STUDY PROTOCOL

PROTOCOL TITLE:
A RANDOMISED-CONTROLLED TRIAL ON THE EFFECTIVENESS OF TOPICAL SESAME OIL IN PREVENTING PHLEBITIS AT INTRAVENOUS CANNULA SITES IN ADULT PATIENTS

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1

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PROTOCOL SIGNATURE PAGE

Protocol Title: A Randomised- controlled trial on the effectiveness of topical sesame oil in preventing phlebitis at intravenous cannula sites in adult patients

Protocol Number: 1

Protocol Version/ Date: 4/ 09 January 2023

Sponsor Name: National Heart Centre of Singapore

Declaration of Investigator

I confirm that I have read the above-mentioned protocol and its attachments. I agree to conduct the described study in compliance with all stipulations of the protocol, regulations and ICH E6 Guideline for Good Clinical Practice (GCP).

Principal Investigator Name: Tan Jia Xing Jasmine

Principal Investigator Signature: 

Date: 09 January 2023

1. BACKGROUND AND RATIONALE

The insertion of peripheral intravenous (IV) cannulas for the administration of medications, fluid and blood products is commonplace in hospitals today (1). Peripheral IV cannulas are minimally invasive and offer physicians and nurses the convenience of administering IV therapy as necessary (2). However, despite the many therapeutic benefits that IV cannulas offer, they can lead to complications such as infiltration, extravasation, bleeding, bruising, infection and phlebitis (2, 3). Of all the aforementioned complications, phlebitis is one of the most common and has been found to affect 5 to 75% of patients undergoing IV therapy in hospitals (4, 5).

Phlebitis refers to the inflammation of the venous tract and its surrounding tissues (5, 6). It can be caused by mechanical trauma, chemical irritation or infectious microorganisms (5, 7). Mechanical phlebitis results when the inserted IV cannula moves within the vein, causing friction and subsequently inflammation (8). Chemical phlebitis is caused by solutions that are hypertonic (osmolality > 500mOsm/litre) or are too acidic or alkali in nature (pH < 5 or pH > 9) (9). Infective phlebitis results when bacteria penetrate the vein, from the time of insertion or the initiation of IV therapy, and colonise the site, leading to inflammation and in serious cases, systemic sepsis (10).

The signs and symptoms associated with phlebitis include varying degrees of one or more of the following: erythema, pain, oedema, warmth, palpable venous cords, and purulent drainage (4). Using the VIP scale as modified by Jackson (4), the phlebitis grading can range from 0, indicating no signs of phlebitis, to 5, with symptoms of redness, pyrexia, a palpable venous cord and purulent drainage (4).

Although phlebitis is not a fatal diagnosis, it may cause permanent damage to the venous endothelium, thereby reducing the possibility of administering IV therapy via the damaged vein in future (11). It has also been found that patients diagnosed with phlebitis after their first IV cannula insertion were 5.1 times more likely to develop post-infusion phlebitis with subsequent cannulations (12). The development of phlebitis often leads to the early withdrawal and reinsertion of the peripheral IV cannula (6). It can cause a disruption in IV therapy, added stress and discomfort to patients, lengthened hospital stays (13), and an increase in healthcare costs (14). As such, the development of a protocol that aids in preventing the exacerbation and reducing the severity of phlebitis in hospitals, is of utmost importance.

While several topical and systemic therapies have been proposed in literature throughout the years, there is a lack of conclusive evidence on the optimal management of phlebitis in clinical practice (15). In all three causes of phlebitis (mechanical, chemical, infective), inflammation of the venous tract and its surrounding tissues will lead to the development and progression of phlebitis-related symptoms at the IV cannula site. As such, the use of anti-inflammatory agents in preventing and treating phlebitis have been widely studied and recommended (7, 16-18).

Oral and topical non-steroidal anti-inflammatory drugs (NSAIDs) have been found to be effective in the prevention (16, 17) and treatment of phlebitis (18, 19). Cokmez et al. (17) observed that the incidence of phlebitis was halved with the daily use of a topical NSAID gel at the cannula site (17). Similar findings were obtained in a study by Babaieasl et al. (16) where the use of topical Diclofenac, produced significantly lower incidences of phlebitis as compared to patients who received EMLA or a placebo. In another study,

both topical and oral Diclofenac were found to be more effective in improving the clinical signs and symptoms of phlebitis when compared against patients who received no intervention (18).

Local inflammation and septicaemia at IV cannula sites have also been found to be correlated with positive cultures of the IV cannulas post removal (17, 20). This is largely attributed to poor practices during IV cannula insertion and drug administration, which increase the risk of bacteria introduction into the vein (10, 16, 21). The use of topical antibiotic and antiseptic agents have thus been advocated for the treatment of phlebitis (22). Antibiotics are however not recommended for local wound therapy, because of limitations in effectiveness and the potential contribution to the formation of antibiotic-resistant strains (23). Antiseptic or plant-based agents like iodine and sesame oil, on the contrary, possess broad spectrum antimicrobial effects, are effective on biofilms, possess anti-inflammatory properties and promote wound healing, without any risk of contributing to bacterial resistance (10, 23, 24, 25, 26).

To date, there have been three studies conducted to evaluate the effectiveness of Povidone-iodine in preventing phlebitis (27-29). In 1980, Noble et al. (27) tested the effectiveness of a daily Povidone-iodine 0.5% dry powder application at IV cannula sites, in reducing phlebitis. Two studies by Thompson et al (28, 29) likewise studied the effectiveness of Povidone-iodine at preventing phlebitis at IV cannula sites, when applied once immediately upon insertion. All three studies (27, 28, 29) found that iodine was not effective in preventing the incidence of phlebitis or reducing the incidence of cannula colonisation (27).

Sesame oil however, has been found to be effective in preventing phlebitis at IV cannula sites in several studies (30, 31, 32). Nekuzad et al. (30) conducted a study on patients undergoing chemotherapy, and found that phlebitis was eight times more frequent in the control group, where no topical agent was applied, than in the intervention group, where topical sesame oil was applied twice a day. Another study by Bagheri et al. (31) found that sesame oil was effective at reducing the prevalence and severity of phlebitis, for patients on IV Amiodarone. 78% of patients in the control group developed phlebitis with the application of a placebo, as compared to 39% of patients in the treatment group with the application of sesame oil at the IV cannula site (31). Of these, 6%, 28% and 44% of patients in the control group developed grade 2, 3 and 4 phlebitis respectively, while 17% and 22% of the patients in the treatment group developed grade 2 and 3 phlebitis respectively. The third study by Pan et al. (32) compared the effectiveness of sesame oil, Vitamin E and Sanyrene oil on preventing phlebitis. It was found that only 37% of patients who had sesame oil applied at the IV cannula site had developed phlebitis, as compared to 43% of patients who received Vitamin E, and 76% of patients who received Sanyrene oil. Sesame oil was thus found to be twice as effective at preventing phlebitis at IV cannula sites, as compared to Sanyrene oil (32).

Though there are no topical agents to date that have been proven to be effective at completely preventing or treating phlebitis, the evidence on sesame oil leads us to believe that it is a safe, readily available, low-cost, and effective agent, that can be used to prevent and reduce the severity of phlebitis at IV cannula sites.

2. HYPOTHESIS AND OBJECTIVES

Hypothesis:

The application of topical sesame oil will be effective at preventing phlebitis at peripheral IV cannula sites in adult patients within the cardiovascular and cardiothoracic department of a tertiary hospital.

Aim of study:

• To determine the effectiveness of topical sesame oil in preventing phlebitis at peripheral IV cannula sites in adult patients within a cardiovascular and cardiothoracic department of a tertiary hospital.

Objectives:

• To measure the incidence and severity of phlebitis at 12 hour intervals, at peripheral IV cannula sites, in adult patients within a cardiovascular and cardiothoracic department of a tertiary hospital.

• To measure the incidence and severity of phlebitis 12 hourly for up to 24 hours post IV cannula removal.

• To compare the incidence and severity of phlebitis at 12 hour intervals, between patients who received topical sesame oil and patients who received topical liquid paraffin oil at the IV cannula site, in adult patients within a cardiovascular and cardiothoracic department of a tertiary hospital.

3. EXPECTED RISK AND BENEFITS

Potential risks:

- Skin irritation from allergic reactions to sesame oil or liquid paraffin oil

Potential benefits:

- Reduced risk in developing phlebitis at the IV cannula site due to the topical application of sesame oil. (direct)

- Gained knowledge with regards to phlebitis risk factors, signs and symptoms and consequences. (Indirect)

4. STUDY POPULATION

4.1. List the number and nature of subjects to be enrolled.

650 adult patients between the age of 21 to 80, and from inpatient wards within The National Heart Centre of Singapore will be recruited, regardless of ethnicity or gender.

4.2. Criteria for Recruitment and Recruitment Process

All newly admitted patients with an existing IV cannula will be approached after being admitted into an inpatient ward. This will take place within 12 hours of the IV cannula insertion. They will not be approached if in distress, drowsy or immediately prior to a surgical procedure. The IV cannula will be tested for patency, and assessed for redness, swelling, pain, a palpable venous cord or pyrexia. If any of these symptoms are present, or if the IV cannula is not patent, the recruitment will be terminated.

4.3. Inclusion Criteria

- Age 21-80
- Patients must speak and understand either English or Mandarin
- Patients who possess a peripheral IV cannula
- IV cannula must have been inserted for less than 12 hours
- IV cannula must be on an upper extremity
- IV cannula must be patent
- IV cannula sites must show no signs of redness, swelling, pain, a palpable venous cord or pyrexia
- Patient must be admitted to a cardiology ward in the National Heart Centre Singapore

4.4. Exclusion Criteria

- Patients who do not speak or understand either English or Mandarin
- Patients with venous insufficiency
- Patients with coagulopathies
- Patients with cognitive or sensory impairments that would inhibit their ability to rate their pain via a Numerical Rating Scale (NRS)
- Patients who are receiving medications that might interfere with timely reporting of adverse events (eg. medications that cause severe drowsiness)
- Patients who report allergies to sesame or liquid paraffin oil
- IV cannulas that were inserted and used for resuscitation
- Patients with existing skin conditions that cause their skin to be red or swollen and might affect the investigators ability to assess for phlebitis
- Patients who possess more than one peripheral IV cannula will only be included in the study once. All subsequent IV cannula insertions will be excluded.

5. STUDY DESIGN AND PROCEDURES/METHODOLOGY

A physical copy of the informed consent form will be provided to the inpatient wards included in the study. Ward staff will also be briefed verbally on the research details, data collection methods and safety information of the study.

Ward nurses will notify investigators, of any patient who has been admitted to the ward with an existing IV cannula, or has had a new IV cannula set in the last 12 hours. The investigators will review the patient's medical history to assess for venous insufficiencies, coagulation disorders, cognitive or sensory impairments, and medications that might interfere with the timely reporting of adverse events. Patients will be approached after being admitted into an inpatient ward, within 12 hours of the IV cannula insertion. They will not be approached if in distress, drowsy or immediately prior to a surgical procedure. The investigator will access the patency of the peripheral IV cannula, and the IV cannula site for signs of redness, swelling, pain, a palpable venous cord or pyrexia. If the patient meets the criteria for inclusion, informed consent will be taken at the patient's bedside, in the presence of a witness, with drawn curtains to maintain privacy, reduce distractions and prevent undue influence from other individuals within the ward. The participant will be given time to consider their participation before giving their response to the investigator at the bedside. If they require more time for consideration, the investigator will leave the bedside and contact them again within 12 hours of IV cannula insertion to confirm recruitment. The investigator will emphasise the patient's right to make their own decision with regards to participating in the study. All details of the study and risks and benefits will be provided without any pressure on the patient to be recruited.

The patient will then be randomly allocated to the experimental or control group with the use of a randomisation software (MS excel). 5 drops/0.25mls of 100% sesame oil or mineral oil will be applied to the IV cannula site, from 3cm above the insertion point to 10cm along the vein, with a width of 2cm on either side (Appendix A). There will be no massaging or manipulation of the infusion site during application.

Demographic and clinical data will be recorded into a table. The patient will be instructed not to wash or wipe the topical agent off. The time and date of the start of treatment applied and subsequent treatments at 12 hour intervals will be documented. At the start of the study and at each 12 hour interval, the investigator will observe for signs of phlebitis using the Visual Infusion Phlebitis scoring tool [Appendix 2], before application of the next treatment. The study investigators will be the only ones applying the treatment/control and completing the data collection form [Appendix 3] every 12 hours. Patient identifiers (name and NRIC) will be verified before every application of the treatment/control and the completion of the data collection form.

Application of the treatment or control will be made every 12 hours for up to 72 hours, where the IV cannula will then be removed according to hospital guidelines. The IV cannula site will be observed, every 12 hours for up to 24 hours post IV cannula removal, for phlebitis or complications.

Patients will be withdrawn from the study the moment they show signs of adverse reactions from the topical treatment or control.

Participants will be involved in the study for a maximum of 96 hours. If the IV cannula is removed accidentally or not due to phlebitis before the 72-hour period is up, re-insertion of a new cannula and re-application of oils will not be done on a new site. The patient's IV cannula site will continue to be observed for 24 hours at 12-hour intervals after cannula removal. The partial data will be kept and analysed. If the patient is discharged before the 96 hour observation period is up, the 24 hour post-removal observation will continue to be carried out at 12 hour intervals, via phone call or video call. The patients' phone numbers will be obtained during the informed consent process, only for follow up purposes.

The application of either sesame oil or liquid paraffin oil is not part of the routine procedures or standard of care in the ward, and will only be applied for the purpose of this research. Both the sesame oil and liquid paraffin oil are marketed products and will be used as per label.

The study is estimated to continue for two years, commencing in February 2022 and ending in December 2023.

At no point of the study will any audio or video recording take place.

All hardcopy research data will be stored in in a locked cupboard with lock and key access within the National Heart Centre, Singapore. All soft copies will be stored in a password protected Laptop belonging to the principal investigator. Only the principal investigator will have access to the research data. All other members of the research team will access the data through the principal investigator. The physical research data will be kept under lock and key for 7 years after the completion of the research study or date of publication of the research using the research data, whichever is later. After which, all data will be destroyed. Hardcopies will be shredded and soft copies will be deleted.

Subjects may withdraw voluntarily from participation in the study at any time. Subjects may also withdraw voluntarily from receiving the study intervention for any reason. Upon withdrawal, IV cannula sites will continue to be observed for 24 hours at 12-hour intervals for potential reactions to the oils or signs of phlebitis. If there are any adverse reactions to the oils or signs of phlebitis during the 24-hour observation period, the patient will be referred to the attending physician and medical treatment will be rendered. The patient will continue to receive follow-up and medical treatment until symptoms have resolved.

The study may be discontinued at any time, if safety issues arise. If the risks to participants unexpectedly outweigh the benefits due to unexpected severe adverse events due to the application of the treatment or control oils, the study may then be suspended until the risk-benefit ratio is re-evaluated.

6. SAFETY MEASUREMENTS

6.1. Definitions

Serious adverse event (SAE) in relation to human biomedical research, means any untoward medical occurrence as a result of any human biomedical research which:

- results in or contributes to death
- is life-threatening
- requires in-patient hospitalisation or prolongation of existing hospitalisation
- results in or contributes to persistent or significant disability/incapacity or
- results in or contributes to a congenital anomaly/birth defect
- results in such other events as may be prescribed

Adverse event (AE) in relation to human biomedical research means any untoward medical occurrence as a result of any human biomedical research which is NOT serious. Adverse event can be any unfavourable and unintended sign (including an abnormal laboratory finding), symptom, or disease possibly/ probably/ definitely associated with the participant in the human biomedical research.

6.2. Collecting, Recording and Reporting of Serious Adverse Events (SAEs) to CIRB

Only related SAEs (definitely/ probably/ possibly) will be reported to CIRB. Related means there is a reasonable possibility that the event may have been caused by participation in the research. Please refer to the CIRB website for more information on Reporting Requirement and Timeline for Serious Adverse Events.

The investigator is responsible for informing CIRB after first knowledge that the case qualifies for reporting. Follow-up information will be actively sought and submitted as it becomes available.

Related AEs will not be reported to CIRB. However, the investigator is responsible to keep record of such AEs cases at the Study Site File.

6.3. Safety Monitoring Plan

All participants will have their IV cannula sites monitored for adverse reactions to the application of the treatment or control oils, and for signs of phlebitis every 12 hours. Participants will also be educated on the signs of allergies or sensitivities to the oils, and the signs of phlebitis. They will be advised to contact the investigators immediately upon detection of adverse reactions or phlebitis. The moment they experience any adverse reactions to the topical oils, they will be withdrawn from the study. A referral will be made to the attending physician in the ward, and treatment will be rendered. The participant will continue to receive follow up, observations and treatment until the reactions or symptoms resolve.

All hardcopy research data will be stored in in a locked cupboard with lock and key access within the National Heart Centre, Singapore. All soft copies will be stored in a password protected Laptop belonging to the principal investigator. Only the principal investigator will have access to the research data. All other members of the research team will access the data through the principal investigator. The physical research data will be kept under lock and key for 7 years after the completion of the research study or date of publication of the research using the research data, whichever is later. After which, all data will be destroyed. Hardcopies will be shredded and soft copies will be deleted.

6.4. Complaint Handling

The investigators in the study will respond to and try to resolve any study-related concern or complaint that is received. If a significant complaint or concern arises, in that a participant's safety, rights or welfare may be severely impacted, it will be reported to the Singhealth Centralised Institutional Review Board (IRB).

7. DATA ANALYSIS

7.1. Data Quality Assurance

Study investigators will be the only ones applying the treatment/control and completing the data collection form every 12 hours. Patient identifiers (name and NRIC) will be verified before every application of the treatment/control and the completion of the data collection form. The principal investigator will perform weekly checks and random audits to ensure that all informed consent forms and data collection forms are completed accurately.

7.2. Data Entry and Storage

Informed consent forms will be on paper. Data will be both on paper, and entered and stored electronically. The physical research data will be kept under lock and key for 7 years after the completion of the research study or date of publication of the research using the research data, whichever is later. After which, all data will be destroyed. Hardcopies will be shredded and soft copies will be deleted.

8. SAMPLE SIZE AND STATISTICAL METHODS

8.1. Determination of Sample Size

Using a power analysis of 20% and a difference of 35%, a sample size of 44 participants is required if subgroup analysis is not required. We then rounded it up to 100 to account for an attrition rate of 5%.

Data will be analysed with the Statistical Package for Social Science (SPSS) software program (v. 28) using descriptive statistics such as relative and absolute frequencies, mean and standard deviation, and inferential statistics such as Chi-square, independent t-test and Hazard ratio.

8.2. Statistical and Analytical Plans

a. General Considerations

The distribution and dispersion of the data will be examined through descriptive numerical summaries and graphical tools such as scatter plots, via SPSS. The data will then be analysed using descriptive statistics such as relative and absolute frequencies, mean and standard deviation, and inferential statistics such as Chi-square, independent t-test and Hazard ratio.

As missing data can potentially spoil or invalidate a study, we will spare no effort in minimising incomplete or missing data. All data will be carefully inspected to identify missing items and outliers. In the analysis of incomplete data, we will consult with a biostatistician regarding the use of incomplete-data analysis strategies that will allow us to utilise the available information effectively.

b. Safety Analyses

All adverse events, such as the development of allergic reactions to the oils, leading to the participant's withdrawal from the study will be collected and tabulated. Incidences and severity of phlebitis experienced during the course of the study will also be collected and tabulated. All adverse reactions and phlebitis incidences will be tabulated for both the treatment and control group. The extent and severity of symptoms will also be documented. For phlebitis incidences, the severity will be assessed with the Visual Infusion Phlebitis (VIP) scoring tool [Appendix 2]. The number of adverse reactions will be summarised for both the treatment and control group. Frequency counts and percentages will be calculated and reported.

c. Interim Analyses

We will compare treatment groups on descriptive and clinical characteristics at baseline to ensure that randomisation has succeeded. SPSS will be used for group comparisons, descriptive calculations and conditional regression modelling. We will examine the distributions of all important variables at baseline and at the end of the data collection period, to assess for covariate imbalance. Formal statistical methods to test for selection bias will be used.

9. DIRECT ACCESS TO SOURCE DATA/DOCUMENTS

The investigators and the National Heart Centre of Singapore will permit study-related monitoring, audits and/or IRB review and regulatory inspection(s), providing direct access to source data/document. All physical data required will be accessed through the primary investigator.

10. QUALITY CONTROL AND QUALITY ASSURANCE

The primary investigator will review all physical data and conduct random audits to assess for adherence with the protocol. She will also assess all data weekly for accuracy and completeness.

11. ETHICAL CONSIDERATIONS

This study will be conducted in accordance with the ethical principles that have their origin in the Declaration of Helsinki and that are consistent with the Good Clinical Practice and the applicable regulatory requirements.

This final Study Protocol, including the final version of the Participant Information and Consent Form, must be approved in writing by the Centralised Institutional Review Board (CIRB), prior to enrolment of any patient into the study.

The principal investigator is responsible for informing the CIRB of any amendments to the protocol or other study-related documents, as per local requirement.

11.1. Informed Consent

Informed consent will be taken at the patient's bedside by an investigator of the study, in the presence of a witness, with drawn curtains to maintain privacy, reduce distractions and prevent undue influence from other individuals within the ward. The participant will be given time to consider their participation before giving their response to the investigator at the bedside. If they require more time for consideration, the investigator will leave the bedside and contact them again within 12 hours of IV cannula insertion to confirm recruitment. The investigator will emphasise the patient's right to make their own decision with regards to participating in the study. All details of the study and risks and benefits will be provided without any pressure on the patient to be recruited.

11.2. Confidentiality of Data and Patient Records

All hardcopy data collected will be stored in a locked cabinet within the National Heart Centre of Singapore. Only the principal investigator will have access to the locked cabinet. Investigators may access the data via the principal investigator. Electronic data will be stored on a password protected laptop belonging to the principal investigator, and access to the data will be restricted to the investigators of this research study.

12. PUBLICATIONS

All investigators involved in this study will be given authorship for scientific publications. Other persons who may have contributed in some capacity, such as those who may have provided advice with regards to the research, or assisted with data analysis, will be acknowledged with their approval. The contributions of each author will be reviewed thoroughly to ensure that they meet the criteria of authorship for the respective journals. Should a journal require assurances that all non-author contributions agree to being named in the acknowledgements, or that no non-author contributors have been omitted from the acknowledgements, signed agreements will be provided on request.

13. RETENTION OF STUDY DOCUMENTS

Records for all participants, including CRFs, all source documentation (containing evidence to study eligibility, history and physical findings, etc.) as well as IRB records and other regulatory documentation will be retained by the PI in a secure storage facility. The records will be accessible for inspection and copying by authorized authorities. The physical research data will be kept under lock and key for 7 years after the completion of the research study or date of publication of the research using the research data, whichever is later. After which, all data will be destroyed. Hardcopies will be shredded and soft copies will be deleted.

14. FUNDING and INSURANCE

Grant

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iii. Amount:	$20090
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List of Attachments

Appendix 1 References

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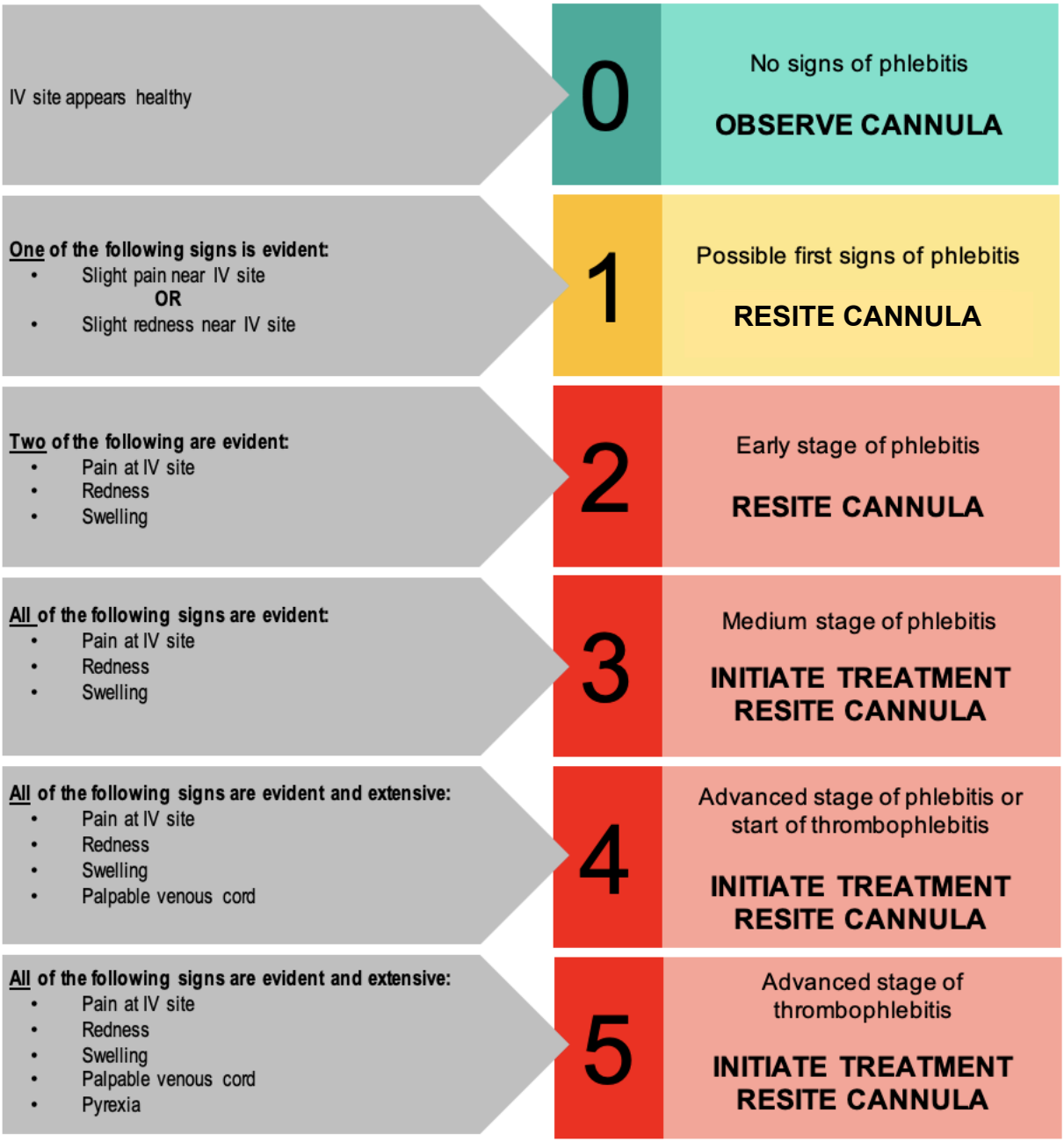
Appendix 2 ***Visual Infusion Phlebitis Scoring Tool***

Visual Infusion Phlebitis Scoring Tool



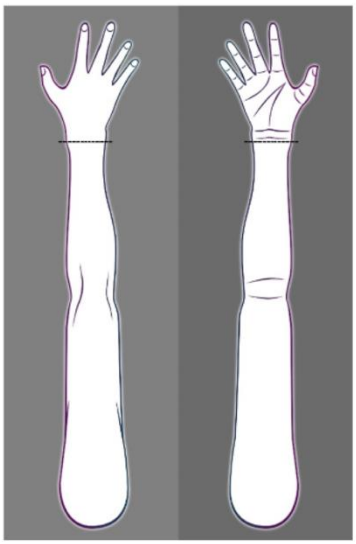
Tool Developed by Andrew Jackson – Consultant Nurse
Intravenous Therapy & Care, The Rotherham NHS Foundation

This tool was modified for use in this study.

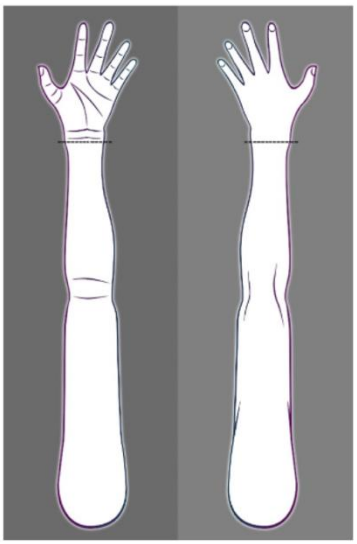
Appendix 3 Data Collection Form

Data Collection Form

Right arm



Left arm



Mark IV Cannula with an "X"

Participant No:_____

Age: _____

Gender: Male / Female

Race: _____

Medications

Oral / IV anticoagulants (if any):

IV Insertion

Date: _____ Time:_____

Size: _____

Site: _____

Inserted at : _____(Dept)

IV Removal

Date: _____ Time: _____

Reason: _____

IV plug assessment	Insertion		Day 1		Day 2		Day 3 (Removal)		Post Removal
	Date		Date		Date		Date		Date
	0 hrs	12 hrs	24 hrs	36 hrs	48 hrs	60hrs	72hrs (Removal)	12 hrs post removal	24 hrs post removal
VIP Score (0-5)									
Treatment/ Control applied (Please tick)									
Current drug infusion									
Other drugs administered via this IV Cannula in the past 12hrs									
Initials									