RE-BLEED: A digital platform for identifying bleeding patients – a feasibility study

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Please declare any/no potential conflicts of interest: None declared

Confidentiality Statement

This document contains confidential information that must not be disclosed to anyone other than the Sponsor, the Investigator Team, HRA, host organisation, and members of the Research Ethics Committee, unless authorised to do so

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2 LAY SUMMARY

Bleeding affects up to 40% of all trauma patients, up to 30% of all surgery patients and is one of the commonest causes of death for women giving birth. The presentation and features of bleeding are

different between patients – in some cases bleeding is very obvious to recognise, but in other cases bleeding is more "hidden", for example in the stomach. Bleeding must be stopped promptly to prevent severe illness or death.

Many studies have shown differences in how patients who bleed are treated. There is also variation in how individual patients respond to the same treatment, with some patients doing better than others. Understanding how variation in practice and patient characteristics affect outcomes will help us design and test improvements in care.seconda

Patients in hospital have regular tests that measure levels of the different types of cells in their blood and its ability to clot. For example, a drop in red blood cells can indicate that patients have suffered bleeding. More advanced blood tests are available that can provide more detailed information on why patients are bleeding and what treatments might be most effective.

This study aims to develop a real-time, hospital-wide digital system to identify patients in hospital who have suffered from bleeding and test whether this system could be used in the future to potentially identify patients to recruit into trials of new treatments or blood tests.

To do this, we will:

- Assemble a panel of experts to identify criteria (for example, specific blood test results and drug prescriptions) that could indicate a patient has suffered from bleeding
- Use historical electronic patient records to test how well these criteria identify patients who have received treatments for bleeding (blood transfusion)
- Develop and refine a web-based digital system where the most useful criteria can be applied in "real-time" to identify bleeding patients
- Test how well the digital platform identifies bleeding patients
- Test whether a significant number of patients identified by the digital platform are willing to allow their routine blood samples tested for blood clotting and endothelial factors.

3 SYNOPSIS

Study Title	RE-BLEED: A digital platform for identifying bleeding patients: a feasibility study
Internal ref. no. / short title	RE-BLEED
Study registration	The study will be registered on clinicaltrials.gov
Sponsor	University of Oxford
Funder	Oxford BRC
Study Design	Study incorporating database analysis, cohort observation and laboratory study
Study Participants	Patients with actual or suspected acquired bleeding
Sample Size	**Retrospective data** Up to 1,750,000 patient admissions (up to 10 years of admissions) **Prospective data** Up to 87, 500 will be screened by the digital platform to identify those who may have bled during the six-month recruitment period. Research nurses will review

	electronic records of patients with potential bleeding (identified by the digital platform), with the aim of gaining consent from at least 50 in the last three months of the study.		
Planned Study Period	1/10/2021 to 31/8/2023		
Planned Recruitment period	**Retrospective data from the period:** 1/3/2011 to 31/8/2022 **Prospective study:** 1/10/2021 to 31/8/2023		
	Objectives	Outcome Measures	Timepoint(s)
Primary	To test whether a digital platform can efficiently identify patients who have suffered a bleeding event and are willing to consent for the routine blood samples to be used in research.	At least 200 patients correctly identified as having suffered bleeding, of which 40 (20%) provide consent	End of study
Secondary	1. To conduct a Delphi process with an expert panel to identify criteria that could be applied in the electronic patient record to identify patients with acquired bleeding 2. To use 10 years' of retrospective data to map bleeding criteria to appropriate data fields within the electronic patient record data sources 3. To encode bleeding criteria into a real-time "algorithm" and display results within a digital web-based platform 4. To measure and refine the accuracy of the algorithm, by	1. List of bleeding criteria 2. Bleeding criteria mapped to appropriate data fields on the electronic patient record 3. Digital platform capable of identifying bleeding patients in real-time 4. Algorithm accuracy before/after refinement 5. List of unique challenges faced by the laboratory team during blood sample retention and analysis 6. Numbers of samples retained and additional blood clotting and endothelial factor results captured from the retained samples.	End of study

	manual review of free-text notes of patients identified as bleeding 5. Assess the feasibility of sample sequestering by the lab 6. Assess the feasibility of performing blood clotting and endothelial factor analysis on the sequestered samples.		
Intervention(s)	**<u>Non-interventional study</u>** • No change to the normal clinical care or treatment of participants.		
Comparator	None (n/a)		

4 ABBREVIATIONS

AVPU	Alert, Verbal, Pain, Unconscious (description of consciousness level)
APTT	Activated Partial Thromboplastin Time
BP	Blood Pressure
CAG	Clinical Advisory Group
CCRG	Critical Care Research Group
CDW	Clinical Data Warehouse
CI	Chief Investigator
CIS	Clinical Information System
CRF	Case Report Form
CTRG	Clinical Trials & Research Governance, University of Oxford
ED	Emergency Department
EDTA	Ethylenediamine tetraacetic acid
HER	Electronic Health Records
GCP	Good Clinical Practice
GCS	Glasgow Coma Scale
GP	General Practitioner
HALT-IT	Haemorrhage ALleviation with Tranexamic acid – InTestinal system
HAT	Hospital Acquired Thrombosis
HAVEN	Hospital Alerting Via Electronic Noticeboard
HRA	Health Research Authority
HTA	Human Tissue Authority

ICD	International Classification of Diseases
ICF	Informed Consent Form
ICO	Information Commissioner's Office
ICU	Intensive Care Unit
IR	Interventional Radiology
IVC	Inferior Vena Cava
JLA	James Lind Alliance
MHP	Major Haemorrhage Protocol
MICE	Multiple imputation by chained equations
NHS	National Health Service
NHS API	NHS Application Programming Interface
ONS	Office of National Statistics
OUH	Oxford University Hospitals NHS Trust
PI	Principal Investigator
PIL	Participant/ Patient Information Leaflet
PPI	Patient and Public Involvement
PR	Pulse Rate
PT	Prothrombin Time
R&D	NHS Trust R&D Department
REC	Research Ethics Committee
SAP	Statistical Analysis Plan
SOP	Standard Operating Procedure
TARN	Trauma Audit Research Network
TXA	Tranexamic acid
UKOSS	United Kingdom Obstetric Surveillance Service
VTE	Venous Thromboembolism
WHO	World Health Organisation
WIMM	Weatherall Institute of Molecular Medicine

5 BACKGROUND AND RATIONALE

What is the health care problem?

Bleeding is a common cause of poor health as well as death (1). A recent UK-wide audit showed that acquired bleeding is most commonly seen in patients admitted for trauma, obstetric, surgical, and gastro-intestinal conditions (2). Bleeding affects up to 40% of all trauma patients, up to 30% of all surgery patients and is one of the commonest causes of death for women giving birth (3). However, bleeding is a treatable and preventable cause of death (4). A recognised feature of deaths due to bleeding is that they often occur soon after bleeding begins, or the patient is admitted to hospital. This emphasises the need for timely interventions (5,6).

Research into acquired bleeding has largely been restricted to clinical trials, focussed on single settings or specific groups of patients. For example, the HALT-IT Trial assessed whether treatment with tranexamic acid is safe and reduced mortality in patients with gastrointestinal bleeding (7). These studies tend to include one clearly defined type of patient with major bleeding and address a single research question. This does not permit a broader investigation of variations in treatment and response across different settings and different groups.

Why is research needed?

The James Lind Alliance's (JLA) research prioritising partnerships on blood transfusion, blood donation and bleeding rated the "management of major bleeding" as a high priority for future research (8). Previous observational studies have revealed considerable variation in treatment and diagnostic testing across different settings and causes of major bleeding. This variation may reflect altered physiological responses to bleeding, which in turn can be impacted by factors such as the patient's age (9,10). There is also considerable variation in response to specific treatments across the patient population (11). Some of this variation will be easy to explain. For example, a young woman bleeding after giving birth will be treated differently from an older patient bleeding after surgery. However, patients with similar types of bleeding can also receive different treatments. To investigate variations in treatment and individual responses requires a detailed understanding of the patient's condition, and of the timing and nature of treatments applied. Moreover, it is likely that some of this variation in practice is due to treatment delays and subsequent impact on patient outcomes, alongside inconsistent uptake of research findings (12).

Complications following treatment for major bleeding include thrombotic events (e.g. pulmonary embolism), which can impact on the long-term health of patients. For example, it is well recognised that trauma and pregnancy are pro-thrombotic conditions, but the balance between bleeding and thrombotic risk remains unclear (13). New resuscitation therapies may be defined by different patterns of risk for thrombosis (14). Understanding natural variation in thromboprophylaxis treatment (e.g. anticoagulants) after major bleeding may help us determine the optimal timing of starting or reintroducing them, potentially giving rise to hypotheses to be tested in a clinical trial.

Aim

Understanding variation in patients' response to treatments for bleeding requires large studies. This study aims to develop a real-time digital platform, whereby bleeding patients among the whole hospital population can be efficiently identified by an algorithm and approached for their consent to participate in research studies. The platform will also integrate multiple sources of patient data, from which study data sets can be automatically created. In this feasibility study, we will assess the accuracy of the algorithm for identifying bleeding patients and whether a significant proportion (25%) of these patients are willing to consent for their data and routine blood samples to be used for research. Once developed, the digital platform could be deployed across multiple sites to facilitate efficient identification of potential participants for future clinical trials.

6 OBJECTIVES AND OUTCOME MEASURES

Objectives	**Outcome Measures**	**Timepoint(s) of evaluation of this outcome measure (if applicable)**
Primary		
To test whether a digital platform can efficiently identify patients who have suffered a bleeding event and	At least 200 patients correctly identified as having suffered bleeding, of which 40 (20%) provide consent	End of study

are willing to consent for the routine blood samples to be used in research.		
Secondary		
1. To conduct a Delphi process with an expert panel to identify criteria that could be applied in the electronic patient record to identify patients with acquired bleeding 2. To use 10 years' of retrospective data to map bleeding criteria to appropriate data fields within the electronic patient record data sources 3. To encode bleeding criteria into a real-time "algorithm" and display results within a digital web-based platform 4. To measure and refine the accuracy of the algorithm, by manual review of free-text notes of patients identified as bleeding 5. Assess the feasibility of sample sequestering by the lab 6. Assess the feasibility of performing blood clotting and endothelial factor analysis on the sequestered samples.	1. List of bleeding criteria 2. Bleeding criteria mapped to appropriate data fields on the electronic patient record 3. Digital platform capable of identifying bleeding patients in real-time 4. Algorithm accuracy before/after refinement 5. List of unique challenges faced by the laboratory team during blood sample retention and analysis 6. Numbers of samples retained and additional blood clotting and endothelial factor results captured from the retained samples.	End of study

7 STUDY DESIGN

This study will use both retrospective and prospectively collected data to develop and test an algorithm to identify patients in hospital with acquired bleeding.

The algorithm will be developed using retrospective data from patients admitted to one hospital over a ten year period. The algorithm will be refined using prospective data collected over a three month period and its accuracy tested prospectively in the final 3 months of the study.

In this latter period, we will also assess the feasibility of consenting patients for the sequestering and subsequent analysis of their left-over blood samples, for additional tests of blood clotting.

8 PARTICIPANT IDENTIFICATION

8.1 Study Participants

In both the retrospective and prospective cohorts, we will screen all adult patients admitted to Oxford University Hospitals NHS Foundation Trust for signs of bleeding.

8.1.1 Retrospective cohort

Inclusion Criteria

- Adults aged between 16 and 110
- Admitted to hospital (OUH) or attended the emergency department between 1/3/2011 to 31/8/2022

Exclusion Criteria

- Patients who inform us directly that they do not wish their records used in this research study
- Patients who have completed the NHS Opt-out.

8.1.2 Prospective cohort

Inclusion Criteria

- Adults aged between 16 and 110
- Admitted to hospital (OUHFT) or attended the emergency department between 1/10/2021 to 31/8/2022

Exclusion Criteria

- Patients who inform us directly that they do not wish their records used in this research study
- Patients who have completed the NHS Opt-out.

9 PROTOCOL PROCEDURES

9.1 Algorithm development and validation

- Conduct a modified Delphi process using a panel of clinical experts to identify a set of starting criteria (algorithm) e.g. transfusion request or absolute/drop in Hb. In the first instance, we will aim to agree broad criteria that maximise the sensitivity of the algorithm.
- The Clinical Data Warehouse (CDW) is a digital resource within the Oxford University Hospitals NHS Trust (OUH) that will provide up to 10 years of retrospective anonymised patient data to the study. This dataset will comprise demographics and diagnostic/therapeutic codes, hospital locations, admission/discharge timings as well as laboratory results, radiology reports, blood product usage and operative management and outcomes. All data will be time-stamped.
- Using this retrospective patient data, we will develop an algorithm by mapping criteria identified by the Delphi process to routinely-collected data sources. We will combine these mapped criteria into a single algorithm to identify bleeding patients. We will assess its sensitivity to identify patients who have received treatments/investigations for bleeding (e.g. urgent endoscopy, prescription of tranexamic acid, blood transfusions). We will calculate basic demographics (e.g. age, mortality rates) for the patient cohort and compare these to previously published data e.g. from the Trauma Audit Network (TARN) audit. We will also look at how individual criteria overlap to see whether we can identify any redundancy in the list of data sources.
- Sources of patient data required by the algorithm will be integrated into a "real-time" digital platform by processing HL-7 messaging from individual hospital IT systems. This will expand on a pre-existing software platform (developed for the HAVEN Study, https://ora.ox.ac.uk/objects/uuid:322561c7-866e-4c1e-bcc1-65da4da477fb) which listens to hospital wide computer systems, integrating relevant data into a real-time research database.
- Using the real-time database, we will implement the algorithm on a lightweight web interface (R Shiny). The interface will include the ability for users to input additional data from the notes review (details below).
- Research nurses will use the interface to identify (up to 200) patients who are potentially bleeding and review their free-text notes in the electronic patient record, notifying attending clinicians when there is no documentation of bleeding. Using the additional clinical information in patients' notes, the nurses will record whether they agree with the output of the algorithm. Where the algorithm has incorrectly identified patients as having bled, the nurses will record the reasons for bleeding based on the clinical information in the notes.
- The expert panel will review the results of the notes review and refine the algorithm to increase its specificity.
- The expert panel will not have any access to confidential patient information.

9.2 Consent patients identified by system for use of surplus routine blood samples in research analysis.

In the final three months of the study, we will prospectively test the accuracy of the algorithm and the feasibility of using the real-time platform for consenting patients to use their data and routine blood samples for future research.

When the algorithm identifies that a patient has met the criteria for bleeding, the platform will:

- Allocate the patient a RE-BLEED study ID.

- Electronic Hospital Record (EHR) data for this entire encounter will be retained in the study database and when the encounter ends the record will be pseudo-anonymised.
- A notification will be sent to the main hospital laboratory requesting that their (left-over) blood samples, once all clinical testing has been completed as part of routine clinical care, be retained for use in the study, pending patient consent. Where consent is not given, the samples will be destroyed as per local protocols.

In order to be able to screen all patients in the hospital, the system must collect data for all adult patients from their admission to their discharge. The records of adult patients admitted to the hospital who do not meet the eligibility at any point during their admission will be destroyed at the point they are discharged from hospital.

9.3 Blood sample handling /temporary storage and testing

Following notification by the electronic identification process, left-over EDTA and citrate blood samples from potentially eligible patients (which were taken as part of normal clinical care) will be transferred to a dedicated `holding area` in the MRC Weatherall Institute of Molecular Medicine (WIMM).

Prior to consent being sought, all sequestered left-over samples will undergo processing to extend their viability for later analysis. This will occur in the holding area. The processing will consist of:

- Citrate samples will be spun down and the plasma and buffy coat will be aliquoted off into separate tubes
- Any remaining serum from a sample will also be aliquoted off

Samples will be processed, frozen and retained by the WIMM (The MRC Weatherall Institute of Molecular Medicine) laboratory in a dedicated area allocated to only this study. The samples will be labelled with the study ID number. Samples will be held (without consent) for a total of 28 days from the time they were taken, to maximise the time and opportunity for the study team to formally consent patients for use of these samples in the study.

Members of the study team will liaise with the clinical care team who will approach the patient and if appropriate introduce the trained study team member. The study team member will then explain the purpose of the study and seek the patient's consent. If consent is obtained, the laboratory will be notified that the sample can retained until the end of the study. If the patient does not consent, the laboratory will be notified to destroy the sample in line with local policies.

If written consent has not been obtained after 28 days from the bleeding episode all samples will be destroyed in line with local policies.

Where consent is provided, plasma samples will be analysed for haemostatic potential using:

- Standard clotting analysis: Prothrombin time (PT) and activated partial thromboplastin time (APTT) (if not already performed as part of the clinical care), clot lysis, thrombin generation, clotting factor levels and the contributing role of platelet factors.
- Fibrinogen concentration

- Endothelial cell markers: Thrombomodulin & syndecan-1

Where possible the tests will be performed on the EDTA and citrate samples to maximise the yield (e.g. endothelial markers). Tests such as those that assess the contributing role of platelet factors, can only be performed on the buffy coat aliquots.

Samples will be destroyed in keeping with standard laboratory practice at the end of the study period (unless the patient has provided specific written consent for their samples to be used in future ethically approved research). The results of these tests will be added to the digital study record. An anonymous version of this data maybe used by future studies and this mentioned specifically on the consent form.

We do not expect the results to be relevant to current or future treatment. However, if an unexpected finding is reported, such as an abnormally low level of a clotting factor, the research team will invite the participant for review by a senior clinician within the Oxford Haemophilia and Thrombosis Centre.

9.4 Consent & patient notification

This applies to the prospective part of the study.

9.4.1 Screening/enrolment

Permission to screen all patients in the hospital by digitally accessing their confidential health records and will be sought from the Confidentiality Advisory Group (CAG). The justification for requiring access to health records without explicit consent is that patients must be identified very rapidly, and at a hospital wide scale, making this not practicable to obtain informed consent.

9.4.2 Dissent

Screening for eligibility will occur digitally and the NHS Opt out will be used as a marker of prior patient dissent. Patients who have completed the NHS Opt out will be removed from the screening process and all associated data will be destroyed.

Contact details for study specific dissent / withdrawal will present on the study website, patient information sheet and patient facing materials such as posters etc. Contact details for the study team / office will be present on these documents and anyone contacting the study team will be able to request for their records to be removed from the study without any effects on their care.

9.4.3 Patients with capacity to consent

Formal written consent will be sought from a subset of patients to analyse surplus clinical blood samples. This will be conducted by group of experienced research nurses.

Patients with the physical and mental capacity to give informed consent will be approached in person during the first 28 days following their episode of bleeding and it will be explained to the patient that they have already had blood samples sent for storage. It will be made clear that these samples have not yet been analysed and that these samples will be destroyed if they do not agree to the samples being used.

For any patient where a sample was retained with the intent to be used in the study but the patient did not regain capacity within 28 days, information will be provided to either a personal or a professional consultee for advice about the research use of the sample (see next section).

After this period has past, if consent has not been obtained, all samples will be destroyed.

Patients or their personal or professional consultee will be provided with:

- RE-BLEED patient information leaflet
- RE-BLEED consent form

The RE-BLEED study documentation will detail no less than: the nature of the study; what it will involve for the participant; the implications and constraints of the protocol; the known side effects and any risks involved in taking part. It will be clearly stated that the participant is free to withdraw from the study at any time for any reason without prejudice to future care, without affecting their legal rights, and with no obligation to give the reason for withdrawal.

The participant or consultee will personally sign and date the latest approved version of the Informed Consent form or Consultee Declaration.

The participant, or their consultee, will be allowed a maximum of 28 days to consider the information, and the opportunity to question the Investigator, their GP, or other independent parties to decide whether they will participate in the study.

Written Informed Consent will then be obtained by means of participant-dated signature (or consultee dated signature) and dated signature of the person who presented and obtained the Informed Consent/Consultee Declaration. The person who obtained the consent will be suitably trained and will have been authorised to do so by the Chief Investigator. A copy of the signed Informed Consent/Consultee declaration will be given to the participant. A copy will be added to the medical notes. The original signed form will be retained at the study site.

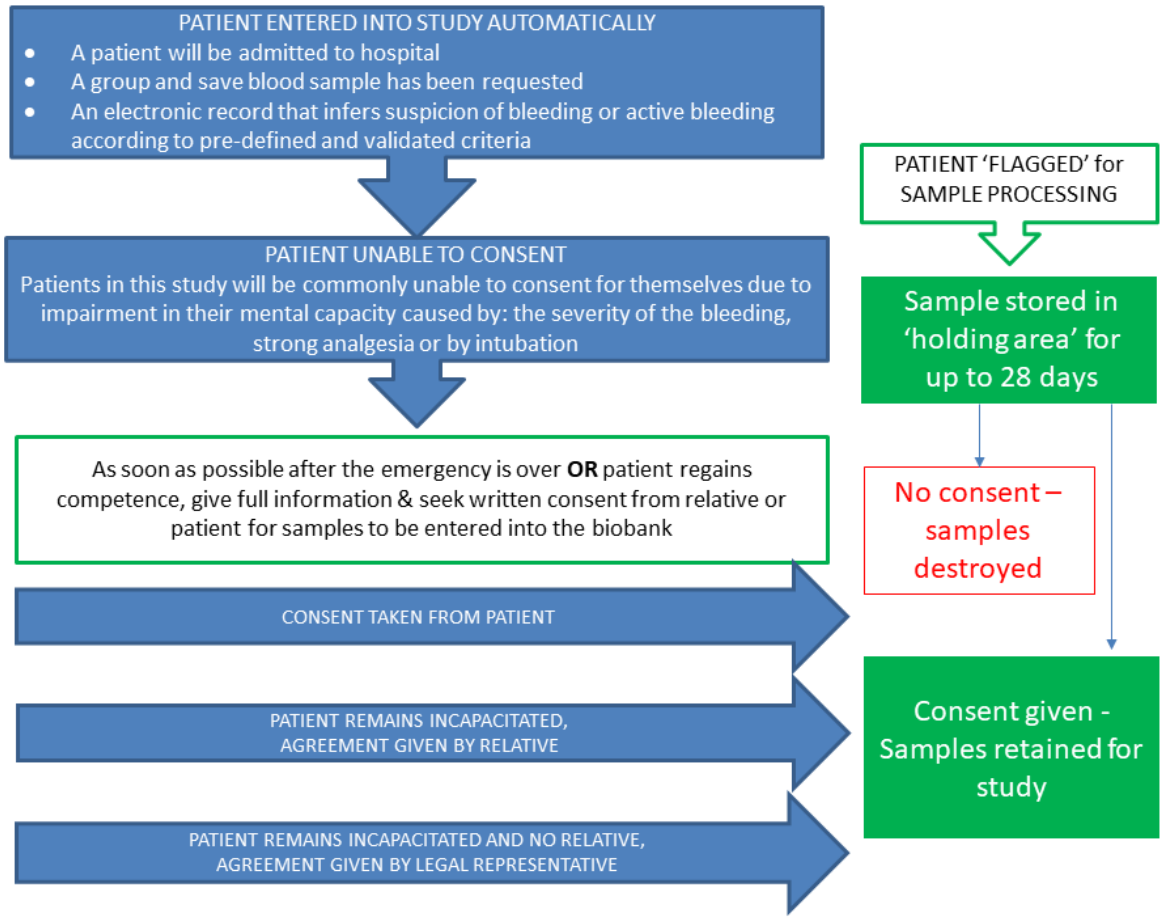

Figure 1 - Consent flow chart

9.4.4 Patients without capacity to consent

Patients who experience an episode of bleeding may transiently experience a lack of capacity to consent, either due to the bleeding itself or the resulting treatment. Bleeding also occurs in those who already lack capacity or in patients who may lose capacity as a result of the event (i.e. trauma with brain injury).

This is a feasibility study trialling a consent model designed to be used in a subsequent interventional trial, of patients during a bleeding episode. A future trial would include randomisation to an intervention, as well as sequestering all available blood samples. Our consent model must be able to include those who lack capacity at the time of bleeding in order to be able to offer an effective future intervention. It is essential that any future study does not exclude those who either had a temporary or permanent lack of capacity, as this would both introduce bias into the study but also deprive the most vulnerable and severely affected from a chance to participate in a study.

Capacity to consent to this study, will be assessed by the clinical team looking after the patient and confirmed by members of the study team. For patients lacking capacity, a personal or professional consultee will be approached.

If a personal consultee is not available, a professional consultee will be consulted. For the purpose of this study, a professional consultee is defined as a clinician (qualified doctor or registered nurse) with

appropriate training (according to local Trust policies) to take on the role of professional consultee. Professional consultees must not be directly involved in the patient's care and cannot be a member of the core study team at site.

If a consultee declines to give consent/advice for the samples and any associated sample data to be retained in the study at any stage, his/her wishes will be respected. A consultee is free to withdraw their support for continuation in the study at any time.

Participants where a consultee has been sought will be visited regularly during their admission, including just prior to discharge. If capacity is regained at any point, then informed consent will be sought. If the patient chooses not to provide consent data and samples will be destroyed. If capacity is not regained, then the samples and data will be included in the planned analysis.

9.5 Description of study intervention(s), comparators, and study procedures (clinical)

This is a non-interventional study. The algorithm within the Digital Platform will identify potential patients with acquired bleeding, of any severity. Once the cohort has been identified, they will be approached to consent for research use of their surplus clinical sample.

9.6 Patient Public Involvement (PPI)

PPI engagement remains integral to this project. The main ethical issue arising from this study is the use of patient information from Oxford University NHS Foundation Trust without consent.

A virtual PPI meeting was held on 14th December 2020, between the study team and the PPI group which included patients who have suffered significant bleeding, their carers, and members of the public. The meeting focused on two specific issues relating to consent: a) we explored the acceptability of using patient identifiable data in this study without consent and b) the use of personal and nominated consultees for advice about blood samples being stored and later analysed.

The members of the PPI group recognised that patients who are suffering from acute blood loss are likely to require rapid and emergent care. Further, the majority, if not all of the participants we would like to enrol in this study will be incapacitated at the time of presentation and routine blood sample collection, due to several factors - including in some cases acute circulatory failure or the need for urgent care and intubation. The PPI group unanimously agreed that data collection for this patient group was acceptable without consent. They were keen to know that patients would not be identifiable by the data that were collected.

A second question of retaining surplus clinical blood samples for research analysis was also explored. Within this study the researchers would like the samples to be retained for them, pending consent from the patients. We would then follow a strict consenting protocol (as set out above and which was explained to the PPI group) which would involve approaching the patient once they had regained competence to provide informed consent, or if this were to not happen to approach a personal consultee. Again, there was unanimous agreement within the PPI group that this route of consenting was acceptable. We discussed approaching relatives for agreement if a patient died and they were

comfortable in general with this, although recognised that a professional consultee could also be used. They were accepting of the option of gaining agreement from an independent professional consultee, although were clear that this route should be 'the last resort'.

The Oxford University Hospitals NHS Foundation Trust patient facing website and privacy notice state that "Information may be used for approved research projects. In most instances the information will be made anonymous so that you cannot be identified. If this is not possible, we will ask your permission or request approval from the Health Research Authority's Confidentiality Advisory Group. If you are not happy with information about you being used in research projects, please speak to your clinical team".

We commit to ongoing PPI/PPIE involvement throughout the lifecycle of the study.

9.7 Early Discontinuation/Withdrawal of Participants

During the course of the study a participant may choose to withdraw at any point.

The patient information sheet and study website will all carry contact details for the study team.

According to the design of the study, participants may have the following two options for withdrawal:

- Withdrawal from screening: Data will be destroyed from the study database
- Withdrawal of consent obtained in prospective recruitment: Data will be destroyed from the study database and the samples destroyed (if applicable).

9.8 Definition of End of Study

The end of study is the point at which all the study data has been entered and queries resolved.

10 SAFETY REPORTING

This is a non-interventional study and at no point will clinical care be modified or affected by the study.

11 STATISTICS AND ANALYSIS

The statistical aspects of the study are summarised below. A statistical analysis plan (SAP) that will be available from the time that the last participant is recruited. The SAP will be finalised before any analysis takes place.

11.1 Description of the Statistical Methods

11.1.1 The plans for the statistical analysis of the study are outlined below. assessed using descriptive statistics. Variables

The following variables will be extracted for each patient admission in the retrospective and prospective cohorts:

- Laboratory data
    - Biochemistry/haematology/transfusion/coagulation data
- Demographics
    - Age, sex, type/site of bleeding
- Prescriptions on admission and through hospital stay
    - Anti-platelets, anti-coagulants etc.
- Vital signs
    - Blood pressure, heart rate, temperature, respiratory rate, level of consciousness (AVPU/GCS), oxygen therapy, sedation (if applicable)
- Procedures as treatments for bleeding:
    - Surgery/Interventional radiology/need for massive transfusion/haemostatic agents/tranexamic acid/uterotonics if obstetric
    - Treatments for VTE
- Prevention (to include IVC filter)
- Treatments
    - If treated pre-hospital, any features of monitoring (e.g. blood pressure) and time from injury to arrival in hospital and interventions (such as tranexamic acid or fluid infusion or blood transfusion).
- Blood sample data / laboratory feedback
    - Number of blood samples successfully retained
    - Number of additional clotting data points obtained via testing the retained samples
    - Challenges faced by the laboratory team during sample retention

11.1.2 Descriptive statistics

We will calculate summary statistics (e.g. demographics, treatments, mortality,) for both the retrospective and prospective cohorts identified by the algorithm.

For continuous variables we will use the median/interquartile range; for binary or categorical variables we will use the proportion. Confidence intervals for proportions were calculated using the Pearson-Klopper method. We will be able to make compare event rates with previously published data (UK, USA, Europe).

11.1.3 Retrospective cohort

As part of algorithm development we will perform additional analyses on the retrospective cohort. These will include exploring specific subgroups (obstetric, gastro-intestinal, emergency surgery, trauma) and examining treatment rates (e.g. rates of tranexamic acid use in post-partum haemorrhage). Results of these more detailed analyses will be compared with previously published data and current clinical guidelines.

11.2 Sample Size Determination

11.2.1 Retrospective data

The retrospective database will contain up to 1,750,000 patient admissions over ten years (based on an estimate of 175,000 admissions to Oxford University Hospitals NHS Foundation Trust each year).

11.2.2 Prospective data

Up to 87,500 records will be screened by the digital platform to identify those who may have bled over 2 three-month periods.

In the first three-month period, research nurses will review electronic records of patients with bleeding (identified by the algorithm), we estimate around 250 will experience a bleeding event. Assuming the algorithm has a sensitivity of 80%, we plan to review 200 electronic records.

In the second three-month prospective period, research nurses will approach patients for consent. Based on the assumption that 200 patients will also be identified by the algorithm in this period, we will aim for at least 40 (20%) of patients to consent to their participation.

We will assess the efficacy of the sample retention process being used by the study. This will include the number of samples successfully retained, the number of additional clotting laboratory resulted gained from these samples and any feedback from the laboratory staff regarding challenges they faced.

11.3 Analysis populations

Analysis population will be based on all the evaluable data collected as far as possible. Any subgroups that will not be included in the analysis will be prespecified in the statistical analysis plan with justification.

11.4 Decision points

There are no decision points in this feasibility study.

11.5 Stopping rules

Formal stopping rules are not considered appropriate for this observational study. A main consideration for terminating the study would be an inability of the iteratively refined algorithm to correctly identify patients with bleeding. All results would be reviewed by the study management team, who would make the ultimate decisions to stop the study.

11.6 The Level of Statistical Significance

The level of statistical significance will be at 5% (2-sided).

11.7 Procedure for Accounting for Missing, Unused, and Spurious Data.

We will use multiple imputation to impute missing covariates (e.g. using the Multivariate Imputation by Chained Equations (MICE) algorithm).

11.8 Procedures for Reporting any Deviation(s) from the Original Statistical Plan

Any deviations from the analysis plan with justification will be reported in the statistical report.

12 DATA MANAGEMENT

This study requires access to large numbers of confidential health care records in order to identify the cohort of interest.

12.1 Data sources

Source documents are where data are first recorded, and from which participants' CRF data are obtained. These include, but are not limited to, hospital records (from which medical history and previous and concurrent medication may be summarised into the CRF), clinical and office charts, laboratory and pharmacy records, diaries, microfiches, radiographs, and correspondence.

CRF entries will be considered source data if the CRF is the site of the original recording (e.g. there is no other written or electronic record of data). All documents will be stored safely in confidential conditions. On all study-specific documents, other than the signed consent, the participant will be referred to by the study participant number/code, not by name.

12.2 Data transfer and analysis

All study data will be encrypted using AES-256 and transferred using either the secure file download service of the OUH or the OUH Citrix environment. Whilst stripped of all direct identifiers, it will still be considered controlled official sensitive data. This is because it will still contain multiple indirect identifiers such as date/time stamps. These are required for the correct analysis of the data (see data dictionary for justification). The data will be transferred on encrypted media chaperoned by a member of the study team from the participating site to the Critical Care Research Group based in Oxford. Here the data will be loaded onto specialist secure hardware held and maintained by the group. This system is referred to as a Data Safe Haven and is a secure computing environment which is designed to store and analyse complex datasets in a manner that is safe and secure. It conforms to NHS Digital Security Toolkit and Cyber Essentials Plus accreditation. The environment is designed so that patient level data never leaves the environment.

12.3 Data recording and record keeping

All study records apart from consent form/consultee declaration will be electronic, and their generation is detailed above.

The participants will be identified by a unique study specific number in any database. The name and any other identifying detail will NOT be included in any study data electronic file.

The ledger(s) that link the source Clinical Information System (CIS) data and the unique study specific number will be held by the Oxford University Hospital NHS Trust and destroyed at the end of the study period. Written CRFs will be kept for those patients that provide consent. CRFs will be generated for

those who are not approached to give consent (and only contribute anonymised data into the study). These written CRFs will be stored in a dedicated storage facility and retained for a minimum of 5 years after the end of the study in keeping with current MRC guidance. Personal data such as contact details that could identify a participant will be destroyed as soon as it is practical to do so and no later than 12 months after the end of the study.

12.4 Access to data

Direct access will be granted to authorised representatives from the Sponsor and host institution for monitoring and/or audit of the study to ensure compliance with regulations.

13 QUALITY ASSURANCE PROCEDURES

The study may be monitored, or audited in accordance with the current approved protocol, GCP, relevant regulations and standard operating procedures.

13.1 Risk assessment

This study is an observational study that does not interact with patients or influence their care. No formal risk assessment will be performed. This study requires access to a large number of confidential patient records.

To mitigate the risk of identification of individual patients in the database and the risk of data loss we will undertake the following precautions:

- All records will be accessed and pseudo-anonymised at the participating site, using a dedicated computer that will conform to NHS information security standards.
- Only pseudonymous patient data will be transferred via secure/encrypted method to the coordinating centre (e.g. Critical Care Research Group (CCRG), Nuffield Department of Clinical Neurosciences, Oxford University).
- Data will be held inside the groups `Data Safe Haven` which will conform to the same NHS standards of information security and cyber security.
- Only pseudonymous data will be held by the CCRG.

13.2 Study monitoring

All study team members will be fully trained in Information Governance, data protection and confidentiality. The study may be monitored, or audited in accordance with the current approved protocol, GCP, relevant regulations and standard operating procedures.

13.3 Study Committees

13.3.1 Study Management Group

Comprising of all the researchers and representative from the PPI group, chaired by Prof Simon Stanworth (CI).

13.3.2 PPI Group

The Oxford Blood Group is Chaired by Dr Catriona Gilmour Hamilton, Haematology Quality Manager: Patient Experience and Engagement, PPI Co-ordinator, (Churchill Hospital, Old Road, Headington. Oxford OX3 7LE)

14 PROTOCOL DEVIATIONS

A study related deviation is a departure from the ethically approved study protocol or other study document or process (e.g. consent process or administration of study intervention) or from Good Clinical Practice (GCP) or any applicable regulatory requirements. Any deviations from the protocol will be documented in a protocol deviation form and filed in the study master file.

15 SERIOUS BREACHES

A "serious breach" is a breach of the protocol or of the conditions or principles of Good Clinical Practice which is likely to affect to a significant degree –

(a) the safety or physical or mental integrity of the trial subjects; or

(b) the scientific value of the research.

In the event that a serious breach is suspected the Sponsor must be contacted within 1 working day. In collaboration with the C.I., the serious breach will be reviewed by the Sponsor and, if appropriate, the Sponsor will report it to the approving REC committee and the relevant NHS host organisation within seven calendar days.

16 ETHICAL AND REGULATORY CONSIDERATIONS

16.1 Declaration of Helsinki

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

16.2 Guidelines for Good Clinical Practice

The Investigator will ensure that this study is conducted in accordance with relevant regulations and with Good Clinical Practice.

16.3 Approvals

Following Sponsor approval, the protocol, informed consent form, participant information sheet and any proposed advertising material will be submitted to an appropriate Research Ethics Committee (REC), Confidentiality Advisory Group (CAG) and HRA, and host institutions for written approval.

The Investigator will submit and, where necessary, obtain approval from the above parties for all substantial amendments to the original approved documents.

16.4 Other Ethical Considerations

If an unexpected finding is reported from the laboratory sample analysis, the participant will be invited to attend a clinic appointment at the Oxford Haemophilia and Thrombosis centre to discuss the finding further.

16.5 Reporting

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

16.6 Transparency in Research

This type of study does not lend itself to registration, but the study team will aim to provide information through a publicly accessible protocol paper describing the aims and methods.

16.7 Participant Confidentiality

The study will comply with the UK-General Data Protection Regulation (UK-GDPR) and Data Protection Act 2018, which require data to be anonymised as soon as it is practical to do so. The processing of the personal data of participants will be minimised by making use of a unique participant study number only on all study documents and any electronic database(s) and the case report form (CRF). The consent form will hold study number, name and participant initials. All documents will be stored securely and only accessible by study staff and authorised personnel. The study staff will at times safeguard the notice of participants' personal data.

17 FINANCE AND INSURANCE

17.1 Funding

This study is funded by the NIHR Biomedical Research Centre for "A data science platform and biobank to rationalise the investigation and treatment of major bleeding" (Application number: BRCRCF20-08)

17.2 Insurance

The University has a specialist insurance policy in place which would operate in the event of any participant suffering harm as a result of their involvement in the research (Newline Underwriting Management Ltd, at Lloyd's of London). NHS indemnity operates in respect of the clinical treatment that is provided.

17.3 Contractual arrangements

Appropriate contractual arrangements will be put in place with all third parties.

18 PUBLICATION POLICY

The Investigators will be involved in reviewing drafts of the manuscripts, abstracts, press releases and any other publications arising from the study. Authors will acknowledge that the study was funded by NIHR Biomedical Research Centre. Authorship will be determined in accordance with the ICMJE guidelines and other contributors will be acknowledged.

19 DEVELOPMENT OF A NEW PRODUCT/ PROCESS OR THE GENERATION OF INTELLECTUAL PROPERTY

Ownership of IP generated by employees of the University vests in the University. The University will ensure appropriate arrangements are in place as regards any new IP arising from the trial.

20 ARCHIVING

At the end of the study, electronic files containing the anonymised retrospective and prospective study datasets will be stored and retained in the CCRG, (University of Oxford) on secure severs (referred to as the Data Safe Haven). This environment stores data in a manner that it can be securely analysed without removing or copying the data from its systems. The data will remain here for at least 5 years in keeping with the MRC Research Framework. After the archiving period has ended, the paper documents and electronic files will be confidentially and securely destroyed in line with University of Oxford guidelines.

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22 APPENDIX A: AMENDMENT HISTORY

Amendment No.	Protocol Version No.	Date issued	Author(s) of changes	Details of Changes made
N/A	2	6/10/21	Robert Hatch and study team	• Added a dissent section • Added further justification for consultee consent
Non Substantial Amendment 1	3	22/11/2021	Robert Hatch	• Added study specific sentence to dissent section
Substantial Amendment 1	4	11/01/2022	Robert Hatch	• Extended study timeframe

Substantial Amendment 2	5	15/08/2022	Robert Hatch	• Extending study timeframe