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| **Title** | **The efficacy and acceptability of low molecular weight heparin (LMWH) administration via a subcutaneous catheter vs subcutaneous injections in both prophylactic and therapeutic settings** |
| **Short title** | **Butterfly** |
| **Protocol Number** | 4 |
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# **Introduction and background**

Low molecular weight heparins such as enoxaparin are frequently for venous thromboembolism (VTE) prophylaxis and treatment in a wide range of patient populations. Long term therapy with daily or twice-daily subcutaneous injections carries significant morbidity, which is particularly relevant in patient groups such as malignancy and pregnancy. Alternate methods of administration such as via a subcutaneous catheter have been trialled in the paediatric setting, and with unfractionated heparin in pregnancy, and offer a potential to reduce the burden of injections, and improve patient quality of life and acceptance of therapy in a multitude of clinical settings including pregnancy and cancer patients[1, 2].

Venous thromboembolic disease poses a significant morbidity and mortality risk across multiple settings, including hospital inpatients, pregnancy, and those with active malignancy. VTE rates are up to 130 times higher in hospitalised patients vs community, pulmonary embolism (PE) being the cause death in up to 1.3% of hospitalised medical patients, with 45% of VTE events occur in the 3 months post discharge[3]. Reported rates of VTE in the community range from 57 to 131 per 100,000 persons, with 28 day case fatality rate of 5% for unprovoked events, 7% for provoked, and 25% in those with active malignancy[4]. In Australia, the annual incidence is estimated at 0.83 per 1000 population, with an overall lifetime risk of 8%, with an estimated economic cost of $1.5 million per person[5]. Conditions such as pregnancy increase the risk of thrombosis, and PE remains a leading direct cause of maternal death[6]. Low molecular weight heparin (LMWH) reduces VTE risk in medical and surgical patients by 60% and 70% respectively, with some studies finding up to 88% risk reduction in the obstetric setting[6-11].

Enoxaparin is a low molecular weight heparin (LMWH) which is widely used in Australia for pharmacologic VTE prophylaxis in hospital inpatients, as well as being the primary LMWH used as parenteral therapy in the outpatient setting [12]. Historical studies have established enoxaparin and other low molecular weight heparins as both safe and effective in prevention and treatment of venous thromboembolism as compared to heparin[13-15]. The predictable pharmacokinetic profile make them easier to use clinically, and minimise the need to monitor drug levels in the majority of patients [10, 12, 16]. As such, there are no clear guidelines on monitoring in the prophylactic setting, though certain patient subsets have been postulated to warrant closer monitoring, including post-surgical patients, obesity (body mass index (BMI) >50kg/m2, renal impairment with CrCl<30mL/min, and pregnancy) [16-19]. Target anti-factor-Xa (anti-Xa) levels in the prophylactic setting have a wide range of definitions, predominantly ranging from 0.2-0.5[20]. Data in the obese population are more limited, however a range of 0.2-0.4 or 0.5 appears consistent from the available literature[20]. Regarding therapeutic dosing and anti-Xa levels with twice-daily dosing, accepted levels range from 0.5-1.0, however, an Australian study demonstrated that among both obese and non-obese patients, peak anti-Xa levels ranged up to 1.2 in a significant proportion of patients without any evidence of increased bleeding[20, 21].

Enoxaparin therapy has been associated with local reactions, including bruising and pain at injection sites, which impacts tolerability of therapy, particularly for those requiring longer durations of treatment[22]. Several studies have assessed various methods of administration, including slower injection, which may reduce symptoms, however data are inconsistent[23, 24]. Broadhurst et al, 2020, performed a systematic review of subcutaneous catheters in adults, paediatrics and palliative populations for a range of interventions, including both medication administration and subcutaneous hydration, finding they were both efficacious and well-accepted in adults, with less clear signals in the paediatric and palliative settings[25]. Based on the pharmacokinetics and bioavailability of enoxaparin, there is unlikely to be a significant difference in bioavailability or peak anti-Xa effect between the two methods of administration, however the data supporting this are limited[31]. In the paediatric setting, use of both intravenous low-molecular-weight-heparin, and via a subcutaneous catheter, such as the Insuflon catheter, have been trialled with promising results[2, 26]. These subcutaneous catheters can remain in situ for 7-10 days, reducing the number of skin punctures required, and have been incorporated into local guidelines at several paediatric institutions[27, 28]. Several studies have further assessed the utility and clinical efficacy of a subcutaneous catheter for enoxaparin administration in the paediatric population, finding that it appears both safe and efficacious[2, 29]. In the adult population however, there is a paucity of published data. Anderson et al, 1993, trialled unfractionated heparin administration via subcutaneous catheter in pregnant women, finding that there was patient preference for using a subcutaneous catheter. There was no direct assessment of drug exposure using this method, and it was not incorporated into routine clinical practice, and in current practice unfractionated heparin is no longer routinely used[1]. A recent study evaluating anti-Xa levels in 21 patients receiving therapeutic anticoagulation compared subcutaneous catheter and subcutaneous injections, demonstrating that both methods resulted in similar peak anti-Xa levels, and that there was no significant drug accumulation via subcutaneous catheter administration. Of note, numbers were small and patients receiving prophylactic enoxaparin, those with renal impairment (CrCl<30mL/min) and pregnant patients were excluded[30]. This requires further evaluation with additional prospective data to support this alternative method of administration, and in a wider patient population, in both the prophylactic and therapeutic dosing settings.

## *Significance*

This trial will further evaluate the efficacy, safety and acceptability of low molecular weight heparin (LMWH) therapy administered by a subcutaneous catheter in adults. Based on existing data, it appears that subcutaneous catheters are an acceptable method of medication administration in adults and pregnant patients, and the limited data appear to show that LMWH can be safely administered via this route without compromising efficacy or safety. This study will aim to further support that LMWH can be administered via subcutaneous catheter, and broaden the included patient groups, including pregnancy and non-dialysis-dependent renal failure. Additionally, it will assess both prophylactic and therapeutic doses, which is of particular relevance in pregnant females requiring extended thromboprophylaxis throughout their pregnancy. This data has potential to change routine clinical practice and reduce morbidity, particularly in specific patient groups such pregnancy and those requiring long term therapy with enoxaparin. Regular monitoring of anti-Xa levels will not be required if this study demonstrates adequate similarity between both methods of administration.

# **Study Outline**

## *Objectives*

To demonstrate proof of concept that subcutaneous catheter administration of LMWH is a safe and acceptable alternative to subcutaneous injections in both the prophylactic and therapeutic settings.

## *Hypotheses*

1. That there is no clinically significant difference in peak anti-Xa levels between therapeutic LMWH administration via a subcutaneous catheter as compared to the current standard of care via subcutaneous injections
2. That there is no clinically significant difference in the proportion of patients within the expected anti-Xa range with prophylactic LMWH dosing via a subcutaneous catheter as compared to the current standard of care via subcutaneous injections
3. That subcutaneous catheter administration of LMWH is an acceptable alternative to subcutaneous injections

## *Design*

Prospective crossover study.

## *Patients*

Inpatients and outpatients in a tertiary public hospital. Patients ≥18 years requiring prophylactic or therapeutic anticoagulation with LMWH.

## *Therapy*

LMWH (therapeutic or prophylactic dose) in those with a medical indication to receive therapy.

## *Measurements*

Peak anti factor Xa (anti-Xa) levels measured on days 2 and 5+/-1 day or LMWH administration via both subcutaneous catheter and subcutaneous injections.

# **Methods**

## *Study design and population*

This is a prospective crossover study to assess efficacy of different dosing methods for LMWH conducted at Monash Health, a tertiary hospital, in the outpatient population. There will be 2 groups, one comprising those on prophylactic dose enoxaparin, and the other therapeutic dosing. The target patient populations will include pregnancy, active malignancy, and non-dialysis-dependent renal impairment. There will be no cut-off at either extreme of body weight. Patients must be stable on either prophylactic or therapeutic LMWH, and those with acute thrombosis within 4 weeks will not be included, though may be enrolled once they are clinically stable on therapy for more than 4 weeks, with a stable LMWH dose and have a documented anti-Xa level within target range on that dose.

## *Study definitions*

Prophylactic dose enoxaparin: 20mg (in renal failure defined as creatinine clearance, CrCl, <30mL/min), 40mg, or 60mg (as per local hospital guidelines in those with weight >150kg) administered once daily.

Therapeutic dose enoxaparin: 1mg/kg bd or once daily, and 1.5mg/kg daily, allowing for variation on this dosing as indicated based on anti-Xa levels.

Target aXa range (therapeutic dose enoxaparin): 0.5-1.2U/mL for those receiving 1mg daily or bd, and 0.8-1.5U/mL for those receiving 1.5mg/kg daily.

Expected aXa range (prophylactic dose enoxaparin): 0.15-0.5U/mL.

Prophylactic dose Dalteparin (Fragmin): 2500 -5000 IU once or twice daily.

Therapeutic dose Dalteparin: 100-120 IU/kg twice daily or as indicated by anti-Xa levels.

Target anti-Xa range (therapeutic dose dalteparin): 0.5-1.5 IU/mL.

Target anti-Xa range (prophylactic dose dalteparin): Poorly defined, 0.15-0.5 IU/mL will be used for this study.

## *Inclusion criteria*

* Adults ≥18 years and able to provide informed consent currently receiving either prophylactic or therapeutic dose enoxaparin
* Stable on current LMWH dose for at least one week
* Anticipated duration of LMWH therapy 4 weeks or longer
* Able to demonstrate competency at self-injecting via subcutaneous catheter
* No risk of major bleeding, as per clinician discretion
* Anti-Xa levels in those requiring them as per standard of care prior to commencement of study
	1. For those with dose titration or clinical concern, demonstration with at least 1 peak anti-Xa level within target range

## *Exclusion criteria*

* Unable to provide informed consent
* Dialysis dependent renal failure
* Inability to comply with testing and follow-up requirements
* Contraindication to anticoagulation therapy
* Acute thrombosis (within 4 weeks of diagnosis)
* Risk of major bleeding necessitating regular anti-Xa levels to assess anticoagulation dose
* Those requiring LMWH dose adjustment for off-target anti-Xa levels
* Upcoming surgery or procedure during the timeframe of the study
* Use of other anticoagulant therapies (see prohibited medications)

## *Trial medication*

Low molecular weight heparins such as enoxaparin and dalteparin are widely used anticoagulant therapies administered as a subcutaneous injection either once or twice per day to prevent or treat blood clots. Dosing is based on weight, clinical indication for therapy, and renal function. Common side effects include bruising, erythema and pain at injection sides, and increased risk of bleeding (both major and minor bleeding). Less common side effects include oedema, nausea, deranged liver function tests, fever, and confusion[34].

### *Concomitant medications*

* Prohibited medications
	1. Alternate anticoagulant therapy, including warfarin and direct oral anticoagulants.
	2. Mifepristone
	3. Vorapaxar
* Permitted medications which may increase bleeding risk
	1. Antiplatelet agents (aspirin, clopidogrel, ticagrelor) as clinically indicated
	2. Non-steroidal anti-inflammatory drugs (NSAIDs) if clinically indicated
	3. Other medications with potential antiplatelet or anticoagulant effect
		+ Fish oil/krill oil, vitamin E
		+ Bruton Tyrosine Kinase Inhibitors (e.g. ibrutinib, acalabrutinib, zanubrutinib)
		+ Selective Serotonin Reuptake Inhibitors (SSRIs)
		+ Alemtuzumab

Dasatinib

Potential side effects:

Very common (>10% or 1 in 10)

1. Increase in liver enzymes (commonly mild and self-limiting)

Common (1-10%, 1 in 100 to 1 in 10)

1. Anaemia (low red blood cells)
2. Nausea
3. Diarrhoea
4. Fever
5. Peripheral oedema
6. Low blood platelet count
7. Minor allergic reactions including itch, erythema
8. Injection site reactions (e.g. pain, bruising, minor bleeding at the injection site)
9. Confusion

Uncommon (<1%, less than 1 in 100)

1. Severe skin irritation at injection sites (rash, urticarial, pruritis)
2. Heparin induced thrombosis and thrombocytopenia (HITT)

Rare (<0.1%, less than 1 in 1000)

1. Severe injection site reactions (bullae, necrosis, alopecia)
2. Severe allergic reactions and anaphylaxis
3. Elevated blood potassium levels
4. Severe bleeding/haemorrhage

### *Safety during pregnancy*

Enoxaparin (Clexane) is widely used during pregnancy and while breastfeeding. It is classified as “class C”, meaning that there is no evidence in animal studies of harm to the baby.

Dalteparin (Fragmin) is less commonly used that enoxaparin, but is also classified as “class C” in pregnancy.

## *Patient recruitment*

Patients will be identified through clinicians in both public and private outpatient clinics, and inpatient wards, through the Monash Health network. Clinicians will be informed of the trial and supplied with contact details of the primary investigators for potential participants. The treating clinician will approach the potential participant with the trial information, and offer to supply the Patient Information and Consent Form, and contact the trial investigators to arrange an appointment to discuss the trial in further detail. This review will be scheduled in the Clinical Trials Unit with the trial investigators, and a follow-up visit for consent will be arranged for those wishing to proceed. Consent visits will be conducted face-to-face in the Clinical Trials Centre.

## *Study procedures*

The trial will have several sequential phases (outlined in Figure 1):

1. Phase A: administration LMWH via a subcutaneous catheter with anti-Xa assessments
2. A ”washout phase”, minimum 5 days of subcutaneous LMWH injections
3. Phase B: administration of LMWH via subcutaneous injections with further anti-Xa assessments
4. Extension phase (optional): participants will have the option to change back to a subcutaneous catheter for LMWH administration with intermittent anti-Xa assessments
5. Follow-up phase: telephone review out to 90 days post completion of Phase B where patients continue subcutaneous LMWH injections (no anti-Xa assessments required)

All consented and eligible patients will undergo a training session with nursing staff on using the subcutaneous catheters prior to commencing the study. Those able to both manage the catheter appropriately and administer the medication will then proceed to self-administer LMWH via this route. Basic dressings, alcohol sterilising wipes and sharps containers will be provided. Due to the negligible dead volume within the catheter, the insuflon does not need to be primed for the patient as per the product information.

Venepuncture will be performed by trained nursing or medical staff in the Monash Clinical Trials Centre to assess peak anti-Xa levels, collected 4 +/- 1 hours post dose, will be measured on days 2, 5 +/- 1, and day 7 if the catheter remains in at that time without complication in Phase A. Following the 5-7 days of administration via subcutaneous catheter, the patients will then switch to subcutaneous injections with a minimum 5 day “washout” period to allow for any potential accumulation of LMWH from the catheter site. Peak anti-Xa levels will then be collected on days 2, and day 5 +/-1 during Phase B, while the patient is receiving LMWH via subcutaneous injection. On site visits will coincide with venepuncture timepoints, at days 2, 5+/-1, 7 (where applicable), then at days 7 and 10 of subcutaneous LMWH injections (see table 1). Follow-up phone calls will be made on days 30, 60 and 90. See figure 1 for further detail.

During Phase A, if the catheter is dislodged, there will be a maximum of 1 replacement per patient, with anti-Xa testing restarting at day 1 on day of replacement. For patients receiving bd LMWH , they will have the option of a second catheter inserted from day 1 to alternate using the 2 catheters if they wish. If this is the preferred option the protocol will be updated accordingly. Indications for catheter removal will include patient request, evidence of infection, or significant bruising/haematoma at the site as per clinician discretion.

Once patients have completed Phase B, they will be given the option of continuing subcutaneous injections, or switching back to the subcutaneous catheter for ongoing LMWH administration. For participants wishing to continue with the subcutaneous catheter, safety will be determined by an independent clinician who is not affiliated with the study team. This will involve clinical review of the patient and associated anti-Xa results. If the patient is deemed safe to continue, they will have the subcutaneous catheters inserted at the Monash Clinical Trials Centre by trained nursing staff, with repeat anti-Xa assessments and independent clinician review on a 4-weekly basis. If after 4 weeks, the participant wishes to self-insert insuflon catheters ongoing, they will be shown by trials nursing staff how to manage this, and supplied with appropriate materials (insuflon catheters, sharps disposal containers, dressings and alcohol wipes. They will be supervised by trials nursing staff when self-inserting the insuflon for the first time, and able to contact trials nursing or medical staff if they have any issues. They may return to the trials nursing staff inserting the insuflon catheter if they prefer. The participant will have the option to continue with the subcutaneous catheter for up to 6 months if there are no safety concerns. If/when they wish to change back to subcutaneous injections then they will enter the follow-up phase as outlined in Figure 1.

### Figure 1. Study outline.

\* +/-1 day permitted for anti-Xa testing. Day 7 testing performed on those in whom the catheter remains in for 7 days.

\*\* An independent clinician not within the study team will review the anti-Xa results for each patient to determine whether they are safe to continue using the subcutaneous catheter.

\*\*\* Anti-Xa results will be reviewed by an independent clinician who is not part of the study team to assess safety. Additional blood tests and anti-Xa levels permitted at clinician discretion.

### Table 1. Visit schedule and assessments

|  |  |  |  |
| --- | --- | --- | --- |
|  |  | Phase A: Subcutaneous catheter | Phase B: Subcutaneous injections |
|  | Screening | Day 1 | Day 2 | Day 3 | Day 5 | Day 7 | Day 7 | Day 10 | Day 30 | Day 60 | Day 90 |
| Clinical assessment/medications | X | X |  |  |  |  |  |  |  |  |  |
| Baseline weight and height | X |  |  |  |  |  |  |  |  |  |  |
| Indication for anticoagulation | X |  |  |  |  |  |  |  |  |  |  |
| SOC bloods (FBE, UEC within 4 weeks of commencement) | X |  |  |  |  |  |  |  |  |  |  |
| Anti-Xa  | X |  | X |  | X | X | X | X | X |  |  |
| Nursing review | X | X | X |  | X | X |  |  |  |  |  |
| Doctor review | X | X |  |  | X |  | X |  |  |  |  |
| Phone review to check medication adherence, bleeding and/or thrombotic complications |  |  |  | X |  |  |  |  | X | X | X |

### Table 2. Extension phase (subcutaneous catheter)

|  |  |  |  |
| --- | --- | --- | --- |
|  | Prior to commencing | Weekly | 4-weekly |
| Independent clinician review of patient and anti-Xa results | X |  |  |
| Anti-Xa\*  |  |  | X |
| Nursing review with catheter change\* |  | X (while nursing staff inserting insuflon) |  |
| Doctor review\*\* |  |  | X |

\* Results to be reviewed (blinded) by a clinician not directly involved in the research team to assess safety.

\*\* More frequent catheter changes with nursing review are permitted as clinically indicated. Recurring frequent catheter changes or complications will be reviewed with the doctor and research team to assess safety and feasibility of continuing on trial.

\*\*\* Additional blood tests will be arranged as indicated clinically

*Laboratory measurements*

The anti-Xa levels will be run at Monash Pathology on the ACL TOP analyser as a one stage chromogenic assay as per standard laboratory operating procedures. The estimated coefficient of variance for this assay is 5%. All anti-Xa samples will be collected in citrate tubes, centrifuged at 3800rpm for 10 minutes and frozen as per local protocols to be run in duplicate for each patient. Anti-Xa levels will not be run in real time unless there is clinical concern. Any results falling outside of the expected range will be phoned through to the study investigators for further assessment and investigation as clinically indicated.

## *Safety assessment*

During Phases A and B, random samples will be selected and run in real time to ensure there is no signal for drug accumulation or inadequate drug exposure. Anti-Xa levels run during the study period will assessed by a clinician not involved with the study to ensure the anti-Xa levels remain in the expected ranges for both patient on therapeutic or prophylactic anticoagulation. Evidence of accumulation of drug exposure using subcutaneous catheters will be measured by performing defined as >50% difference or ≥0.4 absolute difference in the mean peak anti-Xa between day 2 vs day 5 (and day 7 in those applicable). If there are any safety concerns or a safety report is submitted for a participant, copies will be forwarded to appropriate clinical and pharmacy parties.

Prior to and throughout the Extension phase, there will be external clinician review of the patient and anti-Xa levels to ensure results are within expected range, and there are no safety concerns with the patient continuing the subcutaneous catheter. Regular nursing reviews will take place at each catheter replacement and be escalated to a clinician for review as required.

Frozen samples will be stored at Monash Health as per local laboratory guidelines. The samples obtained will not be used for genetic testing.

## *Data security and handling*

Information will be collected on case report forms (CRFs). The original case report forms will be maintained at the Monash Health Haematology Research Unit. All study investigators and trial co-ordinators are required to maintain patient confidentiality. CRFs will be stored at Monash Health in paper form, and progress notes by study investigators will be scanned into the Monash Health Scanned Medical Record system. All paper records will be securely stored by the Monash Health Haematology Research Unit in locked facilities (e.g. locked cabinets). All electronic data will be password-protected. Data analysis will use software including Graph Pad Prism and Microsoft Excel. Data analysis will use de-identified information, using the alphanumeric code assigned to each participant.

Records will be maintained for at least 15 years following study closure.

# **Study outcomes**

## *Primary outcomes*

Therapeutic arm

1. No more than a 30% in median anti-Xa levels in subcutaneous catheter and subcutaneous injections, or an absolute value of 0.3 (based on expected mean anti-Xa of 0.9, and standard deviation of 0.2U/mL)

Prophylactic arm

1. Proportion of patients within the expected anti-Xa (range 0.15-0.5U/mL)

## *Secondary outcomes*

1. The number of patients in whom the catheter remains in for the full 7 days

Therapeutic arm

1. Proportion of peak anti-Xa levels within the expected range (0.5-1.2), with no more than a 30% difference between the 2 administration methods (based on expected mean anti-Xa of 0.9, and standard deviation of 0.2U/mL)
2. Assessing any evidence of accumulation in drug exposure using subcutaneous catheters, defined as >50% difference or ≥0.4 absolute difference in the mean peak anti-Xa between day 2 vs day 5 (and day 7 in those applicable)
3. Feasibility and acceptance of subcutaneous catheters, assessed by an in house quality of life/patient satisfaction survey based on an oncology scoring system assessing acceptability of central venous access devices (CVAD) vs subcutaneous ports (see appendix figures A and B) [32]
4. Complications from the subcutaneous catheter, assessed on days 2, 5+/-1, and day 7 where applicable, by an in house adaptation of the modified PIVC (peripheral intravenous cannula) miniQ score (see appendix figure C)[33]
5. Whether a single subcutaneous catheter or 2 catheters is preferable to patients on bd LMWH dosing

Prophylactic arm

1. An absolute difference of ≤0.15 between both methods of administration

# **Statistical analysis**

We aim to recruit 20 patients receiving therapeutic dose LMWH and 15 receiving prophylactic dose LMWH. Sample size calculations for the therapeutic cohort are based on a mean anti-Xa of 0.9 IU/mL (expected range 0.6-1.2 IU/mL) and standard deviation of 0.2 IU/mL (from local laboratory data), therefore to exclude a mean difference of 0.3 IU/mL between the 2 methods of administration, 15 patients are required to achieve 90% power to exclude this difference with an alpha value of 0.05. In the prophylactic cohort, we expect 70% of patients anti-Xa level with fall within a range of 0.2-0.5 IU/mL. To exclude a 50% difference in the proportion within this expected range (0.2-0.5IU/mL) with 90% power we calculate 10 patients are required again with an alpha value of 0.05. We will accept a wider margin of difference in this group as anti-Xa levels are not routinely measured and there is limited data on what an acceptable peak anti-Xa level is in these patients. To account for incomplete data and participant dropout, we aim to recruit 20 patients to the therapeutic arm, and 15 to the prophylactic arm.

# **Funding**

Funding has been secured through Monash Haematology (AUD$25,000) to cover the cost of the Insuflon catheters, nursing time, collection, handling and running of laboratory testing. Patients will continue on their prior dose of enoxaparin therapy which will be supplied through the pharmacy of their choosing, at the cost as per the Pharmaceutical Benefits Scheme.

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# Appendices

Summary of relevant time points

|  |  |
| --- | --- |
| Time point |  |
| Referral for consideration | Informing clinicians through outpatient clinics at Monash Health and privately, including obstetric clinics |
| Initial review  | Chart review to screen for eligibility. Primary clinician to broach topic with patient and supply PICF.Check that patient has script, standard of care blood tests within 4 weeks (FBE, UEC).Arrange for formal review in MHTP. |
| Screening review MHTP | 30 minute medical review in person (or telehealth/telephone if unable to attend in person).Ensure patient has script and SOC bloods as above – to be arranged if not. Assess suitability and stability on LMWH, including any need for aXa level testing. Change LMWH dosing time to 8am to facilitate peak aXa testing (bring forward 12hrs for following dose then change to 8am ongoing).Supply PICF and field any questions.Baseline height and weight. |
| Consent and D1 of treatment | 30 minute doctor review.30 minute nursing review for training on administration via subcut catheter, insertion of catheter and first dose.  |
| Day 2 | 30 minutes nursing time * Peak aXa level collected in CTC (12pm +/- 1hour for 8am dose)
* Assessment of catheter site (figure C)
 |
| Day 3 | Phone call to patient to ensure they are tolerating the catheter (doctor) |
| Day 5 | 15 minute doctor review30 minute nursing review* Peak aXa level collected in CTC (12pm +/- 1hour for 8am dose)
* Assessment of catheter site (figure C)
* Daily impact of subcutaneous catheter survey supplied (Figure A), to be collected on day 7
 |
| Day 7 | 30 minute doctor review30 minute nursing review* Peak aXa level collected in CTC (12pm +/- 1hour for 8am dose)
* Removal of catheter and assessment of catheter site (figure C)
* Collect patient questionnaire (figure A)
 |
| Washout period, restart at D1 | All patients to revert to subcutaneous injections for a minimum of 5 days |
| Day 7 | 30 minute nursing review* Peak aXa level collected in CTC (12pm +/- 1hour for 8am dose)
* Assess site of previous catheter (figure D)
 |
| Day 10 | 30 minute doctor review15 minute nursing review* Peak aXa level collected in CTC (12pm +/- 1hour for 8am dose)
* Patient acceptance questionnaire completed (figure E)
 |
| Day 30 | Phone call to assess for any bleeding or progressive thrombosis |
| Day 60 | Phone call to assess for any bleeding or progressive thrombosis |
| Day 90 | Phone call to assess for any bleeding or progressive thrombosis |

## Figure A. Daily life impact of subcutaneous catheters (participants to complete)

|  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- |
| How much does the subcutaneous catheter impact on a scale of 1-5, 1 being not at all and 5 being significantly | 1 | 2 | 3 | 4 | 5 | Unsure |
| Showering |  |  |  |  |  |  |
| Sleeping |  |  |  |  |  |  |
| Dressing |  |  |  |  |  |  |
| Exercise |  |  |  |  |  |  |
| Daily activity overall |  |  |  |  |  |  |

Visual analogue scale can be used if required (10 on VAS equates to 5 on numerical scale)

## Visual analogue score for insertion of catheter



## Figure B. Final acceptability of subcutaneous catheters (participants to complete)

|  |  |  |  |
| --- | --- | --- | --- |
|  | Subcutaneous catheter | Subcutaneous injections | Unsure |
| Compared to subcutaneous injections, which did you feel more anxious about  |  |  |  |
| Which method of delivery had more of an impact on your life |  |  |  |
| Which method of delivery resulted in the most pain/discomfort |  |  |  |
| Which method of delivery was the easiest to manage |  |  |  |
| Which method of enoxaparin delivery do you prefer overall  |  |  |  |
| Were there any issues specific to either method |  |  |  |

## Figure C. Complications of subcutaneous catheters (performed by nursing staff days 2, 5 and 7)

|  |  |  |  |
| --- | --- | --- | --- |
|  | Yes | No | Comments/description |
| Pain and tenderness at catheter site\* |  |  |  |
| Redness >1cm from insertion site |  |  |  |
| Swelling >1cm from insertion site |  |  |  |
| Bruising at site |  |  |  |
| Bleeding at site |  |  |  |
| Purulence/evidence of infection |  |  |  |
| Induration of skin at insertion site |  |  |  |
| Partial/complete dislodgement |  |  |  |
| Loose/lifted dressing |  |  |  |
| Required replacement of catheter once |  |  |  |
| Required replacement of catheter more than once |  |  |  |
|  | Yes | No | Comments/description |
| Pain and tenderness at catheter site\* |  |  |  |
| Redness >1cm from insertion site |  |  |  |
| Swelling >1cm from insertion site |  |  |  |
| Bruising at site |  |  |  |
| Bleeding at site |  |  |  |
| Purulence/evidence of infection |  |  |  |
| Induration of skin at insertion site |  |  |  |
| Partial/complete dislodgement |  |  |  |
| Loose/lifted dressing |  |  |  |
| Required replacement of catheter once |  |  |  |
| Required replacement of catheter more than once |  |  |  |

\* Visual analogue scale if answers yes



## Figure D. Review of previous subcutaneous catheter site at Day 7 of subcutaneous injections (by nursing staff)

|  |  |  |
| --- | --- | --- |
| Regarding the previous subcutaneous catheter site and unrelated to subcutaneous injections, is there: | Yes | No |
| Pain |  |  |
| Erythema |  |  |
| Evidence of infection |  |  |
| Bruising or haematoma |  |  |
| Skin induration |  |  |

## Figure E. End of study patient satisfaction survey (participants to complete)

|  |  |  |  |
| --- | --- | --- | --- |
|  |  |  | Additional comments |
| Which method did you prefer overall? | Subcutaneous catheter | Subcutaneous injections |  |
| Where there any disadvantages specific to the subcutaneous catheter? | Yes | No |  |