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Serum blood clotting changes during blood sampling via non-luer one-way filter valve intravenous needle: Implication on the epidural blood patch procedure

Sponsor Reference No: This will be assigned by the Research Office on submission for initial Sponsor review

Ethics Ref: Insert (NB only available once booked into Ethics – do not book into Ethics until authorised by the Sponsor)

Date and Version No: 1/1/17 Version 2

Chief Investigator:	Dr Paul Sharpe
Investigators:	Dr Asif Mahmood
Sponsor:	University Hospitals of Leicester NHS Trust
Funder:	Obstetric Anaesthetists' Association Grant
Signatures:	The approved protocol should be signed by author(s) and/or person(s) authorised to sign the protocol

Confidentiality Statement

All information contained within this protocol is regarded as, and must be kept confidential. No part of it may be disclosed by any Receiving Party to any Third Party, at any time, or in any form without the express written permission from the Chief Author/Investigator and / or Sponsor.

Authors

Dr Asif Mahmood ST5 Anaesthesia Leicester Royal Infirmary

Dr Paul Sharpe Consultant Anaesthesia Leicester Royal Infirmary

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Signature Page

Chief Investigator Name: **Dr Paul Sharpe**_____

Chief Investigator signature: _____

Date: **1/1/16**_____

Sponsor Representative Name: **Carolyn Maloney**_____

Sponsor Representative signature: _____

Date: **1/1/16**_____

Principal Investigator Name: **Dr Asif Mahmood** _____

Principal Investigator signature: _____

Date: **1/1/16** _____

(In cases of Multi-centre studies, this must be replicated for each site)

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1. AMENDMENT HISTORY

Amendment No.	Protocol Version No.	Date issued	Author(s) of changes	Details of Changes made
1	2	1/1/17	Paul Sharpe and Asif Mahmood	**APPENDIX A: STUDY FLOWCHART** Time line edited to allow more time to recruit.

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

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2. SYNOPSIS

Study Title	Serum blood clotting changes during blood sampling via non-luer one-way filter valve intravenous needle: Implication on the epidural blood patch procedure
Internal ref. no.	
Trial Design	Observational Study
Trial Participants	Healthy post natal and non-pregnant participants
Planned Sample Size	Total 50 participants
Follow-up duration	n/a
Planned Trial Period	12 months
Primary Objective	Investigate clotting profile changes due to the use of the new non-luer one-way valve filter needle compared to a standard hypodermic needle.
Secondary Objectives	n/a
Primary Endpoint	Analysis of blood via near patient TEG clotting analysis

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3. ABBREVIATIONS

AE	Adverse event
AR	Adverse reaction
CI	Chief Investigator
CRA	Clinical Research Associate (Monitor)
CRF	Case Report Form
CRO	Contract Research Organisation
CT	Clinical Trials
EC	Ethics Committee (see REC)
GCP	Good Clinical Practice
GP	General Practitioner
GTAC	Gene Therapy Advisory Committee
ICF	Informed Consent Form
NHS	National Health Service
NRES	National Research Ethics Service
PI	Principal Investigator
PIL/S	Participant/ Patient Information Leaflet/Sheet
R&D / R&I	NHS Trust Research &Development / Innovation Department
REC	Research Ethics Committee
SAE	Serious Adverse Event
SAR	Serious Adverse Reaction
SOP	Standard Operating Procedure
SUSAR	Suspected Unexpected Serious Adverse Reactions
TMF	Trial Master File

4. BACKGROUND AND RATIONALE

Patient safety agencies such as the National Patient Safety Agency (NPSA) and European Medicines Agency recommend adoption of equipment that prevents wrong route drug administration[1]. For example medicine intended for the intravenous route should not be possible to be given via the epidural route, hence limiting potentially catastrophic complications associated with human error[2]. However,the epidural blood patch requires equipment that connects to the intravenous and epidural route, as blood is taken from a patient's vein and then it is injected into the patient's epidural space for therapeutic affect. Hence equipment is required that allows blood aspiration from the patient but does not have the potential to inject into the patient hence complying with patient safety agency recommendations. Aspirating blood from the patient via a non-Luer one-way filter valve has the theoretical potential of activating the clotting cascade. If this occurred it could reduce the time the clinician has to utilise the blood before it clots in the syringe. Changes in clotting characteristics also has unknown implications when injected into the epidural space with regards to the therapeutic effect of the procedure.

The epidural blood patch is mainly used in obstetric anaesthesia in the treatment of dural puncture headaches, however it is also used to treat conditions such as spontaneous intracranial hypotension, hence this study involves post natal and non-pregnant populations. This study requires blood to be taken from the study participants via a venepuncture. This will require 12mls of blood to be taken from the patent via a standard 21G hypodermic needle and also 2mls of blood via the new 21G non-Luer one-way filter valve needle. The blood will undergo clotting profile testing. The implications for study subjects would be two venepunctures and a total of 14mls of blood taken. The post natal population would only require one additional venepuncture with the new one-way valve needle as they would already be having bloods taken for their day 2 post elective cesarean section bloods, an additional 9ml of blood only.

5. OBJECTIVES

5.1 Primary Objectives

We aim to determine if there is a difference in the clotting profile values from blood extracted with a normal 21G hypodermic needle vs the new 21G non-Luer one-way filter valve needle.

5.2 Secondary Objectives

Not Applicable

6. STUDY DESIGN

6.1 Summary of Trial Design

This study will be an observational study. The pregnant participants will be recruited from the elective pre-operative caesarean clinic and have their bloods taken on day 2 post natal after their elective caesarean section during their rountine full blood count testing.

The healthy non-pregnant participants will be recruited via posters in the University Hospitals of Leicester.

The blood taken via the two different needles will be analysed via near patient testing with Thromboelastography (TEG) analysis and this will be the end of their study participation.

We will alternate between patients with regards to which needle will be used first during phlebotomy (ie hypodermic needle vs new non-Luer one-way valve filter needle). The punctures will be from separate veins for each of the two needles.

6.2 Primary and Secondary Endpoints/Outcome Measures

Blood taken by each needle from the participants will undergo near patient TEG analysis and we will be investigating the difference in R-Time, the time for a clot to form. The blood will also be sent for laboratory full blood count and clotting profile testing.

7. TRIAL PARTICIPANTS

7.1 Overall Description of Trial Participants

We will enrol pregnant participants who are due to have an elective caesarean section and have no medical condition. Non-pregnant participants will be healthy volunteers.

7.2 Inclusion Criteria

Participant is willing and able to give informed consent for participation in the study.
Male (in the volunteer subgroup) or Female.
Aged 18 years or above.
Within first 2 days post natal for post natal arm of study
Healthy participants must be in good health.
Able (in the Investigators opinion) and willing to comply with all study requirements.
Willing to allow his or her General Practitioner and consultant, if appropriate, to be notified of participation in the study.

7.3 Exclusion Criteria

The participant may not enter the study if ANY of the following apply:
Any medical condition
Post natal women with haemorrhage greater than 1L
Less than 12 hours post prophylactic dalteparin
Any clotting abnormality
On any medication including herbal medication (vitamins taken in pregnancy are acceptable)
Age less than 18 years at recruitment
Adults who are not capable of giving valid consent
Adults with learning disabilities/ difficulties
Adults in emergency situations
Unable to speak or read English
Prisoners
Adults unable to consent for themselves
Any person considered to have a particularly dependent relationship with investigators
Any others deemed to belong to a vulnerable group.
Any other significant disease or disorder which, in the opinion of the Investigator, may either put the participants at risk because of participation in the study, or may influence the result of the study, or the participant's ability to participate in the study.
Participants who have participated in another research study involving an investigational product in the past 12 weeks

8. STUDY PROCEDURES

8.1 Informed Consent

The participant must personally sign and date the latest approved version of the informed consent form before any study specific procedures are performed.
Written and verbal versions of the participant information and Informed consent will be presented to the participants detailing no less than: the exact nature of the study; 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, and with no obligation to give the reason for withdrawal.

The participant will be allowed as much time as wished 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 and dated signature of the person who presented and obtained the informed consent. The person who obtained the consent must be suitably qualified and experienced, and have been authorised to do so by the Chief/Principal Investigator as detailed on the Delegation of Authority and Signature log for the study. The original signed form will be retained at the study site within the Trial Master File (TMF) or Investigator Site File (ISF). A copy of the signed Informed Consent will be given to participants and a copy retained in the participant medical notes.

8.2 Screening and Eligibility Assessment

Pregnant participants will be identified in preoperative clinics for elective caesarean sections. Medical notes will be screened to recruit healthy volunteers.

Non-pregnant healthy participnats will be recruited via poster advertisement placed within University Hospitals of Leicester.

Demographics
The age, gender, days post natal for pregnant women and blood loss will be recorded.

Medical History
We would only recruit participants who do not have any medical conditions.

Concomitant Medication
All over-the-counter or prescription medication, vitamins, and/or herbal supplements will be recorded on CRFs.

8.3 Baseline Assessments

No baseline assessments are required for this research project.

8.4 Randomisation and Codebreaking (if applicable)

All participants will have a paired set of bloods taken with a hypodermic needle and the new on way valve filter needle. We will alternate which needle is used first between patients.

8.5 Subsequent Assessments

Each participant will have blood taken via a normal hypodermic needle and a new non luer one-way valve filter needle. The blood taken with each needle will undergo near patient TEG testing. This will represent the end of the participants research participation

8.6 Definition of End of Trial

The end of trial will be the completion of the 30th paired TEG test in the pregnant group and the 10th in the volunteer group.

8.7 Discontinuation/Withdrawal of Participants from Study Treatment

Each participant has the right to withdraw from the study at any time. In addition, the investigator may discontinue a participant from the study at any time if the investigator considers it necessary for any reason including:

Ineligibility (either arising during the study or retrospective having been overlooked at screening)

Significant protocol deviation

Significant non-compliance with treatment regimen or study requirements

An adverse event which requires discontinuation of the study or results in inability to continue to comply with study procedures

Developing a medical condition

Consent withdrawn

Lost to follow up

If participants are withdrawn from the study they will be replaced and data acquired from withdrawn participants will be destroyed. The reason for withdrawal will be recorded in the CRF.

If the participant is withdrawn due to an adverse event, the investigator will arrange for follow-up visits or telephone calls until the adverse event has resolved or stabilised.

8.8 Source Data

Source documents are original documents, data, and records 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, 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). In this study the CRF will be used as the source document to aid recruitment of participants from the preassessment elective caesarean section clinic.

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.

9. TREATMENT OF TRIAL PARTICIPANTS

9.1 Description of Study Treatment

Participant involvement in the study involves allowing phlebotomy to be taken with the two different needles.

9.2 Storage of Study Equipment or Related apparatus

The new non-Luer one-way valve filter needles will be stored in the anesthetic office situated in the maternity unit at Leicester Royal Infirmary.

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10. SAFETY REPORTING

10.1 Definitions

10.1.1 Adverse Event (AE)

An AE or adverse experience is:

Any untoward medical occurrence in a patient or clinical investigation participants, which does not necessarily have to have a causal relationship with this treatment.

An AE can therefore be any unfavourable and unintended sign (including an abnormal laboratory finding), symptom or disease temporally associated with the the study, whether or not considered related to the study.

10.1.2 Adverse Reaction (AR)

All untoward and unintended responses related to the study.

All cases judged by either the reporting medically qualified professional or the sponsor as having a reasonable suspected causal relationship to the study qualify as adverse reactions.

10.1.3 Severe Adverse Events

To ensure no confusion or misunderstanding of the difference between the terms "serious" and "severe", which are not synonymous, the following note of clarification is provided:

The term "severe" is often used to describe the intensity (severity) of a specific event (as in mild, moderate, or severe myocardial infarction); the event itself, however, may be of relatively minor medical significance (such as severe headache). This is not the same as "serious," which is based on patient/event outcome or action criteria usually associated with events that pose a threat to a participant's life or functioning. Seriousness (not severity) serves as a guide for defining regulatory reporting obligations.

10.1.4 Serious Adverse Event or Serious Adverse Reaction

A serious adverse event or reaction is any untoward medical occurrence that at any dose:

- Results in death,
- Is life-threatening,

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.

- Requires inpatient hospitalisation or prolongation of existing hospitalisation,
- Results in persistent or significant disability/incapacity, or
- Is a congenital anomaly/birth defect.
- Other important medical events*

*Other events that may not result in death, are not life threatening, or do not require hospitalisation, may be considered a serious adverse event when, based upon appropriate medical judgement, the event may jeopardise the patient and may require medical or surgical intervention to prevent one of the outcomes listed above.

10.1.5 Expected Serious Adverse Events/Reactions

This study is not expected to cause any serious adverse events or reactions. The main issues to note would be difficult phlebotomy which would be uncomfortable and phlebotomy can lead to brusing. None of these would require reporting.

10.1.6 Suspected Unexpected Serious Adverse Reactions

A serious adverse reaction, the nature or severity of which is not consistent with the applicable product information

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10.2 Reporting Procedures for All Adverse Events

All AEs occurring during the study observed by the investigator or reported by the participant, whether or not attributed to study, will be recorded on the CRF.

The following information will be recorded: description, date of onset and end date, severity, assessment of relatedness to study, other suspect device and action taken. Follow-up information should be provided as necessary.

AEs considered related to the study as judged by a medically qualified investigator or the sponsor will be followed until resolution or the event is considered stable. All related AEs that result in a participant's withdrawal from the study or are present at the end of the study, should be followed up until a satisfactory resolution occurs.

Any abnormal results from the laboratory full blood count or clotting profile will be shared with the patient, the patients clinical team or GP in the case of the volunteer limb.

It will be left to the investigator's clinical judgment whether or not an AE is of sufficient severity to require the participant's removal from treatment (see section 7.7). A participant may also voluntarily withdraw from treatment due to what he or she perceives as an intolerable AE. If either of these occurs, the participant must undergo an end of study assessment and be given appropriate care under medical supervision until symptoms cease or the condition becomes stable.

The severity of events will be assessed on the following scale: 1 = mild, 2 = moderate, 3 = severe.

The relationship of AEs to the study will be assessed by a medically qualified investigator.

10.3 Reporting Procedures for Serious Adverse Events

All SAEs, except those expected ones defined in section 10.1.5 that do not require immediate reporting (see 10.1.5), must be reported to the Sponsor within one working day of discovery or notification of the event. The Sponsor will perform an initial check of the information and ensure that it is reviewed at the next R&I Management meeting. All SAE information must be recorded on an SAE form and sent to the Sponsor using the appropriate reporting form and the contact details on there. Additional information received for a case (follow-up or corrections to the original case) needs to be detailed on a new SAE form which must be sent to the Sponsor using the appropriate reporting form and the contact details on there.

The Sponsor will report all SUSARs to the Research Ethics Committee concerned. Fatal or life-threatening SUSARs must be reported within 7 days and all other SUSARs within 15 days. The CI will inform all investigators concerned of relevant information about SUSARs that could adversely affect the safety of participants.

In addition to the expedited reporting above, the CI shall submit once a year throughout the study or on request an Annual Report to the Ethics Committee which lists all SAEs / SUSARs that have occurred during the preceeding 12 months.

11. STATISTICS

11.1 Description of Statistical Methods

The primary outcome for this study is change in time to initiate clot formation, as measured by the R time using thromboelastography. As subjects are to be exposed to both study limbs the data collected will be analysed using paired tests for statistical differences. The variation is different for non-pregnant and post natal subjects, therefore we have calculated sample size for each of the two study populations separately. As the sample size is small it is unlikely that the results will be normally distributed, therefore non-parametric test will be employed. As the sample sizes are small we do not anticipate needing any interim analysis. There is no plan to compare non-pregnant and post natal groups, only the within group differnces.

11.2 The Number of Participants

We have used established reference ranges for TEG pqarameters in pregnant and non-pregnant populations to allow us to calculate an estimated standard deviation of the difference in R times for paired data to inform our power calculation. To see a 25% reduction in R time, with an alpha error of 5% and a beta error of 20% (power 80%) we require 10 non-pregnant subjects and 30 post natal participants.

11.3 The Level of Statistical Significance

Alpha error of 5%, beta error 20%, power 80%

11.4 Criteria for the Termination of the Trial.

The trial will be terminated when 10 non-pregnant volunteers and 30 post natal volunteers have completed the study protocol.

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

The trial will be terminated once we have 40 complete data sets. There will be no unused data sets. Spurious data will be excluded from analysis and will require additional recruitment.

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

We don't anticipate any variation from our statistical plan, however this would be explained in the final report if required.

11.7 Inclusion in Analysis

All evaluable patient data will be analysed to a total of 10 non-pregnant and 30 post natal participants have completed the intervention arms of the study.

12. DIRECT ACCESS TO SOURCE DATA/DOCUMENTS

Direct access will be granted to authorised representatives from the sponsor, host institution and the regulatory authorities to permit trial-related monitoring, audits and inspections.

13. QUALITY CONTROL AND QUALITY ASSURANCE PROCEDURES

The study will be conducted in accordance with the current approved protocol, ICH GCP, relevant regulations and standard operating procedures.

Regular monitoring will be performed according to ICH GCP. Data will be evaluated for compliance with the protocol and accuracy in relation to source documents. Following written standard operating procedures, the monitors will verify that the clinical trial is conducted and data are generated, documented and reported in compliance with the protocol, GCP and the applicable regulatory requirements.

14. CODES OF PRACTICE AND REGULATIONS

14.1 Ethics
Describe ethical considerations relating to the trial. Include general and study specific ethics considerations.

14.2 Sponsor Standard Operating Procedures
All relevant Sponsor SOPs will be followed to ensure that this study complies with all relevant legislation and guidelines

14.3 Declaration of Helsinki
The Investigator will ensure that this study is conducted in full conformity with the current revision of the Declaration of Helsinki (last amended October 2000, with additional footnotes added 2002 and 2004).

14.4 ICH Guidelines for Good Clinical Practice
The Investigator will ensure that this study is conducted in full conformity with relevant regulations and with the ICH Guidelines for Good Clinical Practice (CPMP/ICH/135/95) July 1996.

14.5 Approvals
Once Sponsor authorisation has been confirmed, the protocol, informed consent form, participant information sheet and any proposed advertising material will be submitted to an appropriate Research Ethics Committee (REC), regulatory authorities (MHRA in the UK), and host institution(s) for written approval.
Once Sponsor authorisation has been confirmed, the Investigator will submit and, where necessary, obtain approval from the above parties for all substantial amendments to the original approved documents.

14.6 Participant Confidentiality
The trial staff will ensure that the participants' anonymity is maintained. The participants will be identified only by initials and a participants ID number on the CRF and any electronic database. All documents will be stored securely and only accessible by trial staff and authorised personnel. The study will comply with the Data Protection Act which requires data to be anonymised as soon as it is practical to do so.

14.7 Other Ethical Considerations
Not Applicable

15. DATA HANDLING AND RECORD KEEPING

Describe method of data entry/management

All study data will be entered on to SPSS version22 for Mac OS.
The participants will be identified by a study specific participants number in a database. The name and any other identifying detail will NOT be included in any study data electronic file.

16. STUDY GOVERNANCE

16.1 Trial Steering Committee (TSC)

The Trial Steering Committee will include Dr Paul Sharpe and Dr Asif Mahmood. They will meet on multiple occasions throughout the course of the study. A minimum of once every 4 months.

16.2 Data Safety Monitoring Committee (DSMC)

The Data Safety Monitoring Committee will include Dr Paul Sharpe and Dr Asif Mahmood. They will meet on multiple occasions throughout the course of the study. A minimum of once every 4 months.

17. FINANCING AND INSURANCE

Research Costs – We will be applying for a Obstetric Anaesthetists' Association Grant

Cost of single tests: FBC: £6.66, INR/APTT: £7.88, Fibrinogen: £7.94, Thromboelastography: £8.20

TEG Quality Control Check: £16.50 max 4 required (Total cost £66)

Administration fee for laboratory: £200

Pregnant Participants: 38 INR/APTT (£299.44) and 38 fibrinogen: (£301.72)

Post Natal Participants: 12 FBC (£79.92), 12 INR/APTT (£94.56), 12 fibrinogen (£95.28)

Total 100 Thromboelastography (£820)

Total Cost: £1956.92

The equipment (one-way non-luer filter valve needle) will be provided free of charge by Intervene, the company that produces them.

- ***NHS Treatment Costs*** – *not applicable*
- ***NHS Support Costs*** – *not applicable*

18. PUBLICATION POLICY

Any publication will include authors Dr Asif Mahmood and Dr Paul Sharpe. We will acknowledge the funding acquired from an Obstetric Anaesthetists' Association Grant. The results of the study will be disseminated to publications aimed at obstetric anaesthesia. The results will be presented to the manufacturers of the new non-Luer one-way filter needle, 'Intervene'.

19. REFERENCES

(1) Recommendations to prevent administration errors with Velcade (bortezomib). EMA/34910/2012. European Medicines Agency. http://www.ema.europa.eu/docs/en_GB/document_library/Medicine_QA/2012/01/WC500120701.pdf (accessed 10/10/2015).

(2) National Patient Safety Agency Patient Safety Alert. Safer spinal, epidural and regional anaesthesia devices – Part A. October 2009. http://www.nrls.npsa.nhs.uk/resources/patient-safety- topics/medical-device-equipment/?entryid45=94529 (accessed 10/10/2015).

20. APPENDIX A: STUDY FLOWCHART

Tasks	Duration	Sept 2016 to Dec 2017	Jan 2017 to August 2017	Jan 2017 To August 2017	September 2017 to October 2017
Setting up project, ethics approval, liaising with recruiting centres	4 months				
Identification and recruitment	8 months				
Phlebotomy and TEG analysis, data collection and data analysis	8 months				
Paper preparation and presentation of the findings	2 months				