 2 = In the weeks after giving blood 3 = In the weeks prior to and after giving blood
eatTyp_more_a	Thinking about the changes you make, do you eat more or less red meat as a result of giving blood	1 = more 2 = less 3 = the same 4 = I do not eat red meat
eatTyp_more_b	Do you eat more or less white meat or fish as a result of giving blood	1 = more 2 = less 3 = the same 4 = I do not eat white meat or fish
eatTyp_more_c	Do you eat more or less eggs as a	1 = more

	result of giving blood	2 = less 3 = the same 4 = I do not eat eggs
eatTyp_more_d	Do you eat more or less dairy foods (cheese, milk etc.) as a result of giving blood	1 = more 2 = less 3 = the same 4 = I do not eat dairy foods
eatTyp_more_e	Do you eat more or less green vegetables as a result of giving blood	1 = more 2 = less 3 = the same 4 = I do not eat vegetables
eatTyp_more_f	Do you eat more or less lentils or beans as a result of giving blood	1 = more 2 = less 3 = the same 4 = I do not eat lentils or beans
eatTyp_more_g	Do you eat more or less fruit as a result of giving blood	1 = more 2 = less 3 = the same 4 = I do not eat fruit
eatTyp_more_h	Do you eat more or less snacks e.g. biscuits, cakes, crisps as a result of giving blood	1 = more 2 = less 3 = the same 4 = I do not eat snacks
eatTyp_more_i	Do you drink more or less tea or coffee as a result of giving blood	1 = more 2 = less 3 = the same 4 = I do not drink tea or coffee
eatTyp_more_j	Do you drink more or less alcohol as a result of giving blood	1 = more 2 = less 3 = the same 4 = I do not drink alcohol
pa_change	Thinking about your usual levels of physical activity (including general walking, cycling, housework etc.) have you changed these as a result of giving blood?	1 = yes 2 = no
pa_day	How much physical activity do you do on the day that you give blood	1 = Much more than usual 2 = Slightly more than usual 3 = About the same 4 = Slightly less than usual 5 = Much less than usual
pa_week	How much physical activity do you do in the week after you have given blood?	1 = Much more than usual 2 = Slightly more than usual 3 = About the same 4 = Slightly less than usual 5 = Much less than usual
work	How do you spend most of your time at work?	1 = sitting 2 = standing / walking 3 = Manual work/some physical effort 4 = Heavy manual/physical work 5 = do not work 999 = don't know / prefer not to answer
leisure	Please indicate how active you are outside work (including travel to and from work, activity in the home and in your leisure time)	1 = inactive 2 = moderately inactive 3 = moderately active 4 = very active 999 = don't know / prefer not to answer

Annex 2.11

HEADER: Thank you from COMPARE – 1st questionnaire and next appointment

Thank you for completing the first of your two questionnaires for the COMPARE study and, also, for making your next study donation appointment on <<**Date**>>.

At this next appointment your haemoglobin levels will be measured using NHSBT'S standard test and also by alternative methods which will involve you:

- Providing an extra drop of blood from the same finger-prick used for NHSBT's standard test
- Wearing a clip device around your finger for about 1 minute
- Providing a small research blood sample at the time of make your routine donation (this will not require an additional needle).

Your attendance at this visit is very important to our research and we will remind you of your appointment in the week before it is due.

If you have any questions about the study, please contact our helpdesk (using details below). You can also keep up to date with study progress at www.COMPAREstudy.org.uk

Best wishes

COMPARE Study Team

0800 021 7182

Annex 2.12

HEADER: Thank you from COMPARE – 1st questionnaire and next appointment

Thank you for completing the first of your two questionnaires for the COMPARE study and, also, for helping us with our research.

You are due to attend your second study donation visit <<**12 weeks**>> <<**16 weeks**>> after your most recent visit on <<**add date**>>. At this next appointment your haemoglobin levels will be measured using NHSBT'S standard test and also by alternative methods which will involve you:

- Providing an extra drop of blood from the same finger-prick used for NHSBT's standard test
- Wearing a clip device around your finger for about 1 minute
- Providing a small research blood sample at the time of make your routine donation (this will not require an additional needle).

Your attendance at this visit is very important to our research. We appreciate that it's not always possible to book an appointment in advance. However, if you can do this it's more likely that there will be a slot available when your 2nd COMPARE visit is due. To book an appointment, please either use the donor portal or call NHSBT's National Call Centre on 0300 123 2323.

If you have any questions about the study, please contact our helpdesk (using details below). You can also keep up to date with study progress at www.COMPAREstudy.or.uk

Best wishes

COMPARE Study Team

Tel: 0800 021 7182

Annex 2.13

HEADER: Thank you from COMPARE – 1st questionnaire and next appointment

Thank you for <<**completing the questionnaire for the COMPARE study and, also, for**>> helping us with our research. <<**If you have not already completed the questionnaire we sent you about 3 weeks ago there's still time to complete it**>>

As you were deferred from donating at your last appointment, it will not be necessary for you to make a second study visit but the <<**data and**>> research samples that you've kindly provided will make a valuable contribution to our research.

If you have any questions about the study, please contact our helpdesk (using details below). You can also keep up to date with study progress at www.COMPAREstudy.org.uk

Best wishes

COMPARE Study Team

Tel: 0800 021 7182

Annex 2.14

SUBJECT LINE: COMPARE study – your 2nd donation visit

Dear Donor,

Thank you for taking part in the COMPARE Study.

When you joined COMPARE, you kindly agreed to return for a 2nd donation visit at your standard donation interval, i.e. 12 weeks for men and 16 weeks for women.

This is courtesy reminder that your 2nd donation visit is due in 7 days on <<*insert date here*>>.

If you would like to review again what the COMPARE study is all about, please go to this link: www.comparestudy.org.uk

If you are no longer able to attend this appointment, please make any changes or cancellations via the Blood Service self-service system: www.blood.org.uk or by calling the NHSBT National Contact Centre on 0300 123 23 23.

Thank you for your continued support of our research.

Kind regards,

The COMPARE team.

Freephone: 0800 XXX XXXX (Mon-Fri: 09:00 to 17:00)

Email: helpdesk@comparestudy.org.uk

Annex 2.15

Thank you very much for attending your 2nd visit as part of the COMPARE Study. Your support is very important to the success of this research and is helping to safeguard the wellbeing of all blood donors in the future.

During your involvement in COMPARE your pre-donation haemoglobin levels have been tested using both the current and alternative methods. We would now be very grateful if you could complete a short questionnaire about your experience of and preferences for each of these methods. It should take approximately 5 minutes to complete. ***Please do your best to answer every question.***

The password required to begin the questionnaire will arrive in a separate email entitled "**COMPARE Key**" Once you have the password, please return to this email and click on the link below to access the questionnaire:

LINK

If you are unable to access the questionnaire with the link above, please copy and paste the following into a new window in your internet browser: fulllinktoquestionnairehere.com

Thank you very much for taking the time to complete the questionnaire. Your answers will be treated as strictly confidential and will only be used for medical research. If you have any questions please contact the COMPARE team using the details below.

Many thanks,

The COMPARE team.

Freephone: 0800 021 7182 (Mon-Fri: 09:00 to 17:00)

E-mail: helpdesk@comparestudy.org.uk

Annex 2.16

SUBJECT LINE: COMPARE study – questionnaire reminder (Part 2)

Dear Donor,

Thank you once again for taking part in the COMPARE Study. One week ago we emailed you a link to the second part of the COMPARE study online questionnaire. If you have completed the questionnaire in the last 24 hours please discard this reminder. If not, we would be very grateful if you could complete the questionnaire – it takes about 5 minutes. Please click the link below to access the questionnaire:

LINK

The password to begin the questionnaire was sent to you one week ago in an email entitled "**COMPARE Key"**. If you have any trouble finding the password please contact the helpdesk using the details below.

If you are unable to access the questionnaire with the link above, please copy and paste the following into a new window in your internet browser: fulllinktoquestionnairehere.com

Thank you very much for taking the time to complete the questionnaire. Your answers will be treated as strictly confidential and will only be used for medical research. If you have any questions please contact the COMPARE team using the details below.

Many thanks,

The COMPARE team.

Freephone: 0800 021 7182 (Mon-Fri: 9:00 to 17:00)

E-mail: helpdesk@comparestudy.org.uk

Annex 2.17

Dear Donor,

Thank you once again for taking part in the COMPARE Study. Three weeks ago we emailed you a link to the second part of the COMPARE study online questionnaire. If you have completed the questionnaire in the last 24 hours please discard this reminder. If not, we would be very grateful if you could complete the questionnaire - it takes about 5 minutes. Please click the link below to access the questionnaire:

LINK

The password to begin the questionnaire was sent to you three weeks ago in an email entitled "**COMPARE Key"**. If you have any trouble finding the password please contact the helpdesk using the details below.

If you are unable to access the questionnaire with the link above, please copy and paste the following into a new window in your internet browser: fulllinktoquestionnairehere.com

Thank you very much for taking the time to complete the questionnaire. Your answers will be treated as strictly confidential and will only be used for medical research. If you have any questions please contact the COMPARE team using the details below.

Many thanks,

The COMPARE team.

Freephone: 0800 021 7182 (Mon-Fri: 9:00 to 17:00)

E-mail: helpdesk@comparestudy.org.uk

ANNEX 2.18

COMPARE: a study of haemoglobin testing methods and to create a bioresource for future research into donor and public health

INFORMATION LEAFLET

We would like to invite you to join the COMPARE study which is led by doctors and scientists at the University of Cambridge, NHS Blood and Transplant (NHSBT) and National Institute for Health Research (NIHR).

To help protect the health of blood donors, it's a requirement to find out whether a donor's blood haemoglobin levels are adequate. However, it's not clear what the best method is for rapidly measuring haemoglobin levels. So, this study of 31,000 blood donors aims to provide a clear answer.

The study is comparing the method of haemoglobin testing used by NHSBT with promising and newer approaches used by blood services in Europe and the USA. The results should help safeguard the well-being of future blood donors and define best practice for England's blood service. A further objective is to create a bioresource of healthy volunteers using samples and data collected during the study to be used in future approved research projects looking at donor and public health.

Before you decide whether to participate, it's important for you to understand why the study is being done and what is involved. Please take the time to read the following information carefully, and discuss it with others if you wish.

If anything is not clear, or if you would like more information, please call the freephone number on 0800 XXX XXXX (Monday to Friday: 0900h - 1700h) to talk to a member of our study team or email helpdesk@comparestudy.org.uk.

Many thanks for taking the time to consider taking part in the COMPARE study.

Dr Emanuele Di Angelantonio	Dr Gail Miflin	Prof John Danesh
NHSBT & University of Cambridge	**NHSBT**	**University of Cambridge**

The COMPARE Study

University of Cambridge, Department of Public Health and Primary Care

Wort's Causeway, Cambridge CB1 8RN

Email: helpdesk@comparestudy.org.uk

Freephone: 0800 XXX XXXX

Website: www.comparestudy.org.uk

Why is the study needed?

To help protect the health of donors, it's a requirement to find out whether a donor's blood haemoglobin levels are adequate. The blood service in England screens potential donors with an initial finger prick ("copper sulphate") test. For people suspected of having inadequate haemoglobin levels, a more precise ("HemoCue") test is then immediately done using a venous blood sample. However, blood services in different countries use different screening approaches. We are leading a study of 31,000 donors to compare different methods. The goal is to help safeguard the well-being of future blood donors and define best practice for NHSBT.

What haemoglobin tests are being compared?

This study is comparing the method used by NHSBT with a promising and a newer approach which involves a non-invasive light-shining device ("spectrometer") placed over a finger for about one minute, which avoids taking a blood sample altogether

What will I be asked to do if I participate?

You will be asked to do the following **today**:

- complete a consent form agreeing to participate in this study
- provide a sample of your blood (~16mL, equivalent to about 3 teaspoons) for research. This sample will be obtained from the same venepuncture used in your routine donation
- wear a clip device around your finger for about one minute for a non-invasive haemoglobin test

About one week from today, you will receive an email message asking you to complete a brief (15 minute) online questionnaire about your personal details, health, and lifestyle. We will also ask about your individual characteristics that are associated with skin tone (e.g. eye and hair colour) to evaluate variability in the performance of the non-invasive devices according to skin tone.

Who is eligible for the study?

We are inviting all blood donors who usually give blood at one of about 10 selected mobile donation sessions. You **are eligible** to take part in the study if you are:

- aged 18 years or older.
- willing to undergo an additional haemoglobin measurement.
- willing to provide a small sample of blood for research, even if your haemoglobin levels are slightly below the threshold for donating blood.
- willing to complete an online questionnaire at home (and, thus, provide your email address).

Do I have to take part?

No, it is completely up to you. If you decide to take part you will be asked to sign a consent form (see the end of this leaflet for a sample copy). You are free to withdraw at any time, without giving a reason. Your decision will have no influence on your blood donation now or in the future.

What should I do if I want to take part?

If you would like to join the study, then all you need to do is let your donor carer know. Your carer will take you through the consent form and answer any questions you might have.

How will my blood samples be used?

Research samples will be measured within one day of collection for a "gold standard" full blood count and then frozen. Stored samples of separate blood components (e.g., plasma, serum, DNA) will be:

- kept securely at a central laboratory, labelled only with a unique study number
- used for medical and health-related studies that have relevant scientific and ethics approval
- used to measure blood substances ("biomarkers") that reflect health status (e.g., iron levels)
- used to study your DNA and related substances to find out, for example, how genes regulate blood cells and haemoglobin levels. Genes are made up of DNA and you have two copies, one from your mother and the other from your father. Researchers can now read a large fraction or the entire genetic code within days to really understand the role of genes in health and disease. We will test for many genes and determine the sequence of part of or your entire genetic code.
- in addition to this initial study, your samples and data on your full DNA (genetic) code will be used in a number of future approved research projects investigating donor and public health. The results may not be known for several years. As they are not performed in the same way or to the same laboratory standard as clinical tests you will not be informed of any incidental findings. Researchers using your sample will only be provided with anonymised data which ensures they cannot link the sample or data to you by name.

How will my study information be used?

Your study information will be used to compare different haemoglobin testing methods, and serve as a resource to help answer wider health questions in approved studies. We are asking for your permission to access your medical and other health-related records, and for the long-term confidential storage and use of this data for future health-related research purposes with relevant approvals. We are asking for your permission to invite you to further studies, which you will be able to accept or decline on a case-by-case basis.

Are there any benefits for me in joining the study?

You will not receive an immediate benefit. However, the study's findings should help safeguard the well-being of future blood donors and define best practice for England's blood service.

Are there any additional risks for me in joining the study?

No. Your safety will be looked after by NHSBT in the usual way. That is, you will receive the **usual** screening test for haemoglobin levels and you will need to be within the safe range to be eligible to donate. If your haemoglobin levels are not adequate, you will not be allowed to donate blood. However, you will be asked to give a small research blood sample (~16mL) because it's important to compare the different screening methods in people with lower haemoglobin levels.

How will information about me be kept confidential?

We will protect your privacy and ensure confidentiality through several measures:

- At the donation session, your consent to take part in the study will be recorded on a form that will contain your name. The form will be stored in a secure location, separately from the study data.

● Limited personal information will be accessed and retrieved from the national NHSBT database (PULSE). This will include your email address and telephone number for study communication only. In addition we will retrieve your Donor Number and NHS number. These personal data will be stored in a secure location, separately to the study database.

● Your samples will **not** include any personal identifying details and will be stored using a unique, anonymous study identification number.

● A single table linking your study identification number to your NHSBT Donor Number and your NHS number will be stored on a separate password-protected location which may be accessed only by scientists given the specific approval of the senior study investigators.

● The link table will be used to retrieve relevant health information from your medical and other health-related records. Personal identifying details will have been removed and replaced by the unique anonymous study identification number.

● Study data will be stored in a restricted-access database not connected to the NHSBT database containing your personal details. The study data will be linked to your study identification number. Access to the study database will be password-protected and will be used only by named researchers working on this study under the direct supervision of the senior investigators.

● Your study data will include results from laboratory measurements using your blood sample; this will include data on the sequence of your entire genetic code. Because this code is unique to you, it is, in principle, possible for someone to identify you from these data. However, the risk of this happening in practice is small. This is because such an occurrence would require that a researcher not only has your anonymised genetic sequence data from the COMPARE study but also has a) comparable data on your genetic sequence from another source which identifies you and b) the computing systems to match the two sequences. While this is technically possible, the risk of identification is remote due to the safeguards described above.

● Your personal details provided during the study will be stored in a secure location, separately from the study database and used for the purpose of study communication. Personal information will only be linked to the study database with the permission of the senior investigators.

What will be stored on the study database?

Confidential information that will be stored on the database (i.e., information that can be linked to your personal identifiers only with the permission of the senior investigators) will include:

● Relevant information from your NHSBT donor record, such as sex, month and year of birth, details of your donation history and blood group

● Data from the study's online questionnaire

● Results from laboratory measurements using your blood sample, including DNA

● Information on health outcomes collected from routine medical and other health-related records.

How do I withdraw if I want to do so?

You can withdraw from the study at any time and without giving a reason. However, the benefits of the study will be increased if few people withdraw from it, so please discuss any concerns with us in advance. To discuss withdrawing from the study, please call freephone 0800 XXX XXXX (Monday to Friday 0900h - 1700h) or write to helpdesk@comparestudy.org.uk or our postal address. In the unlikely event of you losing capacity (including death) to decide on continued participation in the study, the blood samples and personal data collected will continue to be used confidentially in connection with the purposes for which consent has been granted.

Who will be able to use my information and samples?

Your information and samples will be available only to researchers who have relevant approvals for their planned research. This could include researchers who are working in other countries (including outside the EEC) and in commercial companies who are looking for new treatments or laboratory tests. Insurance companies and employers will not be given any individual's information, samples or test results, and we will not allow access to the police, security services, relatives or lawyers, unless forced to do so by the courts.

There will be a requirement to publish the results of any research arising out of the samples and data collected during the study to ensure others can benefit from it. Our website will include a list of reports arising from the study. The website will not contain any personal information.

We generally do not plan to provide feedback of results. However, we would communicate results to you that would have an immediate impact on your healthcare (such as finding cells in your blood that may suggest a significant health problem e.g. leukaemia). In this case, we will inform an NHSBT medical professional about the nature of the problem, and about who you are. An NHSBT medical professional would then use the routine procedures applicable in the NHS to get in touch with you and offer advice, which may involve contacting your GP.

Who is organising and funding the study?

The University of Cambridge, NHS Blood and Transplant and National Institute for Health Research.

Who has approved the study?

Research in the NHS is reviewed by independent groups of people ("Research Ethics Committee") to protect your safety, rights, wellbeing and dignity. This project has been reviewed and was given a favourable review by the << to be added>> Research Ethics Committee.

What will happen if an invention is made using my sample?

You are giving your sample as an absolute gift, i.e., without receiving a payment and without attaching conditions. This study is operating on a non-commercial basis, meaning it does not sell your sample to make a profit and will not allow anyone else who is working with the sample to do so either. However, if samples are made available to other research institutions or to private-sector research partners, a fee may be charged to cover the operational costs.

In the future, your sample may help researchers in the public and private sector to make an invention, e.g., to develop a new product to diagnose, prevent or treat disease. If an invention results from the research undertaken with your sample you will not receive any compensation or payment. The study investigators may work together with commercial companies to develop inventions for the benefit of patient and donor care; and we hope that such products are brought into use by the NHS to improve health care in the future.

What happens if something goes wrong?

The risk of participants suffering harm as a result of taking part is minimal. Nevertheless, insurance is in place to provide compensation for any negligent harm caused by participation.

Who do I contact if I have any concerns?

If you have any concerns or complaints about anything to do with the COMPARE study then you can telephone the freephone number on 0800 XXX XXXX (Monday to Friday 0900h - 1700h) to

speak to a member of the study team or email us at helpdesk@comparestudy.org.uk. Alternatively, if you would like to write to us, please send your letter to the COMPARE study coordinator, University of Cambridge, Department of Public Health and Primary Care, Wort's Causeway, Cambridge CB1 8RN.

COMPARE STUDY CONSENT FORM ('DONOR COPY')

Chief Investigators: Dr Emanuele Di Angelantonio and Professor John Danesh

University of Cambridge and NHS Blood and Transplant

Blood Donor ID number:

You need to tick <u>all boxes from 1 to 9</u> to be eligible to take part in the study

1. I confirm that I have read and understood the COMPARE participant information leaflet (Stage 2) dated XX.XX.XX (version X) for the above study. I have had the opportunity to ask questions, and these have been answered fully.	☐
2. I understand that my participation is voluntary and that I am free to withdraw at any time without giving any reason.	☐
3. I understand and grant permission for relevant sections of my blood donation records to be retrieved and used by the study team.	☐
4. I give permission for long-term, anonymised storage of my blood samples (including DNA) for health-related research purposes (even after my incapacity or death), and relinquish all rights to these samples which I am donating to the study.	☐
5. I understand that information held by the NHS and records maintained by the NHS Information Centre and the NHS Central Register may be used to provide information about my health status and I give permission for long-term anonymised storage and use of this and other information about me, for health-related research purposes (even after my incapacity or death).	☐
6. I agree to provide an email address and for my contact phone details to be given to members of the study team, to send me communications about the study. I will maintain the email address provided or, if necessary, supply a new one in the future.	☐
7. I understand that none of my results (other than those which have an immediate impact on my health care) will be given to me and that I will not benefit financially from taking part (e.g. if research leads to commercial development of a new treatment or blood test).	☐
8. I understand I may be contacted by the COMPARE study team about further studies, which I will be able to accept or decline on a case-by-case basis.	☐
9. I confirm that I am 18 years or over.	☐
10. I agree to take part in the above study.	☐

Participant name:	Signature:	Date:

ANNEX 2.19

COMPARE STUDY CONSENT FORM ('DONOR COPY')

Chief Investigators: Dr Emanuele Di Angelantonio and Professor John Danesh

University of Cambridge and NHS Blood and Transplant

Blood Donor ID number:

You need to tick <u>all boxes from 1 to 9</u> to be eligible to take part in the study

11. I confirm that I have read and understood the COMPARE participant information leaflet (Stage 2) dated XX.XX.XX (version X) for the above study. I have had the opportunity to ask questions, and these have been answered fully.	☐
12. I understand that my participation is voluntary and that I am free to withdraw at any time without giving any reason.	☐
13. I understand and grant permission for relevant sections of my blood donation records to be retrieved and used by the study team.	☐
14. I give permission for long-term, anonymised storage of my blood samples (including DNA) for health-related research purposes (even after my incapacity or death), and relinquish all rights to these samples which I am donating to the study.	☐
15. I understand that information held by the NHS and records maintained by the NHS Information Centre and the NHS Central Register may be used to provide information about my health status and I give permission for long-term anonymised storage and use of this and other information about me, for health-related research purposes (even after my incapacity or death).	☐
16. I agree to provide an email address and for my contact phone details to be given to members of the study team, to send me communications about the study. I will maintain the email address provided or, if necessary, supply a new one in the future.	☐
17. I understand that none of my results (other than those which have an immediate impact on my health care) will be given to me and that I will not benefit financially from taking part (e.g. if research leads to commercial development of a new treatment or blood test).	☐
18. I understand I may be contacted by the COMPARE study team about further studies, which I will be able to accept or decline on a case-by-case basis.	☐
19. I confirm that I am 18 years or over.	☐
20. I agree to take part in the above study.	☐

Participant name:	Signature:	Date:

Time samples collected (*using 24 hour clock*)	☐☐ : ☐☐

ANNEX 2.20

COMPARE STUDY CONSENT FORM ('STUDY COPY')

Chief Investigators: Dr Emanuele Di Angelantonio and Professor John Danesh

University of Cambridge and NHS Blood and Transplant

You need to tick <u>all boxes from 1 to 9</u> to be eligible to take part in the study

21. I confirm that I have read and understood the COMPARE participant information leaflet (Stage 2) dated XX.XX.XX (version X) for the above study. I have had the opportunity to ask questions, and these have been answered fully.	☐
22. I understand that my participation is voluntary and that I am free to withdraw at any time without giving any reason.	☐
23. I understand and grant permission for relevant sections of my blood donation records to be retrieved and used by the study team.	☐
24. I give permission for long-term, anonymised storage of my blood samples (including DNA) for health-related research purposes (even after my incapacity or death), and relinquish all rights to these samples which I am donating to the study.	☐
25. I understand that information held by the NHS and records maintained by the NHS Information Centre and the NHS Central Register may be used to provide information about my health status and I give permission for long-term anonymised storage and use of this and other information about me, for health-related research purposes (even after my incapacity or death).	☐
26. I agree to provide an email address and for my contact phone details to be given to members of the study team, to send me communications about the study. I will maintain the email address provided or, if necessary, supply a new one in the future.	☐
27. I understand that none of my results (other than those which have an immediate impact on my health care) will be given to me and that I will not benefit financially from taking part (e.g. if research leads to commercial development of a new treatment or blood test).	☐
28. I understand I may be contacted by the COMPARE study team about further studies, which I will be able to accept or decline on a case-by-case basis.	☐
29. I confirm that I am 18 years or over.	☐
30. I agree to take part in the above study.	☐

Participant name:	Signature:	Date:
Staff member name:	Signature:	Date:

Office use only. For completion by NHSBT staff.	
Blood donor ID number:	
Please confirm that the donor is (i) aged at least 18 years, and (ii) willing to provide an email address for study correspondence:	**YES** ☐ **NO** ☐

ANNEX 2.21

NHS Blood and Transplant

COMPARE Study Project

Business Requirements Specification

Business Objects Reports

Version 1.0

Authors: Carmel Moore, Mat Walker and Susan Mehenny

Date: 13 August 2015

Document Control

This document is only valid on the day it was printed.

Summary of changes

This section records the history of significant changes to this document. Only the most significant changes are described here.

Version	Date	Author	Description of change
0.1	31/07/12	Carmel Moore	Initial version for review
0.2	03/08/15	Carmel Moore	Updated version following comments from Mat Walker and Susan Mehenny
0.3	07/08/15	Carmel Moore	Updated version following additional comments from Mat Walker and Carmel Moore
1.0	13/08/15	Carmel Moore	Version 1.0 for sign-off

Where significant changes are made to this document, the version number will be incremented by 1.0.

Where changes are made for clarity and reading ease only and no change is made to the meaning or intention of this document, the version number will be increased by 0.1.

Approvals and Reviews

The approvals below are for all documents which form part of this process (narrative, process flow, forms, meeting charters, etc). Revisions of these documents are approved and reviewed by the job roles identified below. The formal approvals are stored in the Programme Document Library on SharePoint

Approvers:

This document was approved by:

Name	Title	Date
Mat Walker	Senior Data Manager (University of Cambridge)	
Susan Mehenny	COMPARE study – Project Lead (NHSBT)	
Kate Holmes	Information Governance Officer (NHSBT)	
Stuart Halson	Head of Business Intelligence and Data Management (NHSBT)	

It should be noted that the data to be included in the Business Objects reports and outlined in this User Requirements Specification are included in a wider Information Sharing Protocol for sign- off by the NHSBT Caldecott Guardian and the Pulse data asset owner.

Reviewers:

This document was reviewed by:

Name	Title	Date
Mat Walker	Senior Data Manager (University of Cambridge)	
Susan Mehenny	COMPARE study – Operational Change Manager (NHSBT)	
Kate Holmes	Information Governance Officer (NHSBT)	
Stuart Halson	Head of Business Intelligence and Data Management (NHSBT)	

References

The following documents are referred to in this document: -

NHSBT/UoC Information Sharing Protocol **<<ref** to be added when available**>>**
System Level Security Protocol – **<<ref** to be added when available**>>**

Please note this document does not seek to outline the methodology for transfer of the data, just the requirements for the data to be transferred. Full details can be found in the documents listed above which are available from the Project Team. Signed copies are held by Dr Lorna Williamson, NHSBT Caldicott Guardian.

Table of Contents

1 Introduction

1.1 Background

Blood services are mandated to measure the haemoglobin concentration of potential whole blood donors in advance of each donation, both to protect the health of donors (ie, to prevent collection from anaemic donors) and to ensure the quality of blood products. The European legislation on selection criteria of blood donors states that haemoglobin levels should be ≥125g/L for women and ≥135g/L for men to allow blood donation. However, despite such legislation, even within Europe national blood services use varying haemoglobin screening approaches. This situation reflects a lack of rigorous evidence to support a single optimal policy.

NHSBT currently use a “copper sulphate finger prick test” on capillary blood to measure pre-donation haemoglobin level, and if this test indicates that the haemoglobin levels are low, donors are asked to provide a sample of venous blood for further testing using the more precise “Hemocue” test. However, this method has limitations. In an analysis of data from 45,000 donors who gave blood in England during 2012-14, we found that almost 10% were judged to have been inappropriately bled (ie, they had haemoglobin levels below the EU directive cut-off points) when the current NHSBT approach was compared against the “gold standard” haematology analyser.

There are about 1.3 million blood donors each year in England who provide a total of 1.9 million donations. Given NHSBT's duty of care to such a large group of volunteers, there is a fundamental need to determine the optimum method to measure haemoglobin concentration in advance of each donation in order reduce the number of donors inappropriately bled.

An important objective of NHSBT, and a major motivator of the current proposal, is also to move towards a more donor-friendly approach to measure haemoglobin level. In some parts of Europe alternative approaches to haemoglobin screening have been adopted. However, their comparative merits have not been robustly evaluated.

To our knowledge, there are no previous (or planned) studies in the UK or elsewhere that aim to compare different strategies to measure haemoglobin levels in blood donors.

The NHSBT and University of Cambridge (UoC) Project Teams have worked closely together to develop an end to end operational design for the COMPARE study and to identify detailed requirements for data transfer between the two parties to achieve the objectives of the study.

Integral to the agreements reached have been:

- Ensuring that UoC are provided with all relevant data to achieve the scientific objectives of the study and comply with safety and research governance requirements.
- Ensuring the Research Study database can be populated in the most efficient manner;
- Confirming that clear rationale exists for all personal identifiable data (PID) to be exchanged for our donors;
- Ensuring that the consent documentation[3], which is to be completed and signed by participating donors, makes it explicitly clear what level of PID is to be divulged;
- Ensuring that all data required is provided to UoC and so reducing the need for UoC to directly access donor records from Pulse[4]:

[3] All donor-facing study documentation has been subject to approval by Ethics Committee.
[4] Access to the Donor Management Application in PULSE is granted to nominated users in UoC’s Research Team with honorary NHSBT contracts.

- Involvement of NHSBTs Information Governance Security representatives to ensure that PID being exchanged is relevant and that the method by which it is to be exchanged is secure.
- Alignment to the overall Information Sharing Protocol (ISP) document which is to be produced, the ISP will cover off the systems specifications, security methodology around the data transfer and the wider access of UoC to the Donor Management Application within Pulse.

It has been determined that the most appropriate means of extracting and providing the data required from Pulse to support the Study is via a suite of Business Objects reports. This paper sets out to outline the business requirements for these reports and will also become an appendix to the overall ISP.

1.2 Vision

Overview

We will compare the following three haemoglobin tests which are used by various blood services in major Western industrialised countries against the results of a "gold standard" haematology analyser and against the results of the current NHSBT method:

1) "Post-donation" method: This method involves using haemoglobin levels obtained from a "gold standard" haematology analyser at the most recent blood donation visit to predict the donor's haemoglobin level at the next visit (ie, typically 12-16 weeks later)

2) Capillary point-of-care test: This method involves taking a drop of capillary blood after a finger-prick (ie, the same finger-prick used for NHSBT's routine copper sulphate test) and measuring haemoglobin levels using a rapid Hemocue test. (NB: The point-of-care Hemocue test involves capillary blood, whereas NHSBT's currently used Hemocue test involves a venous blood sample).

3) Non-invasive strategy: This method involves either of two hand-held spectrometer devices (ie, MBR Haemospect® versus Orsense NMB200®) that estimate haemoglobin levels by shining a light on the skin of a donor's finger.

Recruitment

Recruitment will take place at least 10 NHSBT mobile teams in England. All donors attending a donation session of a relevant mobile team will be invited to join the study and if they are interested in taking part will be provided with a copy of the COMPARE study information leaflet.

Two-stage study

There will be two stages of recruitment

Stage 1 (weeks 1 to 29): This stage will involve a head-to-head comparison, in a common set of about 12,500 participants, of the three new methods and NHSBT's current method for haemoglobin testing. As the post-donation methods requires participants to attend two successive blood donation visits, we will enrol about 18,000 donors at an initial donation visit in order to yield an anticipated 12,500 participants who attend two successive visits. This assumes a non-attendance rate of 30% at the second visit.

It would be ideal to conduct a head-to-head comparison of the two non-invasive in the same set of 12,500 participants. However, such an approach would likely be too time-consuming and disruptive to NHSBT's high-throughput service. As such Stage 1 participants will receive only one non-invasive measurement of their haemoglobin levels by either Haemospect or Orsense. In order to conduct a head-to-head comparison of these two devices a second phase of the study will be conducted.

Stage 2 (weeks 29 and 37): This will involve the enrolment of a further approximately 13,000 participants, focusing on the comparison of the two different non-invasive spectrometry devices. Selection of mobile donation centres will be done in way to over-sample donors of non-European ancestry (eg, those of African, Middle Eastern, and South Asian ancestry) during the second stage of recruitment because a key question for non-invasive spectrometry is the performance of devices in people with different skin colour and tone.

Donors who have consented to participate will have a Comms code placed on their donor record at the time of recruitment at the Donor Centre. These Comms codes will be:

CP1 for Stage 1 donors
CP2 for Stage 2 donors

NHSBT Business Object will interface to Pulse and extract the data identified. The data extraction will be completed by automated processes, then placed in encrypted protected zip files and transferred when complete via email to the UoC email address for the COMPARE study.

The automated business objects solution will:

- negate the need for paper based information being sent to Cambridge and manually keyed into the Research Database
- Create 6 Separate Business Objects Reports exporting to .csv format
- Create formatted Excel Reports for the Admin Hub

All data to be sent to the UoC will be in .csv files and have no formatting other than a delimiter to allow for importing into the research database.

1.3 Scope

Creation of Business Objects reports containing the data extraction on the study donors for the duration of the study. These reports are required by the UoC and NHSBT for the following reasons:

- For UoC – to populate their Research Study database for the purposes of achieving all scientific, ethical and research governance requirements related to the project
- For NHSBT – to provide management reporting information on Centre recruitment progress and to allow monitoring of donors throughout the Study

UoC have identified and defined 6 reports that they will require, containing differing data strings from within Pulse.

- Data will only be included on those donors who have consented to participate in the Study
- Reports will be in .csv format, to be saved as a zipped file with encryption known only by certain members of the UoC Research Study Team, and emailed to a nominated email address at UoC
- The NHSBT Admin hub requires all reports requested to be in an Excel Spreadsheet format.

Additional Requirement:
NHSBT Admin Team also require the same reports as UoC but these reports to be supplied in Excel format These reports needs to be saved direct to the National G Drive with a unique file format name so as not to replace previous files as the project goes forward. The folder location will be G:\006 Donor Services\059 Interval Study

1.4 Objectives

The overall goal is to, as far as possible, automate the transfer of data relating to donors who consent to take part in the study and to track their progress

- Provide a secure and efficient means by which agreed data can be provided to UoC to allow creation of an accurate Research Study Database;
- Eliminate the need for paper based activity and manual transfer of participating donor information to the UoC Research Study Database
- Allow UoC to monitor and report on participation during the study

- Enable the transfer of data between NHSBT and the UoC to be automated as far as is possible
- Provide the NHSBT Admin Hub with all relevant information to monitor recruitment progress

1.5 Key Success Criteria

Factors critical to the success of the delivery of this activity are:

- Availability of resource from within the Business Objects Team to develop and test the solution;
- Access to and input from business representatives to test and validate the developing solution;
- Input from Key NHSBT Staff to facilitate solution definition and development;
- Resource and support from UoC to test and accept the solution;
- Ongoing support and change management support from the Business Objects Team to operate and maintain the solution.

2 Detailed Business Requirements

This section has been split into:

- Reports required by UoC (2.1)
  - UoC #1 – Baseline Data
  - UoC #2 – Appointment and Attendance Data
  - UoC #3 – Deferral Data
  - UoC#4 – Adverse Event Data
  - UoC#5 – Microbiology and Deaths
  - UoC#6 – Summary characteristics of donors

- Reports required by NHSBT Admin Team (2.2)
  - NHSBT #B – Appointment Data

2.1 Business Objects reports required UoC

Business Objects Report 1 – Baseline Data

data description	comments
donor Number	the 9 character donor number
DIN	used to reconcile with Biocentre sample lists
centre	Mobile session code
preferred e-mail	E-mail to be included, i.e. that which has the preferred contact flag associated with it
Validated email flag	Indicate whether email address provided above is validated or unvalidated
gender	used by UoC for validation of web based questionnaires
month of birth	used by UoC for validation of web based questionnaires
year of birth	used by UoC for validation of web based questionnaires
NHS number	For records where this information is held. This data is unvalidated
donation date	Date of the donation when donor joined COMPARE
Donation outcome	Outcome of the donation when the donor joined COMPARE
donation deferral	Deferral information for the donation at which donor joined COMPARE

This report is to be generated for all donors with Comms code CP1 & CP2 added during the recruitment phase only - expected duration 37 weeks (however this may be longer if the consent rate is slower than anticipated).

Note for Developer:

- All Deferral History is to be included; files to be supplied to UoC will include DAT725, DAT200, DAT201 & DAT1328. All reports containing Deferral History must exclude codes TMH, TMV, TMW, TMX, TMY or TMZ from any reports to be sent to UoC.

Features:

- New donors will be added each day
- All donors with a Comms code CP1 & CP2 to be included
- All donors with a Comms code CP3 to be excluded
- The report will be trimmed to remove donors who have been on the report for > 8 weeks

This report is required daily; the information will need to be encrypted as it contains PID data before being transferred to Cambridge for use within the research database.

Data is required is a .csv format with separation character to be agreed and notified.

This report is required from Day 1 of recruitment and hence should be **prioritised** in terms of development. The Study cannot commence without it being in place.

Business Objects Report 2 – Appointment and Attendance data

data description	comments
donor Number	the 9 character donor number
DIN	used to reconcile with Biocentre sample lists
Comms code	CP1, CP2
DHC flag	
Appointment date	
Appointment time	To estimate time between blood collection and analysis
Attendance date	
Attendance outcome	
centre	Mobile session code
Mobile Phone Number	Include preferred mobile phone number.

This report is to be generated on donors Comms codes CP1 and CP2 and will be required from day 1 of Recruitment to the final Donation visit of last participation.

Features:
- New donors will be added each day throughout the recruitment period
- Data on each participant will be added to rather than overwritten
- Data will allow UoC to check appointments have been made and attended by Stage 2 participants

This report is required daily
Data is required in a .csv format with separation character to be agreed and notified

Notes for Developer:
- When an Outcome of attendance is not an 01 Bled we will require the linked reject code to be displayed in the report.
- The report should show multiple attendances for the same date if they occur.

Business Objects Report 3 – Deferral Information

data description	comments
donor Number	the 9 character donor number
deferral date	
deferral date lapsed	
deferral code	

This report is to be generated on donors with Comms codes CP1 and CP2 and will be required from day 1 of Recruitment to the final Donation visit of last participation.

Note for Developer:
- To include active deferrals only i.e. when the suspension date is in the future; files to be supplied to UoC will include DAT725, DAT200, DAT201 & DAT1328. All reports containing Deferral History must exclude codes TMH, TMV, TMW, TMX, TMY or TMZ from any reports to be sent to UoC.

Features:
- New donors will be added each day throughout the recruitment period
- Data will be provided on occurrences over the last 24 hours
- Deferral codes will include non-bled codes, low hb and Hemocue measurement

This report is required daily No PID data is in this report

Data is required is a .csv format with separation character to be agreed and notified

Business Objects Report 4 – Adverse Events

data description	comments
donor Number	the 9 character donor number
AE dates	
AE codes	

This report is to be generated on donors with Comms codes CP1 and CP2 and will be required from day 1 of Recruitment to the final Donation visit of last participation.

Features:
- New donors will be added each day throughout the recruitment period
- Data will be provided on occurrences over the last 2 weeks

This report is required every two weeks – No PID data is in this report

Data is required is a .csv format with separation character to be agreed and notified

Business Objects Report 5 – Microbiology and Deaths[5]

data description	comments
donor Number	the 9 character donor number
Donor status	DEATH or POSITIVE MICROBIOLOGY

This report is to be generated on donors Comms codes CP1 and CP2 and will be required from day 1 of Recruitment to the final Donation visit of last participation.

Features:
- Data will be provided on occurrences since the last report (frequency to be confirmed)
- No information will be provided on the specific +ve Microbiology marker
- No information will be provided on cause of death (UoC will investigate the potential to obtain additional information on cause of death through Health and Social Service Information Centre)

This report is required monthly – No PID data is in this report

Data is required is a .csv format with separation character to be agreed and notified

Business Objects Report 6 – Summary characteristics of participants

For the purposes of analysis a one-off report will be required describing the characteristics of participants. This one-off report will include the same set of variables as provided for the INTERVAL cohort and which are detailed in **Appendix B.**

[5] Deaths will be differentiated from +ve micro-biology, where source tables allow.

Appendix A – Reports due dates and frequencies

Business Object Reports – Frequencies and Due Dates For UoC presented in .csv format					
Report No.	**Contents**	**Frequency**	**1st issue date**	**Last issue date**	**Notes**
1	Baseline Data	Daily	Day 1 Recruitment	End Recruitment	
2	Appointment & Attendance Data (incs mobile phone)	Daily	Day 1 Recruitment	End Study	
3	Deferral Information	Daily	Day 1 Recruitment	End Study + 3 months	This information will be collected for several months (suggested 3) after the end of the study for the purposes of safety reporting.
4	Adverse Events	Every 2 weeks	Day 1 Recruitment	End Study + 3 months	This information will be collected for several months (suggested 3) after the end of the study for the purposes of safety reporting.
5	Microbiology & Deaths	Every 4 weeks	Day 1 Recruitment	End Study + 3 months	This information will be collected for several months (suggested 3) after the end of the study for the purposes of safety reporting.
6	Summary characteristics of participants	One-off report	End Recruitment	N/A	This report will be generated using the same code developed to retrieve the same data for INTERVAL participants

Appendix B:

Name	Description
Demographics	
1. ETHNICITY	Ethnicity of Donor
2. SEX	Gender of Donor
3. DOB	Date of birth of donor (MM/YYYY)
4. CORDST	Correspondence destination description
5. STATUS	Donor activity state (Based on http://pkb/concepts/900/tables/donact.htm, but only for active/inactive)
6. FIRST_ATTENDANCE (BLDAT)	Date of donor's first donation whether successful or not
7. REGISTRATION_DATE	Donor's date of registration
8. ABORH, ABOGRP and RHGRP	Donor's ABO & Rh group
9. LSOA (code and name)	Calculation of Lower Super Output Areas (LSOA) from postcode
10. DISTANCES	Donor's nearest donor centre from their home address (as the crow flies)
11. SHORTHAND_CODE	Shorthand code for FCT1 to FCT6 (e.g. R1R2 or R2r)
Donation history (summary data going back as far a possible)	
12. FIRST_DONATION	Date of donor's first successful donation
13. FIRST_PROCTYPE	Donation type of donor's first successful donation
14. CENTRE_COUNT	Count of donations at donor centres (limited due to archiving)
15. MOBILE_COUNT	Count of donations at mobile venues (limited due to archiving)
16. WHB_COUNT	Count of whole blood donations
17. APH_COUNT	Count of component donations
18. NOVV	Number of fainting incidents (from DONDET)
19. NOPPCK	Number of part packs given (from DONDET)
20. NOHAEM	Number of bruising incidents (from DONDET)
21. NOCALL	Number of session invitations (from DONDET)
22. NODNTS	Number of 01 outcome attendances by this donor (from DONDET)
23. NOLOW	Number of low HB outcomes (from DONDET)
24. NOREJC	Number of rejects (from DONDET)
25. NODNA	Number of DNAs (from DONDET)
26. RELFCT	Reliability factor - 1 = best, 5 = worst (from DONDET)
27. UNKNOWN_VENUE_ COUNT	Count of donations at unknown venues, caused by old venues not being linked to valid sector codes in VENUE.SECTORCD (limited due to archiving)

Individual sessions data	
DHATTEND	
28. RESTYPE, RESCODE and RESDESC	Outcome/attendance code of each donation
29. PROCCODE, PROCDESC and PROCTYPE	Donation type of each donation
30. BLDATE	Dates of each donation attendance
31. CALLED and CALLEDDESC	Called to session flag
32. VOLUM	Pack weight at session
33. APPSTATE and APPSTATEDESC	Attendance of donor at appointment
34. VENUE_TYPE	Venue type of each donation
DONDEF	
35. DEFERCD and DEFERDSW	Type of deferral and description
36. DEFERDUR	Duration of deferral
37. DEFERDTE	Date deferral was placed on PULSE
38. SUSPDATE	Suspended until date
39. DATEDEL	Date deferral removed
MEDHIS	
40. DATENT	Date of entry (of adverse event)
41. MEDCOD	Medical code
42. MCDDECW	Long medical condition description

ANNEX 2.22

WITHDRAWAL FORM (NO FURTHER CONTACT)

Donor Number: _____

Title of project: COMPARE study

Chief Investigator/s: Dr Emanuele Di Angelantonio and Professor John Danesh

Please take time to carefully read this form if you want to withdraw your consent for further participation in the study and contact by the COMPARE team. If you agree to the statements below please sign and return the form to:

COMPARE Study
University of Cambridge,
Department of Public Health and Primary Care,
Wort's Causeway,
Cambridge
CB1 8RN

.

I withdraw my consent for further participation in the COMPARE study. I understand that:

- a record of my signed consent and withdrawal and any further communications with the COMPARE team will be kept as a record of my wishes;
- archived samples derived from my blood and collected during the COMPARE study may be used in future research
- information obtained until the date of withdrawal will remain on the research database and will be used for future research
- access to my medical and other health-records will continue and new information will be added to the research database;
- withdrawal does not extend to other studies that I have consented for whilst being part of other NHSBT Research panels

First Name and Surname	Date of Birth	Date today	Signature

For further information about the COMPARE Study, please call the freephone number on 0800 XXX XXXX, or email
helpdesk@comparestudy.org.uk

ANNEX 2.23

WITHDRAWAL FORM (NO FURTHER USE)

Donor number: _____

Title of project: COMPARE Study

Chief Investigator/s: Dr Emanuele Di Angelantonio and Professor John Danesh

Please take time to carefully read this form if you want to withdraw your consent for (1) further participation in the study and contact by the COMPARE team (2) use of previously collected samples and data for future research (3) further access to your medical and other health-related records. If you agree to the statements below please sign and return the form to:

COMPARE Study
University of Cambridge,
Department of Public Health and Primary Care,
Wort's Causeway,
Cambridge
CB1 8RN

.

I withdraw my consent for further participation in the COMPARE study. I understand that:

- a record of my signed consent and withdrawal and any further communications with the COMPARE team will be kept as a record of my wishes;
- archived samples derived from my blood and collected during COMPRE study will be removed from the repository and destroyed;
- information and results obtained until the date of withdrawal cannot be erased from the research database, but no new data will be added and existing data will not be used anymore;
- access to my medical and other health-records will cease on the date of this withdrawal;
- this withdrawal does not extend to other studies that I have consented for whilst being part of other NHSBT Research panels

First Name and Surname	Date of Birth	Date today	Signature

For further information about the COMPARE Study, please call the freephone number on 0800 XXX XXXX, or email helpdesk@comparestudy.org.uk

ANNEX 2.24

SUBJECT LINE: COMPARE study – questionnaire invite

Dear Donor,

Thank you very much for taking part in the COMPARE study and attending your second donation visit. Your support is very important to the success of this research and is helping to safeguard the wellbeing of all blood donors in the future.

You kindly completed an online questionnaire regarding your experience of having your haemoglobin levels measured by different methods. We would be grateful if you would also complete a questionnaire concerning your general health and lifestyle. It should take approximately 10 minutes to complete. **Your responses will be very important in answering the study's questions about optimum haemoglobin screening methods.**

The password required to begin the questionnaire will arrive in a separate email entitled "**COMPARE Key**" Once you have the password, please return to this email and click on the link below to access the questionnaire:

LINK

If you are unable to access the questionnaire with the link above, please copy and paste the following into a new window in your internet browser: fulllinktoquestionnairehere.com

Thank you very much for taking the time to complete the questionnaire. Your answers will be treated as strictly confidential and will only be used for medical research. If you have any questions, please contact the COMPARE team using the details below.

Many thanks,

The COMPARE team

Freephone: 0800 021 7182 (Mon-Fri: 09:00 to 17:00)

E-mail: helpdesk@comparestudy.org.uk

COMPARE Email_questionniare (Part 1 re-invite, Stage 1) V1 05.07.2016

ANNEX 2.25

SUBJECT LINE: COMPARE study – questionnaire invite

Dear Donor,

Thank you very much for taking part in the COMPARE study and attending your second donation visit. Your support is very important to the success of this research and is helping to safeguard the wellbeing of all blood donors in the future.

If you haven't completed the COMPARE questionnaire, there is still time to do this. You will be asked questions about your general health and lifestyle as well as your experience with the different methods for testing haemoglobin levels. It should take approximately 15 minutes to complete. **Your responses will be very important in answering the study's questions about optimum haemoglobin screening methods.**

The password required to begin the questionnaire will arrive in a separate email entitled "**COMPARE Key**". Once you have the password, please return to this email and click on the link below to access the questionnaire:

LINK

If you are unable to access the questionnaire with the link above, please copy and paste the following into a new window in your internet browser: fulllinktoquestionnairehere.com

Thank you very much for taking the time to complete the questionnaire. Your answers will be treated as strictly confidential and will only be used for medical research. If you have any questions, please contact the COMPARE team using the details below.

Many thanks,

The COMPARE team

Freephone: 0800 021 7182 (Mon-Fri: 09:00 to 17:00)

E-mail: helpdesk@comparestudy.org.uk