JRMO Research Protocol for Interventional Studies

Full Title	**D**elivery and **I**mplementation of a **R**andomise**d** **C**rossover Trial on **T**hrombosis.
Short Title	DIRECT
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1. Contents

Glossary

CI	Chief Investigator
CRF	Case Report Form
CTRG	Clinical Trials & Research Governance, University of Oxford

CTSU	Clinical Trials Service Unit
DMC	Data Safety and Monitoring Committee
DIRECT	Delivery and Implementation of a Randomised Cluster Trial on Thrombosis
GCP	Good Clinical Practice
GP	General Practitioner
HRA	Health Research Authority
HTA	Health Technology assessment
ICF	Informed Consent Form
ITT	Intention-to-treat
MSK	Musculoskeletal
NHFD	National Hip Fracture Database
NHS	National Health Service
RES	Research Ethics Service
PI	Principal Investigator
PIL	Participant/ Patient Information Leaflet
R&D	NHS Trust R&D Department
REC	Research Ethics Committee
SOP	Standard Operating Procedure
TMG	Trial Management Group
TSC	Trial Steering Committee
VTE	Venous Thromboembolism

2. Signature page

Chief Investigator Agreement

The study as detailed within this research protocol will be conducted in accordance with the principles of Good Clinical Practice, the UK Policy Framework for Health and

Social Care Research, and the Declaration of Helsinki and any other applicable regulations. I delegate responsibility for the statistical analysis and oversight to a qualified statistician (see declaration below).

Chief Investigator name: Professor Xavier Griffin

Signature: _____

Statistician's Agreement

The study as detailed within this research protocol will be conducted in accordance with the current UK Policy Framework for Health and Social Care Research, the World Medical Association Declaration of Helsinki (1996), principles of ICH E6-GCP, ICH E9 - Statistical principles for Clinical Trials and ICH E10 - Choice of Control Groups.

I take responsibility for ensuring the statistical work in this protocol is accurate, and I take responsibility for statistical analysis and oversight in this study.

Statistician's name: Dr Thomas Hamborg

Signature: _____

3. Summary and synopsis

Short title	DIRECT
Methodology	A multicentre, pragmatic, standard-of-care controlled, cluster (hospital) randomised, single crossover, registry-enabled non-inferiority trial and parallel economic analysis.
Research sites	96 England and Wales NHS sites

Objectives / aims	*Primary* To estimate and draw inferences on the risk differences between firstline VTE thromboprophylaxis management strategies including aspirin versus LMWH of the co-primary outcomes of VTE events, combined PE and DVT, within 90 days (efficacy) and major bleeding events within 28 days (safety) after hospital admission following index hip fracture. *Secondary* 1) To quantify the observed differences in VTE cause-specific mortality between the trial treatment groups at 90 days after hospital admission. 2) To quantify the observed differences in bleeding and cardiovascular cause-specific mortality between the trial treatment groups at 28 days after hospital admission. 3) To assess the differences in hospital resource use and costs between the trial treatment groups at 90 days after hospital admission. 4) To model the long-term differences between the trial treatment groups in quality-adjusted life years (QALYs) and healthcare costs and assess the cost-effectiveness of allocation to aspirin vs control in the trial.
Number of participants	21,194 participants across 96 hospitals
Inclusion and exclusion criteria	Adults from 60 to 150 years sustaining fragility hip fracture identified by their entry into UK hip registries.
Statistical methodology and analysis	The target of estimation is the participant average treatment effect. The method of estimation is a cluster-level analysis with the crossover difference per cluster as the outcome in a weighted regression model (weighted by cluster size) using robust (sandwich) standard errors. Harmonic mean weights of the number of participants in the two periods will be used to account for unequal cluster sizes. This method has been shown to be appropriate for cluster crossover trials with rare outcomes. The primary analyses will test between-group differences in the proportion of participants developing VTE or major bleeding for noninferiority of aspirin at an absolute risk margin of 0.855% and 0.723%, respectively, on an intention-to-treat basis. Treatment effects will be presented as absolute risk differences and 95% confidence intervals will be examined to determine whether non-inferiority can be concluded. If non-inferiority is demonstrated superiority will be assessed based on overlap with the 'no difference between groups' margin.
Study duration	33 months

Project funding period	DIRECT has received NIHR funding for 45 months

4. Introduction

4.1 Background

Hip fracture is one of the biggest challenges faced by patients and healthcare systems. In the UK and across the world, hip fracture is the commonest fragility fracture that requires inpatient hospital treatment. A recent report from the National Hip Fracture Database (NHFD) showed that more than 72,000 people sustained hip fracture in 2022, accounting for £1.1 billion in hospital care costs and consuming 2% of the total NHS budget.[1] As a consequence of the aging population, the annual incidence of hip fractures is projected to rise to more than six million worldwide,[2] and to add an extra cost of 25 million a year by 2030. The 30 days mortality associated with a hip fracture is 6.7%[3] in the UK and for the survivors the associated reduction in health-related quality-of-life is very considerable, equivalent to that of a stroke.[4] Venous thromboembolism (VTE) is a major global cause of morbidity and mortality.[5,6] An estimated 10 million episodes are diagnosed yearly; over half of these episodes are associated with hospital admission, known as hospital-acquired VTE (defined as occurring during admission and up to 90 days post discharge), and can result in significant loss of disability adjusted life years.[7]

Hospital associated VTE is a top priority patient safety issue in hospitalised patients;[8] all patients admitted to hospital, including those with a hip fracture, are risk assessed and those at risk are given thromboprophylaxis according to NICE guidelines.[9] Deep vein thrombosis (DVT), or a clot in the veins of the leg, is a common and painful complication of surgery for hip fracture and risks the clinically dangerous condition of pulmonary embolism (PE) where a blood clot developed in the leg travels through the venous system to the lung. This can be a cause of life-threatening cardiovascular collapse and death. The proportion of patients with hip fracture that develop initially asymptomatic or clinically apparent VTE may be as great as 40%, two-thirds of these hospital-acquired VTE are DVT and one third PE.[9]

Prevention of VTE remains one of the key priorities for the NHS,[10,11] since amongst all hospital inpatient episodes, VTE was estimated to be the cause of 25,000 preventable deaths every year in the UK before thromboprophylaxis was used.[9] As well as the clinical impact of VTE, there are considerable costs associated with treating VTE events. Overall, treating acute VTE was estimated to cost the NHS £640 million per annum in 2005.[9]

4.2 Clinical data

Patients sustaining hip fracture are known to be at considerably increased risk of developing a VTE compared with a matched, uninjured, population.[9] This can be attributed to a combination of their demographic characteristics, notably their older age (mean 83 years), their frailty and co-morbidities, and the index injury which limits their mobility, each of which are strong predictors of VTE risk. For similar reasons their risk of bleeding when treated with thromboprophylaxis is also elevated. Furthermore, it is common for older, frail people to be receiving anticoagulants or anti-platelet drugs prior to an index hospitalisation; classical drug efficacy trial designs would exclude such individuals and the applicability of trial inferences from other populations to the hip fracture population is therefore limited. The unique characteristics of this population are well recognised; the Department of Health and Social Care VTE risk assessment tool[9] identifies hip fracture as sufficient alone to

prompt thromboprophylaxis and the NICE guidance has a chapter dedicated to this specific population.[9]

Until relatively recently thromboprophylaxis for VTE in the hip fracture population was not widely prescribed and there was considerable variation in practice between hospitals. This variation in practice has been addressed to a great extent as a result of the publication and update of clinical guidelines by NICE.[9,11]

However, the recommendation made by NICE in 2018 for this population was controversial. One of the larger trials conducted in people with hip fracture is the Pulmonary Embolism Prevention (PEP) trial, published in 2000, evaluating the use of aspirin as an alternative to low molecular weight heparins (LMWH).[12] The guideline committee noted that PEP was a complex trial that included mixed interventions. The data reported included just over 50% of participants treated with either LMWH or unfractionated heparin, and around 30% using graduated compression stockings. It is not reported how many participants received both heparin and stockings, or who had aspirin alone or no prophylaxis at all. The study also reported only a post hoc analysis for the combined outcome of PE and symptomatic DVT. The trial showed a reduction in symptomatic VTE events using aspirin (plus or minus stockings) without the use of heparin. The outcomes of major bleeding or clinically relevant non-major bleeding were not adequately reported in the study. Overall, the trial suggested that aspirin offers a clinically relevant and significant benefit in reducing symptomatic VTE (RR 36%, 95% CI 19,50), bleeding risk was not reported and the risk of bias in the trial was assessed to be severe. Taking these limitations together, the guideline committee decided to exclude the trial from the evidence that formed the basis of the recommendation in the current NICE guidance.[9]

We have performed a systematic review of randomised trials conducted since the NICE guidance was released (2018), revealing no new population-specific trials and the evidence from other non-hip fracture orthopaedic populations has only added to the uncertainty. The CRISTAL trial[13] of people undergoing elective total hip replacement (THR) and total knee replacement (TKR) for arthritis found LMWH was superior to aspirin (risk difference (RD) 1.97%, 95%CI 0.54, 3.41). This trial recruited a patient group with a median age 20 years younger than people with hip fracture, two thirds of whom underwent TKR - a known risk for VTE - and not THR and was conducted in an elective setting with patients who had undergone pre-operative optimisation not possible in the fracture population.

Conversely, PREVENT Clot[14], in a heterogenous and much younger population with limb fractures (only 1103 participants had a femur fracture and were aged at least 60 years of a total sample of 12,211), found no difference between LMWH and aspirin in VTE or bleeding risks (RD 0.0%, 95%CI –0.43,0.43 and – 0.54%, 95%CI –1.78,0.69 respectively). Similar findings have been reported in the smaller ADAPT RCT.[15] In these two trials very few of the participants had hip fractures and most underwent very different operative procedures with much lower absolute VTE risks.

Given the inadequacy of the population-specific literature and heterogeneity between effect estimates in the other orthopaedic trials, The American College of Chest Physicians concluded that any one of a number of agents, including both LMWH and aspirin, may be appropriate for prophylaxis for hip fracture.[16] In 2022, The American Academy of Orthopaedic Surgeons were unable to recommend any one agent.[17] Global opinion leaders have once more fallen back on observational data and

unconventional study designs to support aspirin as an alternative.[18,19] Consequently, variation exists in national and international practice; NICE summarised:[9]

"{If a trial was conducted}…future VTE prophylaxis guidance would be able to definitively state whether aspirin is a clinical and/or cost-effective method of prophylaxis. If aspirin were effective, then a definitive study would fundamentally change the recommendation."

Patients have prioritised this uncertainty in a recent James Lind Alliance partnership, stating a strong preference for an oral agent such as aspirin, if it were a clinically effective alternative.[20] The cost of aspirin is only a fraction of the cost of LMWH, potentially reducing the annual cost of hip fracture management by £27 million .[9] Aspirin is cheaper, available orally and more acceptable - it would be a preferred treatment compared to LMWH if efficacious and safe.

4.3 Rationale

There remains considerable uncertainty around the risk benefit and cost effectiveness of different thromboprophylaxis strategies and agents for this specific, unique, population. The evidence to support the current NICE recommendation was acknowledged by the guideline committee to be of very low quality and was based upon just two studies.[9] Hence there is considerable variation in first-line therapeutic agent and duration of treatment in the UK; observational studies suggest 60% compliance with the NICE guidance.[21] NICE, therefore, prioritised research into the clinical- and cost-effectiveness of different drug strategies for VTE thromboprophylaxis in hip fracture as a 'Top 5 Research Recommendation' in the recent update to the guidance.[9]

Existing RCTs and network meta-analyses are underpowered to detect clinically important effects in outcomes relevant to patients such as PE and death. Clinical guidelines are based upon proxy outcomes and inferred effects[9] or observational designs.[17,19] The scale required to address this research question demands dataenabled methodologies described in the health data research UK (HDRUK) "Better, Faster and More Efficient Clinical Trials". Only by pairing the scale of routinely collected health data with a robust RCT methodology can we answer this question quickly and robustly. Our proposed trial provides a route to directly establishing clinical- and cost-effectiveness of different thromboprophylaxis strategies.

5. Study objectives

5.1 Primary objective

To estimate and draw inferences on the risk differences between first-line VTE thromboprophylaxis management strategies including aspirin versus LMWH of the co-primary outcomes of VTE events, combined PE and DVT, within 90 days (efficacy) and major bleeding events within 28 days (safety) after hospital admission following index hip fracture.

5.2 Secondary objectives

1) To quantify the observed differences in VTE cause-specific mortality between the trial treatment groups at 90 days after hospital admission for index hip fracture event.

2) To quantify the observed differences in bleeding and cardiovascular causespecific mortality between the trial treatment groups at 28 days after hospital admission for index hip fracture event.
3) To assess the differences in hospital resource use and costs between the trial treatment groups at 90 days after hospital admission for index hip fracture event.
4) To model the long-term differences between the trial treatment groups in quality-adjusted life years (QALYs) and healthcare costs and assess the costeffectiveness of allocation to aspirin vs control in the trial.

5.3 Primary endpoint

Efficacy: **Hospital associated thromboses (HAT) within 90 days of hospital admission for index hip fracture event** (the period during which incident thromboses are classified as related to an index hospital stay). Algorithms for identifying events in administrative databases have previously been validated in The Million Women study.[22] Records from hospital episode statistics (HES) and SMR01 from 947,454 participants in the Million Women study, of whom 90,259 underwent an inpatient surgical procedure during the study period, were analysed to estimate the relative risk of hospital associated VTE in the surgical population compared with the internal control population within the study.[23] 5689 women suffered a new VTE event, defined as a new diagnosis of PE (ICD-10 code I26) or DVT (ICD-10 codes I80-I82) in any diagnostic position or as any underlying cause for a death.

Relative risks for VTE varied significantly over time, reaching a peak in the third postoperative week, where the risk was 110 times higher than the background control risk. The risk remained highest in women undergoing major orthopaedic surgery at all time points. This elevated risk persisted for 90 days, which is why this duration is used as the cutoff for defining HAT.

Based upon the validated approaches within these studies and exploration of the event distribution in our preparatory work[24] we will similarly define VTE events as any hospital spell with associated ICD-10 codes for pulmonary embolism, phlebitis, thrombophlebitis, other venous embolism or thrombosis (I26, I80-I82) in any diagnostic position or death with these diagnoses (underlying or significant).

Safety: **Major bleeding events within 28 days of hospital admission for index hip fracture event** (the duration of anticoagulant drug prescription recommended following hip fracture when an incident bleed is plausibly related to thromboprophylaxis). Algorithms for identifying events in administrative databases have been validated in the ASCEND study.[25]

Adjudicated trial data concerning major bleeding events (the primary safety outcome), sourced directly by self-report from the 15,480 participants in the ASCEND study, were compared to determine agreement with data from linked routinely collected NHSE administrative datasets. Randomised trial comparisons were also repeated using these routine data.[26] Agreement was good for definitions constructed around anatomical bleeding site and the diagnostic position (first or secondary compared with any) of the bleeding code within the routine records; As an example, the intracranial haemorrhage agreement between data sources was substantial (kappa 0.73, 95% CI 0.67-0.80) and the upper gastrointestinal bleeding was moderate (kappa 0.58 (95%CI 0.50-0.65). Repeating the ASCEND randomised

comparisons using the routine data found estimated relative and absolute effect estimates similar to analyses of adjudicated datasets and made no change to the inferences drawn.

Based upon the validated approaches within the ASCEND trial and exploration of the event distribution in our preparatory work[24] we will similarly define major bleeding as any hospital spell with associated ICD-10 codes for intracranial haemorrhage (I60021, I29), upper gastrointestinal bleed (I850, K226, K250-K256, K260- K276, K280K922) (both in any position); haematuria (R31, N421), respiratory (R040-R042, R048, R049, J942), lower gastrointestinal (K625, K922) or other.

5.4 Secondary endpoints

- All-cause mortality risk at 90 days following surgery determined from the registers of deaths in each devolved country. This global measure will capture benefits and harms associated with both treatments.
- VTE associated mortality at 90 days following surgery determined from the registers of deaths.
- Bleeding and cardiovascular cause-specific mortality at 28 days following surgery, when thromboprophylactic drug exposure has terminated, determined from the registers of deaths.

6. Study population

Existing infrastructure in each cluster already reports patients admitted with incident acute hip fractures to the NHFD. The NHFD will therefore form the register of all individuals participating in the trial. Those individuals that do not meet the eligibility criteria to be enrolled in the registry will be excluded.

NHFD processes patient identifiable information without prospective consent approved under exemptions that fall within section 251 to the Health and Social Care Act 2012. As part of these approvals all participating hospitals publish fair processing notices, which are also available on the registry websites. Alongside these notices, we will be producing a notice for this trial including the processes for withdrawal. Coupled with this, we will engage with the principal professional stakeholders and patient advocacy groups to advertise the trial prior to opening sites in an effort to fully inform potential future patients.

6.1 Inclusion criteria

Adults between 60 and 150 years old sustaining fragility hip fracture identified by their entry into NHFD.

6.2 Exclusion criteria

Individuals who do not meet the eligibility criteria to be enrolled in the NHFD registry

Hip fracture individuals above 150 years of age.

6.3 Vulnerable participant considerations

The trial will include the large and vulnerable subgroup of individuals presenting with acute hip fracture that have co-incident acute or chronic cognitive impairment

The CI is responsible for ensuring that all vulnerable participants are protected and participate voluntarily in an environment free from coercion or undue influence.

7. Study design

A multicentre, pragmatic, standard-of-care controlled, cluster (hospital) randomised, single crossover, registry-enabled trial reporting a single-sided comparison for noninferiority of a first-line thromboprophylaxis strategy including aspirin compared with
LMWH.

The study is supported by the Orthopaedic Trauma Society (OTS), British Orthopaedic Association (BOA), British Society for Haemostasis and Thrombosis, British Geriatric Society and, the patient charity Thrombosis UK, demonstrating multidisciplinary and multi-agency support for the study.

7.1 Internal pilot

We have set clear and challenging progression criteria for an internal pilot phase which we believe best mitigate risk for the Funder. These progression criteria are necessarily different to an individually randomised trial and are instead focused around the key uncertainty of this design – can we deliver 96 clusters with their randomised allocation in place, ready to open to recruitment at month 18 of the trial schedule. Close monitoring of additional progression criteria by the oversight committees are laid out for the remainder of the trial.

7.2 Main RCT

Hospital thrombosis committees will be identified for each of the hospitals (the clusters) and act as gatekeepers. All clusters will be allocated randomly to one of the two first-line thromboprophyalxis strategies for a minimum of 4 weeks wash-in period prior to the beginning of the first period of the trial and then crossover to the alternative strategy for the second period after a two months washout. The duration of each period is 5 months. Half the clusters will be randomised to start with the control strategy and half with the test strategy (see paragraph 8.7). These strategies will form the routine first-line thromboprophylaxis policy at each hospital for all patients admitted with acute hip fracture to that hospital during the trial recruitment phase. Patients attending each cluster with a hip fracture, during the two windows of recruitment, will be identified by their entry into the national registry of patients with hip fracture.

Participant identification necessarily will only occur after treatment since this registry is not updated live. All outcomes will be collected from national, routine administrative datasets through proven linkages. Initial within-trial follow-up will be for 90 days, the conventional end point for the definition of hospital-acquired thrombosis.

7.3 Modelling and long-term follow-up

We will model the hip fracture population with population-specific event rates informed from linked population data and the literature and treatment effect estimates from this study. This will allow efficient, value for money inferences to be made about long-term sequelae of VTE events and determine whether further detailed long-term follow-up of participants would be worthwhile. We plan life course follow-up using data from national routinely collected administrative datasets. This will facilitate efficient, longer-term trial driven clinical- and cost-effectiveness studies

8. Study procedures

8.1 Cluster eligibility

Almost 175 NHS hospitals treat patients with hip fracture in England and Wales . Eligible hospitals will be those that submit greater than 90% baseline data to the England and Wales hip fracture registry, National Hip Fracture Database (NHFD). In 2023 all hospitals in the UK treating patients with hip fracture fulfilled this criterion.[3]

8.2 Cluster recruitment

The trial will be advertised through professional conferences and networks, with the help of the regional NIHR Research Delivery Network and through word of mouth. Sites will be selected based on suitability. A local invitation pack which includes a Site Feasibility Questionnaire (SFQ) will be provided to potential sites. Each site will identify a member of the local thrombosis committee to act as Principal Investigator (PI). The PI will need to utilise links with local clinicians to establish the acceptability of the first-line prophylaxis strategies and to co-ordinate the integration of the strategy with local electronic prescribing systems.

8.3 Individual participant identification

Existing infrastructure in each cluster already reports patients admitted with incident acute hip fractures to the NHFD. The NHFD will therefore form the register of all individuals participating in the trial. Those individuals who do not meet the eligibility criteria to be enrolled in the registry will be excluded.

8.4 Consent

This is a trial of two different clinical first-line prophylaxis management strategies – it is not a drug trial. Consequently, in line with the international guidance on consent in cluster RCTs as outlined in the Ottawa[27] and NIH Health Care Systems Research Collaboratory[28] Statements on the ethics of cluster RCTs individual participant consent to participation in the trial is not required. There are a number of similar trials in the UK (e.g. SUDDICU Study)[29] which have also actively involved patients who have confirmed that this approach is appropriate. Our approach here has been approved previously by the MHRA and issued non-CTIMP status, subsequently confirmed by our Sponsor.

Thrombosis committees are the aggregation of local multi-disciplinary expertise concerning thrombosis and bleeding and its prevention in admitted patients. They process national guidance in light of local contexts to produce local protocols and are thus ideally placed to judge that the trial thromboprophylaxis strategies are suitable for their local population.

Data from eligible participants will be routinely entered into the NHFD, the England and Wales national register of patients with hip fracture. This register is typically two to three months out of date, a time at which the vast majority of patients have been discharged from hospital. Mortality at this time is approximately ten percent and one third of patients have chronic cognitive impairment and potentially lack capacity,[3] requiring access to an unknown consultee. We assess, therefore, that participant consent to access their outcome data in the routinely collected datasets would not be possible and plan, therefore, to apply for approval for Section 251 of the 2012 NHS Health and Social Care Act exemption from individual consent from the Health Research Authority, Confidentiality Advisory Group.

8.5 Withdrawal

NHFD processes patient identifiable information without prospective consent approved under exemptions that fall within section 251 to the Health and Social Care Act 2012. As part of these approvals all participating hospitals publish fair processing notices, which are also available on the registry websites. Alongside these notices we will be producing a notice for this trial including the processes for withdrawal.

Coupled with this, we will engage with the principal professional stakeholders and patient advocacy groups to advertise the trial prior to opening sites in an effort to fully inform potential future patients. Finally, data will not be processed for patients who have registered a national opt-out.

8.6 Treatment Allocation

Randomisation will use a 1:1 allocation ratio, stratified by cluster size (dichotomised at the median), using a validated computer randomisation program managed through a secure web-based service by the Pragmatic Clinical Trials Unit. Random permuted blocks of sizes 4 and 6 will be used within strata.

Upon randomisation the central trial office will inform each hospital thrombosis committee of their allocations. Hospitals will be supported to embed the allocated policy into their electronic prescribing systems. Members of the trial team, expert in the use of these systems, will assist local teams at each site.

There will be a run-in period at each site of not less than four weeks so that the policy can be fully implemented into normal practice. A two-month wash-out will be allocated during the crossover event with similar support available at clusters to embed the new strategy locally and within their electronic prescribing systems.

8.7 Health technologies assessed

Hospitals in the UK recommend first-line policies for VTE thromboprophylaxis for all admitted patients, including those with hip fracture, to their clinicians based on the NICE guideline[9] through a central hospital thrombosis committee. Our design is explicitly focussed on testing the real-world impact of any new recommendation and the follow-on change in hospital-level policies as opposed to the relative efficacy of any two drugs.

Therefore, hospitals will be supported to embed a policy through engagement directly with their thrombosis committee. The two thromboprophylaxis policies to be compared will be based around:

Test strategy:

Thromboprophylactic dose aspirin once daily administered orally for 28 days.

Control strategy:

Thromboprophylactic dose LMWH once daily administered by subcutaneous injection for 28 days.

Thrombosis committees will be provided with a full first-line strategy for prophylaxis specifying prescribing details of the allocated chemoprohylaxis with appropriate body mass dosing schedules; alternatives for patients for whom a treatment is contraindicated, bridging regimens for those on long-term anticoagulants and the use of mechanical prophylaxis co-interventions as per the NICE guidance.[9] These

strategies are provided in full in Figures 1 and 2. We also anticipate that a proportion of participants will already be prescribed aspirin for various co-morbidities. In clusters where the allocation is to the policy including aspirin we will continue participants preexisting prescription; where the strategy includes LMWH this will be prescribed in addition as per current NHS standard care. Similarly, some participants will already be prescribed anticoagulant medications prior to the incident hip fracture, such as Direct Oral Anticoagulant Drugs or warfarin. For such individuals, treated in hospitals allocated to the policy including aspirin, bridging anticoagulation will be prescribed in addition to aspirin. These approaches were developed together with our co-applicant clinical and patient experts in thromboprophylaxis, in consultation with wider specialist societies and advocacy groups, to ensure that they reflect current NHS practice and could be implemented in NHS care immediately upon conclusion of the trial.

We will develop an intervention manual and support materials to support each committee to implement the two trial treatment policies within their site. This will describe not only the policy but also steps to implement the initial allocation, to disseminate the updated policy through their site to all clinicians involved in the treatment of people with hip fracture, steps to be undertaken during the washout period and means to implement the alternative policy. Many hospitals now use electronic prescribing systems with automation for prescribing VTE prophylaxis which provides committees a means to operationalise adherence to their prophylaxis guidance. We will utilise these systems to promote fidelity of the interventions and have costed for clinical and hospital IT expert fellows to visit sites to provide direct support to thrombosis committees and hospital Information & Communication Teams.

This trial will provide an effect estimate which is truly applicable to real-world NHS practice and the complex population that presents with hip fracture who are often frail, co-morbid and already prescribed many drugs that may contraindicate or contribute to the effects of thromboprophylactic drugs prescribed de novo during the index admission.

All other components of the care pathway will be delivered in accordance with local hospital policy.

8.8 Masking

This is a highly pragmatic study, testing thromboprophylaxis policies in the ‘real world’ so no effort will be made to mask participants or those delivering care. ‘The trial statisticians and health economists will not have access to unblinded trial data (i.e. data with treatment allocation included, or variables which could predict treatment allocation such as compliance) until after the final statistical analysis plan and health economics analysis plan have been signed off and the database is locked for final analysis..

8.9 Adherence

Cluster-level

We will confirm with the thrombosis committee of each hospital that the randomised policy for each Recruitment Window has been enacted formally within the site through their committee’s governance structure. We will produce a trial intervention manual describing the policy in full as well as the required steps for implementation

of that policy within the site, including where appropriate the creation of PowerForms or similar automations with electronic prescribing systems.

Participant-level

As part of site monitoring, a manual audit of drug prescriptions for participants in a random sample of 10% of sites in each treatment arm will be performed for the first two weeks and a further random week of each Recruitment Window to ensure that the policy is being enacted at participant-level as per the protocol.

8.10 Schedule of assessments

The schedule of trial assessments and data sources are described in Table 1

Measurement	***Data source***	***Time of measurement (from hospital admission)***
Baseline characteristics	NHFD	On entry into registers
• All-cause mortality • VTE associated mortality	• Civil register (deaths) • Statutory Register (deaths)	90 days
Bleeding associated mortality	• Civil register (deaths) • Statutory Register (deaths)	28 days
Hospital acquired thromboses	• HES • PEDW	90 days
Prophylaxis associated bleeding events	• HES • PEDW	28 days
Hospital resource use	• HES • PEDW • NHSBSA	-90 to 90 days

Table 1: Objectives, outcome measures and time-points

***Key**:, **HES**: Hospital Episode Statistics, **NHFD**: National Hip Fracture Database, **PEDW**: Patient Episode Database for Wales, **NHSBSA**: NHS Business Services Authority (prescription dataset)*

8.11 Internal pilot progression criteria

Details of progression thresholds for these criteria are described in Table 2. At the end of the pilot phase, we will review:

- Cluster recruitment will be defined as the number of sites for which we have received formal Confirmation of Capacity and Capability from respective Research & Development offices and participant recruitment as the number of individuals admitted for care of a hip fracture in that site in the immediate preceding 12 months based upon entries in the NHFD .
- Successful embedding of the first randomised intervention within cluster policy and practice treated with the allocated drug.
- Data linkages are approved both in England and Wales.

	Pilot phase

RAG thresholds	<70%	70-100%	≥100%
Number of sites ready to open to recruitment at month 18 with randomised allocation embedded within policy and practice	<67	67-95	≥96
Total number of potentially eligible patient in contributing sites in immediate preceding 10 months	<14,836	14,836-21,193	≥21,194
Average recruitment rate/site/year in the immediate preceding 12 months	<187	187-267	≥268
Action	Design not feasible; consider stopping the trial. Discussions to be held with funder on study future	Review design assumptions Report to TSC; continue but monitor closely. Discussions to be held with funder on study next steps	Design feasible; proceed with study

Table 2: Progression criteria for the internal pilot

8.12 Definition of End of Study

The initial study will report once the full outcome data are available from each of the data controllers. Although the funding for the study terminates at the end of September 2028, long-term follow up is planned for the lifetime of the participants identified within the trial sample. Interval reporting is planned at various timepoints (e.g. five and ten years after the trial recruitment period). As such, the end of the initial part of the study is defined as when the data for the last identified participant has been received, and the end of follow up phase is defined as the timepoint when all identified participants have died. Data will be retained for 25 years after the end of the study for full reporting and response to academic debate unless an extension is agreed with the Sponsor and relevant data controllers.

9. Assessment and management of risk

9.1 Side effects or complications of health technologies

The control strategy replicates the recommended first line NICE Guidance confirmed as current standard care in 80% of patients for hip fracture (unpublished WHiTE cohort; 36 sites, 35,000 patients); the test strategy is that of the Research Recommendation and used in 10% of participants in the WHiTE cohort study.[21]

As such both treatment strategies are usual care and the management of any side effects or complications, given that the treatments are not masked, will be consistent with usual clinical care, managed by local clinical teams.

9.2 Processing of personal, sensitive data

Fair processing notices and means for opting out will be displayed in participating hospitals in clinical areas where participants are likely to be treated for their hip fracture.

10. Statistical considerations

10.1 Sample size

VTE and bleeding risks in our preparatory work were 2.85% and 2.41% respectively and consistent annually from 2011 to 2020.[24] Through discussion with the UK MSK PPI Group & UK Orthopaedic Trauma Society, and considering the valuing of effect sizes in the NICE guidance,[9] we propose risk differences of 0.855% and 0.723% as non-inferiority margins for VTE and bleeding respectively, equating to an acceptable relative risk increase of 30%. This margin is consistent with PREVENT Clot mixed methods elicitation of clinically relevant effect sizes in this population,[43] and align with a discrete choice experiment at which patients' preference shifts from oral drugs to subcutaneous injection for VTE prophylaxis.[30]

178 hospitals treat ~70,000 patients with hip fracture in the UK annually. The harmonic mean annual cluster size is 268.[3] We obtained an estimate of 0.0043 for the intracluster correlation coefficient from our preparatory work[24] and, to be conservative, used a value of 0.005 in the sample size calculation. No relevant estimates are provided in the literature for the correlation within a cluster between two different time periods. Following the recommendation by Hooper et al[31] we use a value of 0.004 (80% of the within-period, within cluster correlation) for this correlation as was used in the CRISTAL trial.[13] For a power of 90% at significance p=0.025 (lower 95% CI limit) for the bleeding outcome 21,194 participants across 96 clusters need to be recruited with 5 months of recruitment to one intervention strategy and 5 months to the other intervention strategy. The power for the VTE outcome with this sample size is 94.2% so that the overall power to declare non-inferiority for both primary outcomes is at least 84.8% assuming zero correlation between the outcomes.

10.2 Statistical analysis

Data will be analysed according to the intention-to-treat principle with clusters analysed according to their assigned allocation sequence. Reporting of the results and flow of participants through the trial will be in accordance with the CONSORT statement and relevant extensions.[32–35] Demographic data will be summarised by period, treatment arm and overall using suitable measures of central tendencies, for continuous data (means and medians), for categorical data (frequencies and proportions) and variability (standard deviation (SD) and IQR).

The two primary endpoints are co-primary, that is, 'success' will only be declared if non-inferiority in both endpoints can be established. Therefore, no multiplicity adjustment of the type-I error rate is required. The target of estimation is the participant average treatment effect. The method of estimation is a cluster-level

analysis with the crossover difference per cluster as the outcome in a weighted regression model (weighted by cluster size) using robust (sandwich) standard errors.

Harmonic mean weights of the number of participants in the two periods will be used to account for unequal cluster sizes. This method has been shown to be appropriate for cluster crossover trials with rare outcomes.[36] The primary analyses will test between-group differences in the proportion of participants developing VTE or major bleeding for noninferiority of aspirin at an absolute risk margin of 0.855% and 0.723%, respectively, on an intention-to-treat (ITT) basis. Treatment effects will be presented as absolute risk differences and 95% confidence intervals will be examined to determine whether non-inferiority can be concluded. If non-inferiority is demonstrated superiority will be assessed based on overlap with the 'no difference between groups' margin.

A subgroup analysis for the primary outcomes will assess whether the treatment effects differ by devolved healthcare jurisdiction (country). We will conduct sensitivity analyses to explore the impact of perceived success (by the hospital thrombosis committee) of implementing the randomised thromboprophylaxis management strategy on inferences, as well as assessing consistency of overall effect estimates with estimates in the selected group of participants for whom participant-level drug prescription information is available.

A detailed SAP with all proposed statistical analyses will be drafted early in the trial and finalised prior to the first data extraction from the source databases. The SAP will be reviewed by oversight committees prior to sign off. Formal interim analyses are not planned.

11. Health economic evaluation

11.1 Within-trial analysis

We will assess the relative cost-effectiveness between intervention strategies from NHS and personal social services perspectives. We will present two sets of analyses. Firstly, key differences in resource use and costs between the two strategies over the 90 days in the trial, including the thromboprophylaxis treatment and hospital resource use will be assessed and presented alongside differences in VTE and major bleed events following intention-to-treat principle. Resources involved in the treatment strategies will be evaluated using study regimens and data from the adherence assessment. Hospital resource use (e.g. days in hospital, readmissions, outpatient appointments/ investigations) will be assessed using the linked participant-level administrative datasets (HES, PEDW and NHSBSA prescriptions). Thromboprophylaxis treatment and hospital care resources will be costed using latest available NHS drug and reference costs. HES, PEDW and NHSBSA prescription data over the previous 90 days prior to participant admission to hospital will inform baseline adjustments when estimating differences in resource use and costs between trial arms.

11.2 Modelling of long-term events

Although the 90 days trial follow-up captures the key adverse outcomes, consequences of these events evolve over a longer term. Long-term sequelae of VTE events, such as post-thrombotic syndrome (PTS) and chronic pulmonary hypertension will not be diagnosed until after 90 days but may have substantial

health impact. In order to derive estimates of the effectiveness of treatments on these long-term uncommon events, we have chosen not to directly observe them within the trial but to derive a model with population specific effect estimates from the trial. This approach will be much more efficient and provide excellent value for money by considerably reducing trial follow-up. If the modelling suggests that our conclusions are sensitive to uncertainty around the impact of treatment on long-term events, then we will seek additional funding to analyse the whole life course of participants and measure long term health outcomes, such as the incidence and severity of PTS.

While previous models of thromboprophylaxis strategies have been published, their relevance is limited due to lack of focus on hip fracture population[9,51] or use of now outdated data.[9] Therefore, while previous models will inform model structure, we will use the contemporary NHS data (i.e. from the 363K NHFD linked with HES and ONS data mentioned above) relevant to target population and control treatment and, if needed, published epidemiological data to inform rates of DVT, PE, PTS, major bleeding and mortality of our target population of people with hip fracture above age 60 years. The model structure is likely to include a short-term decision tree model (e.g. 6 months), informed by key effectiveness and safety outcomes, combined with a long-term Markov model. The Markov model will quantify the QALY losses from any deaths and any ongoing morbidity in the short-term model and will capture the costs and QALY losses over a lifetime horizon. The trial will inform treatment costs and effects with allocation to aspirin vs LMWH strategy.

The linked hospital administrative datasets and NHS reference costs will inform evaluation of costs related to adverse events. External data will inform health-related quality of life associated with adverse events.[37] The quality-adjusted life years and costs in the model will be discounted at 3.5% per year. We will report incremental cost per QALY with aspirin versus LMWH in target population and use probabilistic sensitivity analysis to summarize parameter uncertainty and report probabilities of aspirin being cost-effective at £0 to £30K/QALY thresholds and value of reducing uncertainty in key model parameters.

A health economic analysis plan (HEAP) with full details of all analyses will be finalised prior to the database lock for trial analysis at end of follow-up.

12. Ethics and governance

12.1 Approvals

Following Sponsor approval, the protocol, fair processing notice and other study materials will be submitted to an appropriate Research Ethics Committee (REC), CAG, HRA and relevant data controllers for written approvals.

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

12.2 Issues

Choice of a cluster design

Hospitals aggregate their local expertise in the fields of thrombosis and bleeding into Thrombosis Committees. These committees are responsible for assessing national recommendations issued from guideline bodies, particularly NICE, in the context of their local situation and practice. The committee then issues local hospital policy

guidance which is implemented throughout that hospital. As such a trial testing a policy for thromboprophylaxis is necessarily testing the impact of a hospital-wide policy rather than the administration of a single drug. it is therefore logical to assess the policy at a hospital level and so a cluster design is the most appropriate.

No individual consent process

Given this system of implementing thromboprophylaxis strategies, in accordance with the Medical Research Council advice for cluster randomised trials, we believe that the treatment decision is effectively implemented at a cluster- level even though the intervention is delivered at a participant-level. We have discussed the proposed design with the MHRA, Sponsor and HRA who have agreed that a trial testing policy for first-line VTE thromboprophylaxis is not a Clinical Trial of an Investigational Medicinal Product (CTIMP). There is precedent for such an approach in the UK (SUDDICU Study, NCT02389036), which is also a large cluster randomised trial of different policies of medicinal agents). Both policies are in current use within the NHS and are recommended by NICE. As such the risk associated with participation in the trial is assessed to be low.

In line with the international guidance on consent in cluster randomised trials as outlined in the Ottawa[27] and NIH Health Care Systems Research Collaboratory[28] Statements on the ethics of cluster randomised trials, in our opinion, individual participant consent to participate in the trial is not required.

We propose that each hospital thrombosis committee act as the ‘cluster representation mechanism’. Data from eligible participants will be routinely entered into the NHFD, the national register of patients with hip fracture. We plan to identify participants through the national register of hip fractures. This register is typically two to three months out of date, a time at which the vast majority of patients have been discharged from hospital. Mortality at this time is approximately ten percent and one third of patients have chronic cognitive impairment and potentially lack capacity, requiring access to an unknown consultee.

We will apply for approval for Section 251 of the 2012 NHS Health and Social Care Act exemption from individual consent from the Confidentiality Advisory Group

Knowledge of participants recruited

Eligible patients will receive the treatment the hospital is allocated to at the time of their index presentation, however the entry of participant data in the registry follows later. This is because the emergent nature of treatment of hip fracture follows immediately after the index injury; whereas uploading and processing of the individual participant data in the registry lags behind the index fracture by approximately 3 months.

13. Public Involvement

13.1 Patient and Public Advisory Group (PAG)

Our PAG consists of our two co-applicant members (1 female, 1 male), supported by a wider group of 14 patients and members of the public who have lived experience of hip fracture or are interested in how researchers use routine data for research (participant characteristics 35-78 years, socio-economic groups 2-7, self-reported identity English, Irish, Indian, Bengali and Jamaican). Our PAG members represent

the age group who most commonly suffer hip fracture. This wider group will support our patient co-applicants in how best to communicate to the public and patients with hip fracture, how we plan to the use their routine healthcare data and in the dissemination of results.

13.2 Accessible participant information materials

With our PAG, we will produce a plain English electronic and paper, patient and carer facing, fair processing notice. This will be hosted on dedicated project and Thrombosis UK websites and be visible within clinical areas where this population are treated within the clusters. Our PAG will ensure that the information is appropriately written in plain English, outlining the background, objectives, potential risks and how individuals' data will be used to answer the research questions.

The materials will be prepared in English and the three most commonly used second languages in the UK based upon ONS data. The website will contain embedded videos, resource links, information sheets and signposting pathways to access follow-up in the event of a VTE or bleeding event.

13.3 Mitigating barriers to participation

Given the cluster design and existing ethical approval we do not anticipate significant barriers to participation. We have extensive support from hospitals to participate. We recognise the electronic health record teams will need significant support. This will be to facilitate the communication of which thrombophylaxis strategy to employ for participants using the electronic health record and prescribing systems. We have costed in such support and expect that this should mitigate delays to start.

We will also utilise the associate Principal Investigator scheme and Trainee Clinical Networks, including the British Orthopaedic Trainee Association, to develop clinical research champions at sites. These wider members of the team can provide local support to ensure the study is communicated clearly and again iterating which treatment strategy the hospital will be providing.

We are conscious that this trial design may be less familiar with members of the public. As such we will use this trial for a broader piece of work around communicating the study design to the public. We will produce information on cluster trial design and the use of routine data for research purposes on the study website.

Our PAG will provide guidance into the depth of information we provide, how we provide it (text / infographics / videos etc) and how we ensure a wide reach.

13.4 Keeping participants informed

Our PAG will assist in writing a plain English summary of progress and which can be shared with participants through hospital websites, Thrombosis UK and via noticeboards on wards treating these patients.

We have included costings for a publicly accessible trial website (hosted on QMUL server) that will be kept maintained and developed during the course of the study. In addition to sharing progress, we will host relevant resources and signpost to further information on VTE. Together with our PAG, we will produce an online video to help patients and carers better understand the risk and impact of VTE after a hip fracture. In addition to a website, we will utilise social media to provide updates on study progress and to assist with dissemination. Our social media strategy will involve our

network of national stakeholders (BOA, OTS and Thrombosis UK) allowing us to reach a wide audience.

14. Data management and record keeping

14.1 Data management concept

For the purposes of the trial analyses the trial team will only process linked, deidentified data. In order that this dataset can be created, identifiable NHFD data will be provided to a third party for data linkage. NHFD will send NHS number, date of birth, gender and postcode as well as a unique NHFD patient identifier (deidentified) for linkage. The trial central office will provide similar data for any participants who have withdrawn from the study so that their data are not included in the final linked dataset. The trusted third parties, SAIL in Wales and NHS England in England, will link NHFD data to the relevant civil register of deaths and administrative databases in their jurisdiction.

14.2 Source data

Participants

The National Hip Fracture Database (NHFD) began data collection in 2007; since January 2011 baseline data completeness has exceeded 95%.[3] Data are recorded from patients admitted with hip fracture in England, Wales and Northern Ireland. Data include patients' characteristics, fracture pattern, surgical interventions and measures of process such as time to theatre. These details are typically collected by specialist nurses within each hospital who provide continuity of care to patients with hip fractures and manage submissions to the NHFD. Data from patients aged under 60 are not captured within the database. The database now has >800,000 records from 163 hospitals. The median number of patients per hospital in 2022 was 365 (interquartile range 277-455).[3]

Outcomes

Civil Registration (Deaths) provides a complete register of date and cause of death in England and Wales and is administered by NHS England. Date and causes of death are captured in the register.

Across the UK various data warehouses hold information on patients admitted to NHS hospitals, including diagnostic ICD-10 codes about a patient's illness and procedural codes for surgery (OPCS). We will use these administrative datasets to source additional data. For patients treated in England we plan to use admitted patient care, emergency care, outpatient care and critical care datasets within the Hospital Episode Statistics (HES) database and NHSBSA prescriptions data; in Wales, the Patient Episode Database for Wales (PEDW) derived from the Admitted Patient Care dataset.

14.3 Data flows

A summary of the data flows is at Figure 3.

Identifiable NHFD data will be provided to NHS England (NHSE) and Digital Health and Care Wales for data linkage. NHFD will send NHS number, date of birth, gender and postcode as well as a unique patient identifier for linkage. The legal basis for the NHFD to collect personal data is Section 251 of the NHS Act 2006 (CAG 803(PR11)/2013). The legal basis under which this application for the transfer of data

from NHFD to each of these data controllers, and to enable them to perform linkage on our behalf is section 251 of the NHS Act 2006 and the Health Service (Control of Patient Information) Regulations 2002. The legal basis for QMUL to receive data from each data controller is the Health and Social Care Act 2012.

NHSE will link Civil Registration (deaths) date and cause of death, HES data and NHSBSA data with the unique identifier. Digital Health and Care Wales will link PEDW data with the unique identifier.. QMUL will then receive participant level deidentified data only from each data controller, i.e. the linked data with the unique patient identifier, via Secure File Transfer Protocol. The received data will be stored in the PCTU Data Safe Haven (DSH).

14.4 Data security

Details of the data collected, where it is stored and who has access to it along with a fair processing statement will be available for the public to see on the study website.

The ICO registration number for QMUL is ZA512301. The policy document can be accessed through the link below:

https://online.qmul.ac.uk/privacy-policy.htm

For the purposes of the trial analyses, the trial team will only process linked deidentified patient level data. PCTU at QMUL has an DSP Toolkit (8HN69-PCTU, Publication Status: Standards Met, Date of Publication: 30/06/2024).

The PCTU data security and protection (IG) policy can be found at:

https://www.qmul.ac.uk/pctu/media/pragmatic-clinical-trials-pctu/eventspage/documents/PCTU-Data-Security-and-Protection-(IG)-Policy.pdf

As per the NHS Data Security and Protection Toolkit (DSPT) mentioned above, data received by QMUL will be stored, managed and processed from within the PCTU Data Safe Haven (DSH), which has strict, built-in role-based data access controls (usage requires multi-stage approvals) in place. The DSH also has data handling restrictions, such as very limited access to the Internet, and restricted ability to copy or send data. The DSH is a segregated secure data storage and processing environment accessible only to authorised users via the Citrix secure VPN. Study data will be stored in restricted folders within the DSH, only accessible to authorised staff listed. No study data will be shared outside of the DSH without an appropriate data sharing agreement in place.

The PCTU research privacy statement can be found at:

https://www.qmul.ac.uk/pctu/media/pragmatic-clinical-trials-pctu/eventspage/documents/PCTU-research-privacy-statement-final-v-1.0.pdf

The processing of the requested data will be carried out in the course of its legitimate activities by a QMUL research team. The data processing will be undertaken exclusively by a limited number of experienced members of the research team and will be carried out with appropriate safeguards for the rights and freedoms of data subjects.

All data storage and processing will be carried out in line with QMUL and PCTU SOPs and policies.

14.5 Confidentiality

The data processed for the analysis will be deidentified.

NHS England and Digital Health and Care Wales will provide data in a deidentified format where individuals are not able to be identified. Only the unique ID number on the electronic database will identify database records. Nevertheless, it is worth mentioning that due to the presence of full dates of death (for a small cohort of potential participants), there might be, although very improbable, the possibility of participant re-identification. All documents will be stored securely and only accessible by study staff and authorised personnel.

The researchers will work closely with data controllers to construct a data request that minimises the risk of disclosure. The risk of secondary disclosure will be minimised with use of appropriate study reporting methods e.g. small number suppression.

14.6 Record Retention and Archiving

Data collected directly during the trial will be archived in accordance with PCTU SOPs. Deidentified research data will be archived for 25 years in line with the UK Policy Framework for Health and Social Care Research. The linked, deidentified datasets will be destroyed in accordance with the requirements of the relevant data controllers.

15. Safety reporting

The register of participants exposed to the treatments only mature three months after the exposure, and the sources of the outcome data are not available until between three and six months beyond that. There is no direct participant followup included within the trial procedures. Therefore, outcome data will not be available until the conclusion of the trial. It is therefore not possible for safety data to be collected during the conduct of the trial. Safety outcomes, described above, will be reported as part of the primary analysis.

This trial is highly pragmatic, ‘open-label’ and seeks to evaluate two health technologies already deployed in usual care. Therefore, this balance between the burden on participants of follow-up, the capability of the trial team to monitor safety during the trial and likely additional risk that this presents to patients is reasonable.

16. Monitoring and auditing

The sponsor or delegate retains the right to audit any study, study site, or central facility. Any part of the study may be audited by the funders, where applicable.

On site or remote monitoring will be performed as per the study monitoring plan. Monitoring will include adherence to the allocated treatment strategy.

17. Trial committees

17.1 Trial Management Group

The day-to-day management of the trial will be the responsibility of the Trial Manager, supported by a Senior Trial Manager. This will be overseen by the Trial Management Group, who will meet monthly to assess progress. It will also be the

responsibility of the Trial Manager to undertake training of the research staff at each of the trial centres. The trial statistician, health economist and the information specialist will be closely involved in setting up data capture systems, design of databases and clinical reporting forms.

17.2 Trial Steering Committee

The TSC, which includes independent members, provides overall supervision of the trial on behalf of the funder. Its terms of reference will be agreed with NIHR HTA and will be drawn up in a TSC charter which will outline its roles and responsibilities. Meetings of the TSC will take place at least once a year during the recruitment period. An outline of the remit of the TSC is to:

- monitor and supervise the progress of the trial towards its interim and overall objectives.
- review at regular intervals relevant information from other sources.
- inform the funding body on the progress of the trial.

17.3 Data Monitoring Committee

Given that the there is no safety monitoring within the trial, and that stopping early for futility or an early safety signal is not plausible given the short recruitment window and delayed availability of outcome data, no DMC will be established.

18. Finance and funding

This study is funded by the NIHR Health Technology Assessment Programme (NIHR159321). The views expressed are those of the author(s) and not necessarily those of the NIHR or the Department of Health and Social Care.

19. Indemnity

The insurance that Queen Mary University of London has in place provides cover for the design and management of the study as well as "No Fault Compensation" for participants, which provides an indemnity to participants for negligent and nonnegligent harm.

20. Dissemination of research findings

The dissemination strategy will consist of three workstreams. First, to ensure patients and the public are informed of trial results; second, to engage healthcare providers, and third, to inform national guideline and policymakers.

20.1 Patients, patient advocacy groups & members of the public

The Communications and Marketing team of Queen Mary University will coordinate social media, press and organisational website publicity to maximise exposure. Our PAG will lead dissemination to patients and carers directly through Thrombosis UK and our links with local organisation in East London such a Social Action for Health and Age UK East London, to assist with disseminating to a diverse audience. Our PAG will also work on a wider piece of work around building trust in the use of routine healthcare data for research. This builds upon work being done ensuring that the use of routinely collected data for research is communicated clearly for a wider audience.

20.2 Healthcare providers

We will publish four free-to-access publications in the mainstream scientific literature. In addition to targeting these high-impact peer-reviewed multidisciplinary outputs (e.g., NEJM/Lancet), we will use our professional networks to promote editorial/opinion pieces in specialty specific journals. Trial findings will be submitted for presentations at annual meetings of the appropriate specialist society meetings. We will present the findings to the entire NHS via the NHS national electronic Library for Health (NHS Evidence). International 'reach' of our published research findings will be supplemented by presentations at high visibility meetings.

20.3 National guidelines and policy makers

We will use our co-applicants' established (inter)national networks to disseminate these research findings. We will alert NICE via relevant standing committees and surveillance teams of the results of our study to make recommendations on treatment via NG89 and QS201. We will alert the Royal Colleges of Surgeons and Physicians to results and submit suggested updates to the BOA.

21. Figures

Figure 1: First-line thromboprophylaxis strategies involving LMWH

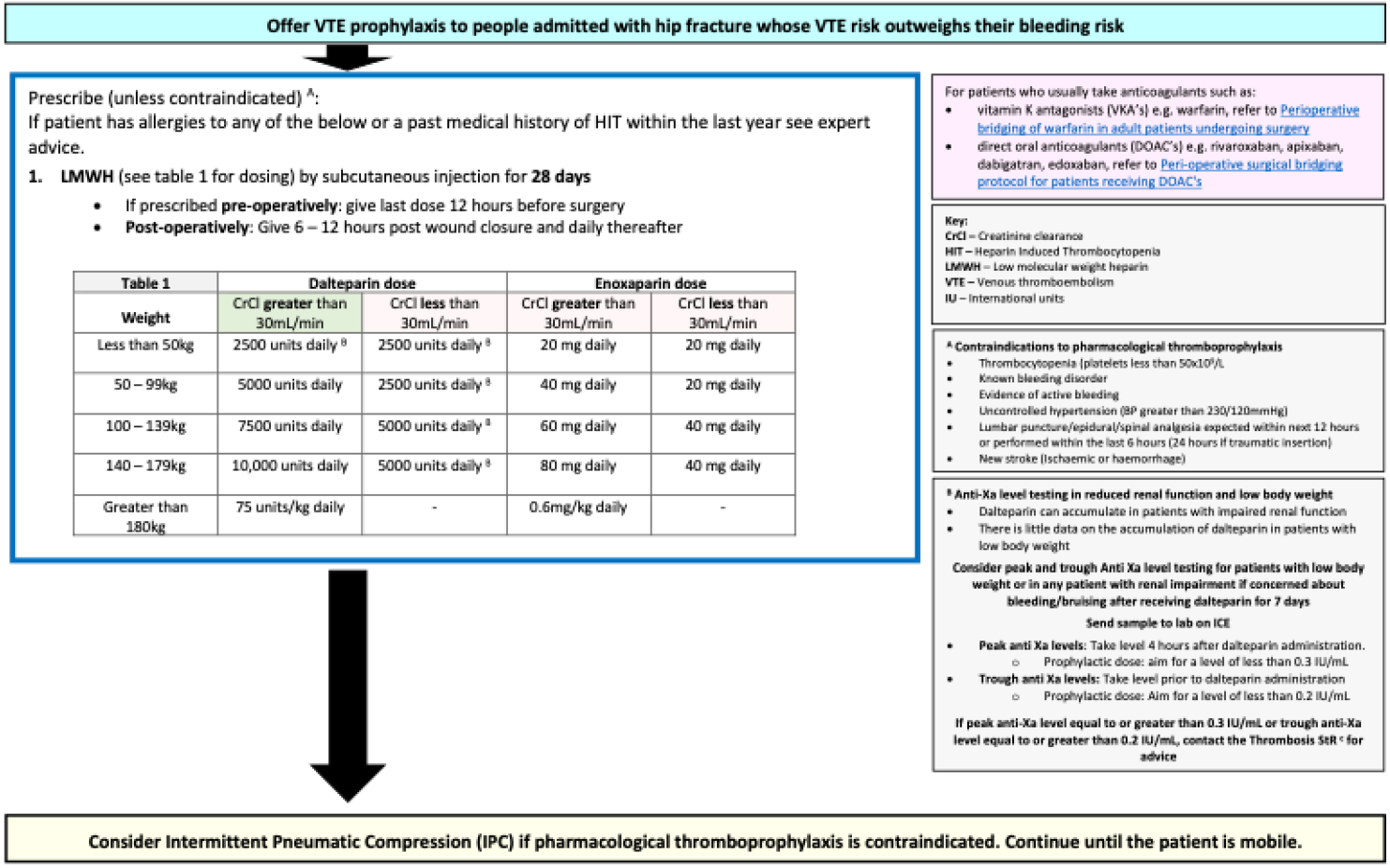


Figure 2: First-line thromboprophylaxis strategies involving aspirin

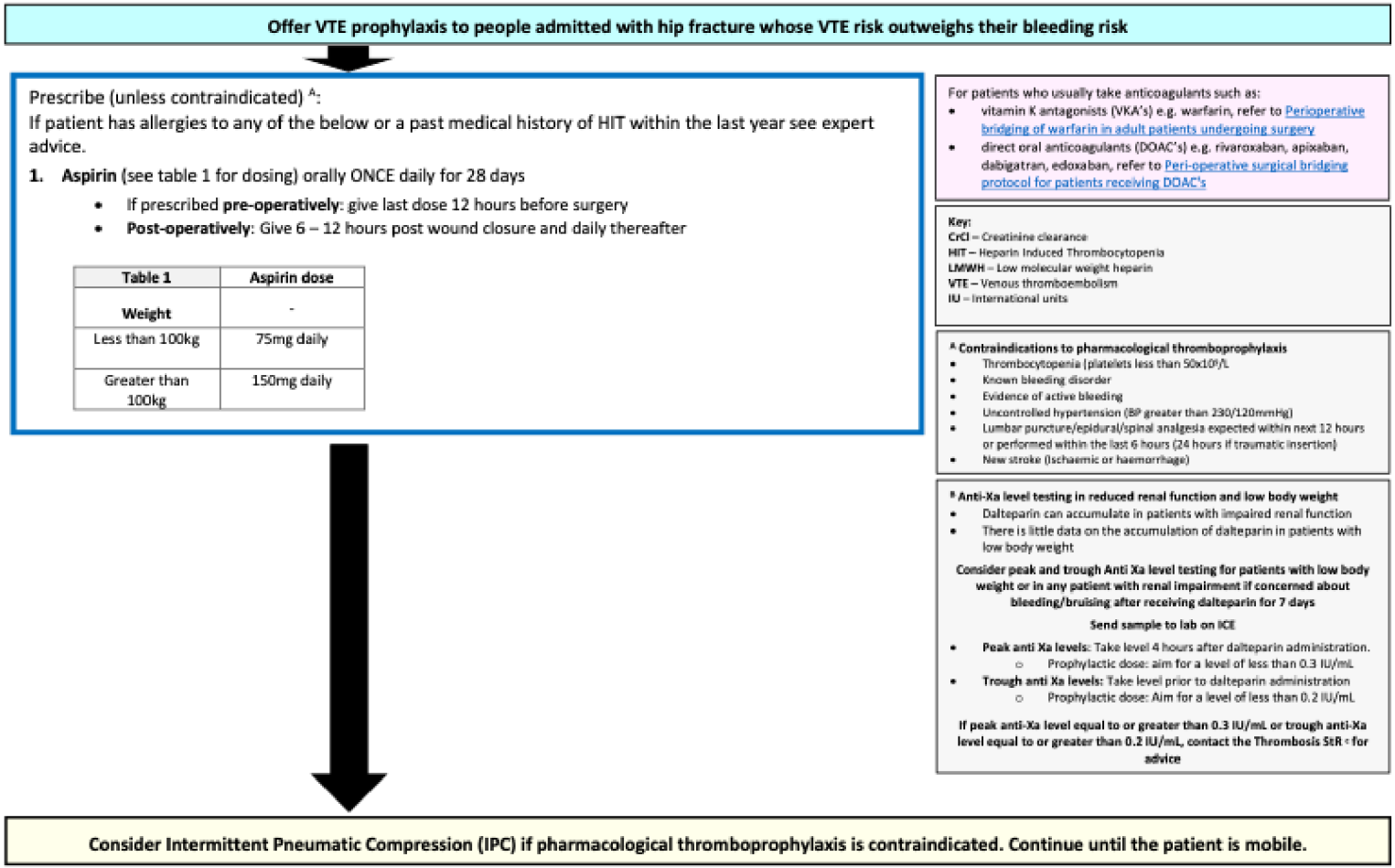
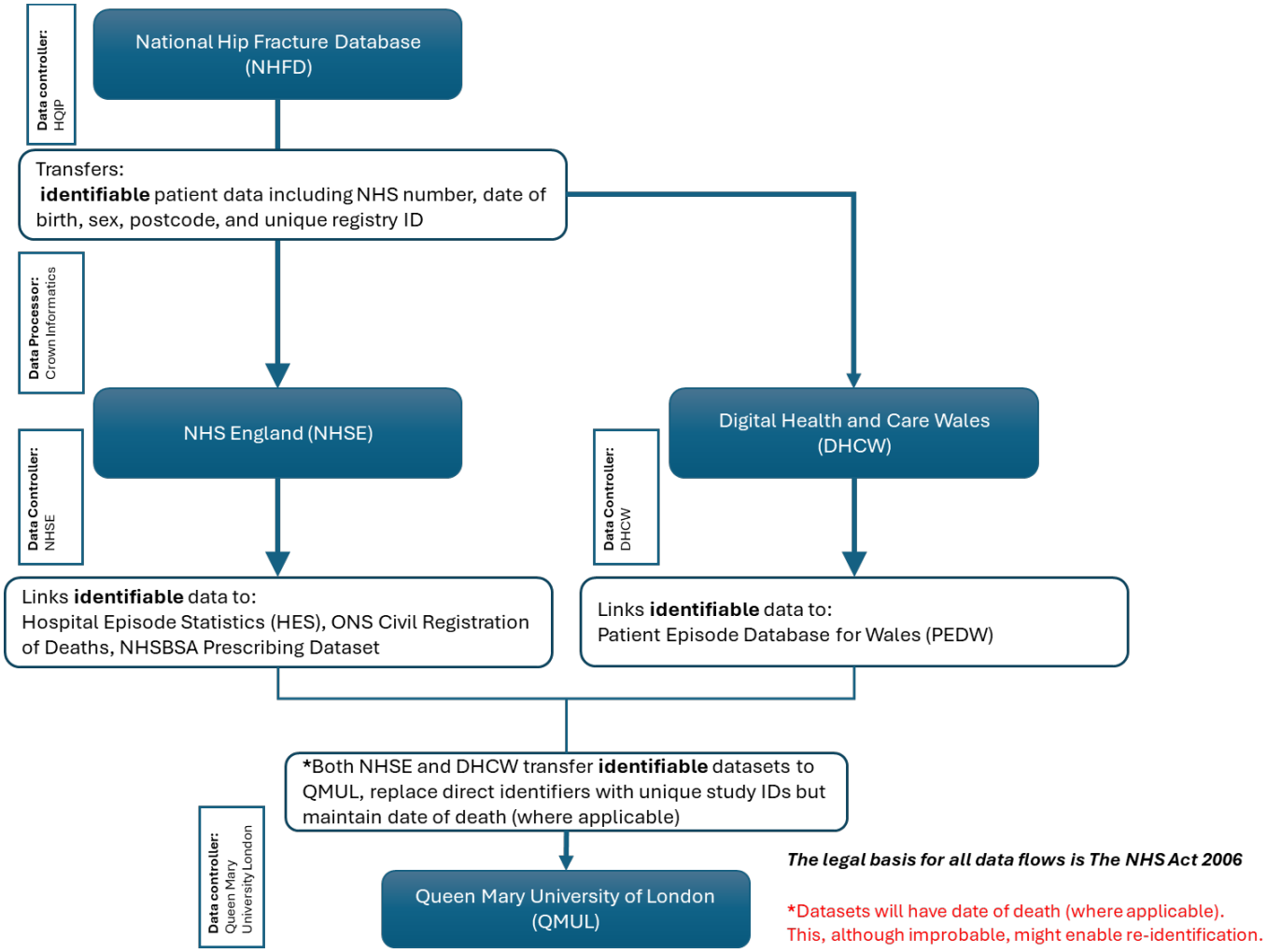


Figure 3: Data flow diagram


Data controller: HQIP
National Hip Fracture Database (NHFD)
Transfers:
identifiable patient data including NHS number, date of birth, sex, postcode, and unique registry ID
Data Processor: Crown Informatics
Data Controller: NHSE
NHS England (NHSE)
Data Controller: DHCW
Digital Health and Care Wales (DHCW)
Links **identifiable** data to:
Hospital Episode Statistics (HES), ONS Civil Registration of Deaths, NHSBSA Prescribing Dataset
Links **identifiable** data to:
Patient Episode Database for Wales (PEDW)
*Both NHSE and DHCW transfer **identifiable** datasets to QMUL, replace direct identifiers with unique study IDs but maintain date of death (where applicable)
Data controller: Queen Mary University London
Queen Mary University of London (QMUL)
The legal basis for all data flows is The NHS Act 2006
*Datasets will have date of death (where applicable). This, although improbable, might enable re-identification.

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23. Protocol Version and Amendment History

Amendment N°	Protocol Version N°	Date Issued	Author(s) of Changes	Details of Changes made
N/A	1.0	10/04/2025	Xavier Griffin	First version
1	2.0	07/07/2025	Nkemjika Abiakam	Changes made to remove all references to Scottish sites and datasets. Collection of HES, PEDW and NHSBSA datasets 90 days prior to participant admission. Changes to dataflow diagram