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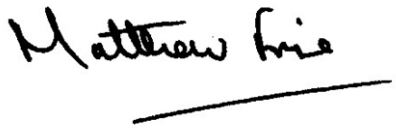
Chief Investigator Signature: 

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1. KEY CONTACTS

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2. LAY SUMMARY

Platelets are cells that circulate in the bloodstream and attach to the wall of a blood vessel when damage occurs so as to form a clot, which prevents or reduces bleeding from the point of damage.

A low level of platelets in the blood – termed thrombocytopenia – is a common finding in many different types of critical illness, and predicts a worse outcome for patients.

Aside from thrombocytopenia, impairments of platelet function also play a role in both disorders of bleeding and in abnormal activation of clotting. One group of patients in whom this is particularly important is those with liver disease, including established liver disorders such as alcohol-related cirrhosis, or liver dysfunction that develops during a period of critical illness, for example as a result of sepsis.

Previous research studies have tended to focus on the number of platelets in the blood rather than their function, because the former is much easier to measure. However, because there is not a simple relationship between the number of platelets in the blood and how well they work, relying simply on measuring the abundance of platelets in the blood may not be a good approach in critically ill patients, particularly those with liver disorders.

In this study we will use state-of-the-art techniques to examine the function of platelets taken from the blood of patients with critical illness and liver disease of different degrees of severity. We will study how changes in platelet function measured in the laboratory relate to problems patients experience during critical illness, such as bleeding, clotting, and organ dysfunction.

The aim is to gain a better understanding of the factors that affect platelet function in critical illness, particularly when liver disease coexists, to support future studies looking at improving treatments for this group of patients.

3. ABBREVIATIONS

CI	Chief Investigator
CRF	Case Report Form
CVC	Central Venous Catheter
EPR	Electronic Patient Record
ESR	Erythrocyte Sedimentation Rate
FBC	Full Blood Count
GCP	Good Clinical Practice
GP	General Practitioner
HRA	Health Research Authority
HTA	Human Tissue Authority
ICF	Informed Consent Form
ICU	Intensive Care Unit
MCA	Mental Capacity Act
NHS	National Health Service
RES	Research Ethics Service
PI	Peripherally Inserted Central Catheter
PICC	Principal Investigator
PIL	Patient Information Leaflet
PPI	Patient and Public Involvement
R&D	NHS Trust R&D Department
RACI	Rehabilitation After Critical Illness
RBFT	Royal Berkshire NHS Foundation Trust
RBH	Royal Berkshire Hospital
REC	Research Ethics Committee
SOP	Standard Operating Procedure

4. BACKGROUND AND RATIONALE

Thrombocytopenia is a frequent laboratory abnormality in critically ill patients, and is a strong and independent predictor of an adverse outcome in this setting.[1] For this reason, many previous studies examining the role of platelets in critical illness have understandably focused on their abundance in the blood.[2, 3]

As evidence of the complexity of the issues surrounding platelet function in critical illness, a 2018 study in critically ill paediatric patients found – somewhat counterintuitively – that among preterm infants with severe thrombocytopenia, a threshold for platelet transfusion of 50,000 platelets per cubic millimeter was associated with a significantly *higher* rate of death or major bleeding than a lower platelet-count threshold of 25,000 per cubic millimeter.[4]

Aside from the absolute number of platelets circulating in the bloodstream, their function and state of activation must be of considerable importance, as has been shown in other conditions,[5] but this aspect of the role of platelets in critical illness has received relatively little attention. As further evidence that platelet function may be more significant than the absolute number of circulating platelets, a 2017 study in adult patients found no association between prophylactic platelet transfusion and bleeding in critically ill patients with thrombocytopenia.[6]

One population in whom disorders of platelet abundance and function are particularly important is patients with liver disease.[7] This same population are at considerable risk of developing conditions that lead to critical illness and the requirement for invasive organ support, and who unfortunately fare particularly badly when they do become critically unwell.

There are remarkably few studies examining the function of platelets in critically ill patients with liver disease.[8, 9] This study aims to increase our understanding of the mechanisms of platelet function that are disturbed in this patient group. An improved understanding of these mechanisms will ultimately benefit patients by offering the opportunity to target platelet dysfunction pharmacologically in interventional studies. It is not anticipated that this study will benefit the patients that take part, but the study will provide a foundation for subsequent work that will improve the treatment of future patients.

We will recruit adult patients requiring admission to the Intensive Care Unit who have evidence of established liver disease or liver dysfunction arising in the setting of critical illness. We will study platelets obtained from the bloodstream of these patients *in vitro* using state-of-the-art assays. The study will also examine platelet function over time in the same individuals over the course of their illness (longitudinal function), by sampling blood from individuals who survive their ICU stay to be discharged to a general ward.

The study will be purely observational. Whilst admitted to the ICU, patients will typically have indwelling vascular access devices, which will allow the sampling of blood without any additional invasive procedures being performed beyond those required for routine care.

5. OBJECTIVES AND OUTCOME MEASURES

Objectives	Outcome Measures	Timepoint(s) of evaluation of this outcome measure (if applicable)
Primary Objective Establish the impact of critical illness and liver disease on platelet phenotype.	Platelet reactivity and function determined using a range of approaches including Platelet Phenomics Analysis, according to the nature of critical illness and liver disease type, burden, and stage.	Blood sampling at day 0 and every 3±1 days thereafter, at a maximum of five time points on ICU and two on the general ward.
Secondary Objectives (i) Determine the impact of platelet phenotype on thrombus formation and experimentally induced thrombosis. (ii) Establish the molecular bases of differential platelet reactivity across the spectrum of liver disease in critical illness.	i) Thrombus size generated using *in vitro* thrombus formation assay. ii) Clotting parameters derived using the technique of thromboelastography and related haemostatic assays. iii) Platelet receptor levels. iv) Proteomic analysis of signalling proteins. v) Signalling-pathway-specific experiments including modelling changes in cell lines.	As above. Additional blood sampling on a single occasion in clinic in the weeks to months following discharge from hospital.

6. STUDY DESIGN

This is a laboratory-based, observational, single centre study, in patients with critical illness and liver disease. Blood samples will be collected in the ICU, medical wards, and on occasion outpatient clinics, and immediately transported in accordance with local standard operating procedure by a member of the research team to the laboratory within the Health & Life Sciences Building at the University of Reading, where a member of Professor Gibbins' group will begin analysing the material. The analysis techniques that will be carried out in the laboratory are described below.

All samples will bear an anonymisation code that will prevent data from being attributed to a specific patient. The research coordinators will possess the coding system which will be stored securely in paper form. Data will be stored in anonymised form at the University of Reading on dedicated computers with secure redundant backup systems. Data will not be communicated by email. Computer storage will be in encrypted form.

An electronic clinical information system known as ICCA (IntelliSpace Critical Care and Anaesthesia, © Koninklijke Philips N.V.) is used within the ICU to collect clinical data in real-time as part of routine clinical care. Variables of interest during the period for which a patient is enrolled in the study, for example requirement for blood transfusion due to bleeding, or administration of vasopressors, will be examined and associations sought between these variables and indices of platelet function. Additionally, the Electronic Patient Record (EPR, Cerner Millennium®) stores data for patients during their entire hospital stay, and will also be interrogated, particularly for those patients continuing to participate following ICU discharge. Access to patient-identifiable data of these sort will only be by members of the study team trained in Good Clinical Practice (GCP) with a substantive or honorary contract at the RBFT.

Professor Gibbins' group have access to a library of data relating to platelet function in healthy individuals, which will permit comparisons with data derived from the present study. Patients admitted to ICU are a highly heterogeneous groups, with a range of pathogens and therapeutic interventions, meaning it would not be meaningful to try to identify a separate critically ill control group. Instead, patients with serve as their own controls as data are collected longitudinally and changes over the course of a period of critical illness are identified. Additionally, since patients with liver disease over a range of severities will be recruited, it will be possible to treat liver disease as a continuous independent variable in the data analyses. A variety of clinically validated scoring systems exist to facilitate this.

7. PARTICIPANT IDENTIFICATION

7.1. Study Participants

Participants will be adult patients with liver disease or dysfunction admitted to the ICU at the RBH.

7.2. Inclusion Criteria

- Admitted to ICU
- Aged 18 years or above

- Evidence of established liver disease, or acute liver dysfunction related to underlying illness, as determined by the clinicians caring for the patient at the time of eligibility assessment.

7.3. Exclusion Criteria

- Patients on P2Y12 inhibitors (including clopidogrel, ticagrelor and prasugrel)
- Patients on treatment-dose anticoagulation, including warfarin or novel anticoagulant drugs
- Patients under 18 years of age
- Active or recent malignancy (< 1 years) or on active treatment

8. PROTOCOL PROCEDURES

8.1. Description of study participants

Thirty adult patients with liver disease or dysfunction admitted to the ICU at the RBH.

8.2. Recruitment of patients

Suitable patients will be identified to the Urgent Care Research team by the clinical team responsible for the patient.

8.3. Consent

Potential participants will first be approached by a member of the clinical team responsible for the patient. The approach will involve determining the patient's capacity to consent to participation, and the recruitment procedure will differ according to whether the patient has the capacity to consent or lacks it due to alterations in consciousness caused by illness and/or therapeutic sedation.

8.3.1. Patients lacking capacity to consent at time of recruitment

Practice for these patients will be as directed by the Mental Capacity Act 2005 (MCA). Advice will be sought from an appropriate consultee to determine if the patient would be likely to agree to enrolment. If the consultee deems the patient would not wish to be involved, care will continue as normal. If the consultee believes the patient would have agreed to participate they will be enrolled in the study. If a personal consultee cannot be identified a professional consultee, independent of the treating and study teams, will be sought. If no consultee can be identified the patient will not be enrolled. The consultee will be allowed as much time as they wish to consider the information, and the opportunity to question the Investigator or other independent parties to decide whether the patient will participate in the study.

8.3.2. Patients having capacity to consent at time of recruitment

A minority of patients may have capacity to give informed consent despite their illness and for these individuals consent will be obtained in the usual way. Written and verbal versions of the Participant Information and Informed Consent will be presented to the participants detailing the nature of the study;

what it will involve for the participant; the implications and constraints of the protocol; and any risks involved in taking part. It will be clearly stated that the patient is free to withdraw from the study at any time for any reason without prejudice to future care, and with no obligation to give the reason for withdrawal.

The patient will be allowed as much time as they wish to consider the information, and the opportunity to question the Investigator or other independent parties to decide whether they will participate in the study. The patient must personally sign and date the latest approved version of the Informed Consent form before any study specific procedures are performed.

Written Informed Consent will be obtained by means of participant dated signature and dated signature of the person who obtained the Informed Consent. The person who obtained the consent will be suitably qualified and experienced, and have been authorised to do so by the Chief Investigator. A copy of the signed Informed Consent will be given to the participant. The original signed form will be retained at the study site. A record of enrolment will be entered into the participant's electronic clinical records.

If a patient who has previously consented to participate loses capacity during the study, then advice will be sought from an appropriate consultee to determine if the patient would be likely to agree to continue to participate in the study (in the manner described in section 8.3.1). When providing informed consent, patients are able to indicate what their wishes would be in such a situation, and this information will assist the consultee in deciding whether or not participation should continue.

8.3.3. Patients regaining capacity whilst hospitalised

Those patients who were enrolled whilst lacking capacity to consent, and who survive and regain capacity during their hospital admission, will be visited by a member of the study team either whilst on ICU of after discharge to a ward, who will explain that they participated in this observational study after advice had been sought from a consultee. Written confirmation will be sought at that time that the patient is willing for the data already collected to be used in the way set out in the patient information sheet (PIS). If the patient does not wish his/her data to be used it will be erased.

8.3.4. Patients dying prior to regaining capacity

Consultee assent will be deemed to stand for those patients who die prior to regaining capacity or who do not regain capacity prior to discharge from RBH.

8.4. Blood sampling

Whilst on the ICU, blood sampling will generally be via an existing indwelling central venous catheter (CVC), peripherally inserted central catheter (PICC) or occasionally an arterial catheter (A-line). Up to 50 ml whole blood will be taken at each time point.

The first sample will be taken at day 0, the day of enrolment to the study. Thereafter samples will routinely be taken every 3 ± 1 days. Occasionally, should there be a significant change in the clinical condition of patient that may be associated with a putative alteration in platelet function, samples may be taken on two consecutive days. The total number of samples taken from each patient will be capped at five to ensure that an excessive volume of blood is not lost as a result of participation in the study.

For patients surviving to discharge from ICU to a ward, consent will be requested for further samples to be taken. As much as possible sampling of blood will be timed to coincide with routine clinical samples, to minimise the need for additional venepuncture, as patients will generally not have indwelling vascular devices in situ following discharge from ICU. These samples are optional and the patient will be free to decline. The total number of samples taken from each patient once on a ward will be capped at two.

Some patients will return to RBH following their discharge from hospital to attend the Rehabilitation After Critical Illness (RACI) clinic, or on some occasions a Liver outpatient clinic. In some cases these patients will be asked if they would be prepared to provide a final, convalescent, sample for the research team. This sample is optional and the patient will be free to decline.

8.5. In vitro platelet and coagulation assays

8.5.1. Platelet aggregation studies

Platelet aggregation will be measured using isolated washed platelets and platelet-rich plasma by optical aggregometry to enable the kinetics and extent of aggregation to be observed. A range of agonists (ADP, collagen, collagen-related peptide, thrombin, U46619) and agonist concentrations will be used. Analysis of the initial kinetics of aggregation will be performed in addition to analysis of aggregation levels/stability over extended periods to assess early and late phases of aggregation. A newly developed high-throughput application of optical aggregometry that is established at the University of Reading will also be used to maximise possible data from small blood samples to enable thorough functional profiling.

8.5.2. Platelet surface receptor expression levels

The expression levels of key platelet receptors will be assessed by flow cytometry. Standard haematological parameters including platelet number and mean platelet volume will be obtained from the patients' full blood count (FBC). The erythrocyte sedimentation rate (ESR) will also be determined to monitor inflammation.

8.5.3. Platelet procoagulant activity

Activated platelets may exteriorise phosphatidyl serine that provides a surface for the assembly of the prothrombinase complex, and therefore the localised generation of thrombin and fibrin generation. Annexin V binding to platelets will be assessed by flow cytometry.

8.5.4. Fibrinogen binding:

Platelet aggregation and thrombus formation is supported through up-regulation in affinity of integrin αIIbβ3 on platelets. Here, integrin αIIbβ3 affinity modulation will be assessed through the measurement of fibrinogen binding to platelets by flow cytometry.

8.5.5. Platelet alpha-granule secretion

Secretion from α-granules will be measured by quantification of the exposure of P-selectin, the cell adhesion molecule, which resides in α-granules and is released to the platelet surface during platelet activation. An established flow cytometry assay will be used.

8.5.6. Platelet adhesion to collagen

Platelet adhesion to collagen may be monitored under static conditions in a 96-well plate, following the labelling of platelets with calcein and measured by spectrofluorimetry.

8.5.7. Thrombus formation

Thrombus formation may be examined using whole blood to assess impact on platelet thrombus formation studied *in vitro* under arterial flow conditions. This will establish whether aspects of thrombus formation are modified in critical illness and liver disease. Whole blood will be labelled with the lipophilic fluorescent dye DiOC6 and perfused over collagen coated within Cellix Vena8 microfluidic flow cells. During perfusion, various parameters of thrombus formation will be measured by confocal microscopy to assess the rate, size, structure and stability of thrombi formed.

8.5.8. Analysis of platelet cell signalling

Following the stimulation of platelets with activators of platelet function, cells will be lysed, cleared of any cellular debris, and protein extracts stored frozen. Should changes in platelet function be observed associated with liver disease, this will allow later detailed analysis of the molecular mechanisms that control platelet function. The following measurements, guided by the outcomes of functional analysis of platelets may be included in these analyses.

8.5.9. Protein tyrosine phosphorylation

Platelets will be stimulated in the presence of eptifibatide to prevent aggregation, lysates prepared and total levels of tyrosine phosphorylation assessed following stimulation with collagen, collagen-related peptide, thrombin, ADP and U46619 by immunoblot analysis.

8.5.10. Platelet signalling pathway analysis

The levels of activation of key proteins within the GPVI and CLEC-2 signalling pathways will be assessed by immunoblot analysis following stimulation with collagen, thrombin or ADP.

8.5.11. Analysis of coagulation factors and plasma constituents

Coagulation factors and other plasma constituents will be measured in plasma samples prepared and stored following collection of blood. Coagulation factors will be measured using a multiparameter haemostasis analyser. The specifics of which plasma constituents will be measured will be dependent on the outcomes of experiments, but will include molecules known to influence platelet function such as soluble GPVI, oxidised LDL and thromboxane B2.

8.6. Sample Handling and Storage

Platelet analysis will begin using fresh blood samples within two hours of sampling. Cells will not be stored beyond these experiments. Platelet protein extracts - rendered acellular - may be stored frozen along with plasma and serum at the University of Reading, for later analysis. While sample documentation, booking in and out and inventory will conform to HTA standards, this type of storage does not require use of an approved HTA storage facility.

8.7. Early Discontinuation/Withdrawal of Participants

During the course of the study a participant may choose to withdraw early at any time. Participants have the following three options for withdrawal:

1) Participants may withdraw from active follow-up and further communication but allow the study team to continue to access their medical records and any relevant data that are recorded as part of routine clinical care.
2) Participants can withdraw from the study but permit data and samples obtained up until the point of withdrawal to be retained for use in the study analysis. No further data or samples would be collected after withdrawal.
3) Participants can withdraw completely from the study and withdraw the data and samples collected up until the point of withdrawal. The data and samples already collected would not be used in the final study analysis.

The type of withdrawal and reason for withdrawal will be recorded in the CRF.

8.8. Definition of End of Study

The end of the study is the point at which all *in vitro* analyses of platelet function have been completed for the final participant recruited.

9. SAFETY REPORTING

9.1. Definition of Serious Adverse Events

A serious adverse event is any untoward medical occurrence that:

- results in death
- is life-threatening
- requires inpatient hospitalisation or prolongation of existing hospitalisation
- results in persistent or significant disability/incapacity
- consists of a congenital anomaly or birth defect.

Other ‘important medical events’ may also be considered a serious adverse event when, based upon appropriate medical judgement, the event may jeopardise the participant and may require medical or surgical intervention to prevent one of the outcomes listed above.

NOTE: The term "life-threatening" in the definition of "serious" 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 which hypothetically might have caused death if it were more severe.

9.2. Reporting Procedures for Serious Adverse Events

A serious adverse event (SAE) occurring to a participant will be reported to the REC that gave a favourable opinion of the study where in the opinion of the Chief Investigator the event was ‘related’ (resulted from administration of any of the research procedures) and ‘unexpected’ in relation to those procedures.

Reports of related and unexpected SAEs will be submitted within 15 working days of the Chief Investigator becoming aware of the event, using the HRA report of serious adverse event form.

10. STATISTICS AND ANALYSIS

10.1. Description of the Statistical Methods

Analysis of data will be conducted by the study statistician. Analysis will depend on the form of data to be analysed, whether these are normally distributed, and thus whether parametric or non-parametric tests should be applied. In most cases, methods such as ANOVA (analysis of variance) and student's t-test will be appropriate.

10.2. Sample Size Determination

The absence of previously published work in this area precludes a detailed power calculation. The sample size is based on variability and scale of effect in changes in Platelet Phenomic Analysis using a patient cohort from an existing study in patients with ischaemic heart disease. Successful completion of this study is expected to produce data of a scale that will allow detailed statistical analysis and permit powering of more detailed mechanistic and ultimately interventional studies in the future.

10.3. The Level of Statistical Significance

A P-value < 0.05 will be taken as statistically significant.

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

We do not plan the use of imputation approaches to account for missing data as these are unlikely to be robust in a small exploratory study of this sort.

11. DATA MANAGEMENT

Security of data collection, handling, transfer, storage and use is a key component of this study and central to the continuing integrity and viability of this research project. Anonymised patient data will be collected at RBH from the electronic clinical records systems (ICCA and EPR) by staff trained in high quality handling and secure procedures. All other information and data will be stored electronically. The security of the database is maintained by the following principles:

• Access to clinical and personal data in the database will be limited to the CI and named clinical research staff and clinicians (typically research fellows, research nurses and data entry staff). Access will be secure and password protected. The research individuals will maintain confidentiality and be trained in database care.

• Any identifiable data (name and hospital number) will be stored on paper with a link to the study identifier, with all clinical and research data stored in a separate database. When data are downloaded for analysis identifiable data will not be included and individuals will only be identified by their study number.

• Responsible members of RBFT, appropriate regulating bodies, and ethics committees may be given access to data for monitoring and/or audit of the study to ensure we are complying with regulations.

The participants will be identified by a unique study-specific number and/or code in any database. The name and any other identifying details will NOT be included in any trial data electronic file.

Fully anonymised data will be stored on the University of Reading data archive repository, which is fully encrypted and password-protected. Data will be retained for 10 years from the end of the study.

12. QUALITY ASSURANCE PROCEDURES

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

12.1. Assessment and Management of Risk

12.1.1. Risk to patients

Patients who have blood samples taken on the ward will have a small risk associated with venepuncture (pain, bleeding, bruising). Risk will be managed as the procedure will be undertaken by trained staff.

If it becomes apparent that while collecting sensitive data from the patient, there is potential risk/harm to them, it will be raised with the suitable body for safeguarding. This is to mitigate harm to the patient.

12.1.2. Risk to staff

Taking blood carries a risk of needle stick injury to the phlebotomist, which in turn carries a risk of exposure to blood-borne infections. This risk will be minimised by a) ensuring staff are adequately trained, b) ensuring staff have been vaccinated against, and show immunity to Hepatitis B, and c) following the RBFT policy for needle stick injury which describes the process of being assessed for and receiving post-exposure prophylaxis.

13. 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 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.

14. 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 study participants; 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 CI, 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.

15. ETHICAL AND REGULATORY CONSIDERATIONS

15.1. Declaration of Helsinki

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

15.2. Guidelines for Good Clinical Practice

The investigator so will ensure that this study is conducted in accordance with relevant regulations and with GCP.

15.3. Approvals

Following Sponsor approval the protocol, informed consent form, participant information sheet will be submitted to an appropriate Research Ethics Committee (REC) and host institutions for written approval.

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

HRA approval will be sought for the study on the basis described in the application form, protocol and supporting documentation.

• Substantial amendments that require review by REC/HRA will not be implemented until that review is in place and other mechanisms are in place to implement at site.

• All correspondence with the REC/HRA will be retained.

• It is the CI's responsibility to produce the annual reports as required.

• The CI will notify the REC of the end of the study.

• 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 and Sponsor. In addition, an End of Study notification and final report will be submitted to the same parties. If the study is ended prematurely, the Chief Investigator will notify the REC, including the reasons for the premature termination.

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

15.4. Regulatory Review & Compliance

The Chief Investigator and Sponsor will ensure that appropriate approvals from participating organisations are in place. Specific arrangements on how to gain approval from participating organisations are in place and comply with the relevant guidance.

For any amendment to the study, the CI or designee, in agreement with the sponsor will submit information to the appropriate body in order for them to issue approval for the amendment.

15.5. Amendments

If the sponsor wishes to make a substantial amendment to the REC application or the supporting documents, the sponsor must submit a valid notice of amendment to the REC for consideration. The REC will provide a response regarding the amendment within 35 days of receipt of the notice. It is the sponsor's responsibility to decide whether an amendment is substantial or non-substantial for the purposes of submission to the REC.

Amendments will also be notified to the national coordinating function of the UK country where the lead NHS R&D office is based and communicated to the participating organisations (R&D office and local research team) departments of participating sites to assess whether the amendment affects the NHS permission for that site. Note that some amendments that may be considered to be non-substantial for the purposes of REC still need to be notified to NHS R&D (e.g. a change to the funding arrangements).

15.6. Peer review

This study is a joint enterprise between by the RBHFT and University of Reading Health Innovation Partnership and has been reviewed by a panel of experts based in both organisations.

15.7. Patient and Public Involvement (PPI)

The study team are very keen that members of the public be active partners in the research process. Patient-facing study documents have been developed in conjunction with patient representatives from the RBFT. The protocol has also been reviewed by the Research Steering group at the RBH, which includes patient advocates.

15.8. Participant Confidentiality

The study will comply with the General Data Protection Regulation (GDPR) and Data Protection Act 2018, which require data to be de-identified 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). All documents will be stored securely and only accessible by study staff and authorised personnel. The study staff will safeguard the privacy of participants' personal data.

15.9. Expenses and Benefits

This is an observational study of hospitalized patients. No expenses will be incurred as a consequence of taking part and no remuneration will be offered.

16. FINANCE AND INSURANCE

16.1. Funding

This study is funded by the RBFT and University of Reading Health Innovation Partnership.

16.2. Insurance

NHS bodies are legally liable for negligent acts and omissions of their employees. If a patient were harmed whilst taking part in a clinical research study as a result of negligence on the part of a member of the study team this liability cover would apply. NHS indemnity operates in respect of the clinical treatment that is provided.

17. DISSEMINATION POLICY

The data arising from the study will be owned by University of Reading and RBFT. The data will be accessible to researchers at the University of Reading and RBFT.

17.1. Publication

The outcomes from this study will be published in peer-reviewed research journals. 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 the relevant funding sources. Authorship will be determined in accordance with the ICMJE guidelines and other contributors will be acknowledged as appropriate.

17.2. Notifying participants of results

There are no plans routinely to notify participants of the results. However, they are able to contact us, as stated in the participant information sheet, for a summary of the key outcomes from this study.

18. REFERENCES

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