JRMO Research Protocol for MHRA Regulated Studies

Full Title

Thromboprophylaxis in Lower Limb Immobilisation (TiLLI): a multicentre study comprising two linked open label phase III randomised controlled trials evaluating the effectiveness and cost effectiveness of different methods of pharmacological prophylaxis for patients with temporary lower limb immobilisation.

Short Title

Thromboprophylaxis in Lower Limb Immobilisation (TiLLI)

Sponsor	Queen Mary University of London Contact person: Dr Mays Jawad Governance Operations Manager Joint Research Management Office Mile End Road London E1 4UJ Phone: +44 (0) 20 7882 7275/6574 Email: research.governance@qmul.ac.uk
IRAS Number	1009305
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REC Reference	24/NW/0166
Chief Investigator	Professor Xavier Griffin Professor of Orthopaedic Surgery Barts Bone and joint Health Email: x.griffin@qmul.ac.uk
Deputy Chief Investigator	Professor Daniel Horner Consultant in Emergency and Critical Care Medicine NCA NHS Foundation Trust Phone: 01612065372 Email: Daniel.horner@nca.nhs.uk

Study Contacts

Trial Coordinator / Study Manager	TiLLI Trial Manager Pragmatic Clinical Trials Unit (PCTU), Queen Mary University of London Yvonne Carter Building 58 Turner Street London,E1 2AB Email: tilli-bjh@qmul.ac.uk
Funder	NIHR Coordinating Centre Alpha House Enterprise Road Southampton S016 7NS Email: postawardsetup@nihr.ac.uk
Clinical Trials Unit	Pragmatic Clinical Trials Unit (PCTU) Centre for Evaluation & Methods Wolfson Institute of Population Health Queen Mary University of London Yvonne Carter Building 58 Turner Street, London, E1 2AB Email: pctu-admin@qmul.ac.uk
Statistician	Thomas Hamborg Pragmatic Clinical Trials Unit (PCTU), Centre for Evaluation & Methods, Wolfson Institute of Population Health, Queen Mary University of London Yvonne Carter Building 58 Turner Street, London, E1 2AB
Trial pharmacist	QMUL Sponsor Pharmacy representative Clinical Trials Pharmacy Royal London Hospital Floor 5, Pathology and Pharmacy Building 80, Newark Street, London, E1 2ES
Committees	**Data Monitoring and Ethics Committee (DMEC)**
(DMEC, TSC, TMG)	Role: To review the trial data throughout the trial and assess whether there are any safety issues that need to be brought to the attention of the Trial Steering Committee, or any ethical

reasons why the trial should not continue.
Chair: Professor Fionnuala Ní Áinle

Trial Steering Committee (TSC)

Role: To provide overall supervision of the trial and ensure that it is being conducted according to the protocol, good clinical practice (GCP) and relevant regulations. To monitor trial progress in relation to recruitment, data capture and completeness, protocol deviations and participant withdrawals.
Chair: Professor Heather Jarman

Trial Management Group (TMG)
Role: To monitor all aspects of the trial conduct and progression, ensuring that the protocol is adhered to.
Chair: Professor Daniel Horner

Committee chairs can be contacted via the TiLLI Trial Manager.

Key protocol contributors

Name	Affiliation	Email address
Steve Goodacre	University of Sheffield	s.goodacre@sheffield.ac.uk
Sarah Davis	University of Sheffield	S.Davis@sheffield.ac.uk
Alun Davies	Imperial College London	a.h.davies@imperial.ac.uk
Jamie Cooper	Grampian University Hospitals NHS Foundation Trust	Jamie.cooper2@nhs.scot
Rhona Sinclair	The Newcastle Upon Tyne Hospitals NHS Foundation Trust	Rhona.sinclair1@nhs.net
Beverley Hunt	Guy's and St Thomas' NHS Foundation Trust	Beverley.hunt@gstt.nhs.uk
Jamila Kassam	Queen Mary University London	j.kassam@qmul.ac.uk
Thomas Hamborg	Queen Mary University London	t.hamborg@qmul.ac.uk
Borislava Mihaylova	Queen Mary University London	b.mihaylova@qmul.ac.uk
Roopen Arya	Kings College Hospital NHS Foundation Trust	roopen.arya@nhs.net
Delphine Douillet	University Hospital Angers, France	delphinedouillet@gmail.com
Kerstin de Wit	Queens University, Ontario	kerstin.dewit@queensu.ca
Matthew Machin	Imperial College London	matthew.machin12@imperial.ac.uk
Chris Bretherton	Queen Mary University London	c.bretherton@qmul.ac.uk
Richard Hooper	Queen Mary University London	r.l.hooper@qmul.ac.uk
Jodie Hutchens	Queen Mary University London	j.hutchens@qmul.ac.uk
Sophie Parker	Queen Mary University London	sophie.parker@qmul.ac.uk

Protocol Version History

Version Number	Version Date	Amendment Number	Summary of Changes
V1.0	26/04/2024	N/A	N/A
V2.0	11/07/2024		Protocol updated following initial regulatory feedback

Contents

II. Glossary of terms and abbreviations

AE	Adverse Event
AESI	Adverse Event of Special Interest
AR	Adverse Reaction
APR	Annual Progress Report
ACTS	Anti-Clot Treatment Scale
CI	Chief Investigator
DMEC	Data Monitoring and Ethics Committee
DSUR	Developmental Safety Update Report
DOAC	Direct Oral Anticoagulant
eCRF	Electronic Case Report Forms
EHR	Electronic Health Records
ED	Emergency Department
ESAIC	European Society of Anaesthesiology and Intensive Care
ESRA	European Society of Regional Anaesthesia and Pain Therapy
EU	European Union
EQ-5D-5L	EuroQol 5 Dimensions 5 Level questionnaire
GCP	Good Clinical Practice
HEAP	Health Economic Analysis Plan
HES	Hospital Episode Statistics
ICD	International Classification of Diseases
ISTH	International Society of Thrombosis and Haemostasis
IMP	Investigational Medicinal Product
IB	Investigators Brochure
LMWH	Low Molecular Weight Heparin
NHS	National Health Service
NIHR	National Institute for Health and Care Research
NICE	National Institute for Health and Social Care Excellence
NSAID	Non-steroidal anti-inflammatory medicinal products
ONS	Office of National Statistics
OPCS	Office of Population Censuses and Surveys
PAG	Patient Advisory Group
PCTU	Pragmatic Clinical Trials Unit
PSSRU	Personal Social Services Research Unit
PTS	Post-thrombotic Syndrome
PI	Principal Investigator
QA	Quality Assurance
QALYs	Quality-Adjusted Life Years
QoL	Quality of Life
QMUL	Queen Mary University London
RCT	Randomised Controlled Trial
RSI	Reference Safety Information
RCEM	Royal College of Emergency Medicine
SMR01	Scottish Morbidity Record 01

SAR	Serious Adverse Reaction
SAE	Severe Adverse Event
SAP	Statistical Analysis Plan
SmPC	Summary of Product Characteristics
SUSAR	Suspected Unexpected Serious Adverse Reaction
TiLLI	Thromboembolism in Lower Limb Injury
TMG	Trial Management Committee
TSC	Trial Steering Committee
POMCTN	UK Perioperative Medicine Clinical Trials Network
VTE	Venous Thromboembolism
VAS	Visual Analogue Scale

III. 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, the Declaration of Helsinki, and the current regulatory requirements, including the Medicines for Human Use (Clinical Trials) Regulations 2004 (UK S.I. 2004/1031) and all subsequent amendments. I delegate responsibility for the statistical analysis and oversight to a qualified statistician (see declaration below).

Chief Investigator name: **Professor Xavier Griffin**

Xavier Griffin

Digitally signed by Xavier Griffin
Date: 2024.07.30 08:42:45 +01'00'

Deputy 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, the Declaration of Helsinki, and the current regulatory requirements, including the Medicines for Human Use (Clinical Trials) Regulations 2004 (UK S.I. 2004/1031) and all subsequent amendments. I delegate responsibility for the statistical analysis and oversight to a qualified statistician (see declaration below).

Chief Investigator name: **Professor Daniel Horner**

Daniel Horner

Digitally signed by Daniel Horner
Date: 2024.07.29 15:36:07 +01'00'

Statistician's Agreement

The study as detailed within this research protocol plan will be conducted in accordance with the principles of Good Clinical Practice, the UK Policy Framework for Health and Social Care Research, the Declaration of Helsinki, and the current regulatory requirements, including the Medicines for Human Use (Clinical Trials) Regulations 2004 (UK S.I. 2004/1031) and all subsequent amendments, and 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 for the statistical analysis and oversight of this study.

Statistician's name: **Dr Thomas Hamborg**

Thomas Hamborg

Digitally signed by Thomas Hamborg
Date: 2024.07.29 15:27:07 +01'00'

Principal Investigator Agreement Page

The clinical study as detailed within this research protocol **(Version 2.0, dated 11/07/2024)**, or any subsequent amendments, involves the use of an investigational medicinal product and will be conducted in accordance with the UK Policy Framework for Health and Social Care Research , the World Medical Association Declaration of Helsinki (1996), Principles of ICH-GCP, and the current regulatory requirements, as detailed in the Medicines for Human Use (Clinical Trials) Regulations 2004 (UK S.I. 2004/1031) and any subsequent amendments of the clinical trial regulations.

Principal Investigator Name: _____

Principal Investigator Site: _____

Signature and Date:

IV. Synopsis

Full title	Thromboprophylaxis in Lower Limb Immobilisation (TiLLI): a multicentre study comprising two linked open label phase III randomised controlled trials evaluating the effectiveness and cost effectiveness of different methods of pharmacological prophylaxis for patients with temporary lower limb immobilisation.
Short title and / or acronym	Thromboprophylaxis in Lower Limb Immobilisation (TiLLI)
Sponsor	Queen Mary University London
MHRA Risk level	Type A = No higher than the risk of standard medical care (studies are those testing authorised medicinal products in accordance with the marketing authorisation in an EU member state).
Phase of the trial	III
Medical condition or disease under investigation	Prevention of venous thromboembolism (VTE) in at risk population
Study design and methodology	A pragmatic, open-label, linked pair of randomised controlled trials with common outcomes and parallel economic analysis each with internal pilot phases, conducted across 30 NHS sites
Planned number of participants	The target accrual for TiLLI-High is 4354 participants. The target accrual for TiLLI-Low is 5690 participants.
Objectives	To estimate and draw inferences on the difference in a composite outcome of net clinical benefit, including symptomatic VTE events (any deep vein thrombosis or pulmonary embolism), major bleeding or cause-specific mortality (death from either pulmonary embolus or major bleeding) between treatment groups within 90 days of randomisation.
Inclusion and exclusion criteria	***Inclusion criteria*** 1. Age 16 years and above 2. Placed in temporary lower limb immobilisation (rigid cast or brace) as a result of an injury that occurred within the last 7 calendar days ***Exclusion criteria*** 1. Hospital admission is required direct from the emergency department, minor injuries unit, or fracture clinic setting with an expected length of stay >2 calendar days. 2. Absolute contraindication or known hypersensitivity to anticoagulants, including history of end stage renal failure (eGFR <20ml/min/1.73m^2), hepatic

	failure or use of concomitant systemic treatment with azole-antimycotics (such as ketoconazole, itraconazole, voriconazole and posaconazole), HIV protease inhibitors (e.g., ritonavir) or active substances strongly inhibiting elimination pathways such as CYP3A4 or P-gp (such as clarithromycin, erythromycin or dronaderone) or a history of heparin induced thrombocytopenia. 3. Pregnancy, actively seeking conception, or active breastfeeding. 4. Preceding use of anticoagulant treatment for > 3 calendar days at prophylactic or therapeutic dose. 5. Previous enrolment in the TiLLI study. 6. Non-rigid immobilisation (crepe bandage, tubigrip support, strapping). 7. Time since prescription of rigid immobilisation > 3 calendar days. 8. Co-enrolment onto a CTIMP where an anticoagulant is administered. 9. People lacking the capacity to consent. 10. Inability or refusal to use acceptable contraception* up until after the last administration of IMP. Only applicable for women of childbearing potential who have been randomised to receive apixaban or rivaroxaban. * List of acceptable contraception can be found in protocol section 7.0 eligibility criteria.
Investigational Medicinal Product(s)	Rivaroxaban 10mg once daily, via oral ingestion Apixaban 2.5mg twice daily, via oral ingestion Parenteral Low Molecular Weight Heparin (LMWH) or fondaparinux at standard prophylactic dose (determined by individual NHS trusts), via subcutaneous injection, as licensed for prevention of VTE.
Treatment duration	Drug treatments will be provided for the duration of immobilisation or up to 42 days (whichever is earlier), in accordance with current NICE guidance.
Follow up duration	90 Days
End of Trial definition	The end of trial will occur when the 90-day follow-up data for the final participant recruited has been entered on the study database.

1.0 Introduction

1.1 Background

What is the clinical problem being addressed?

Venous thromboembolism (VTE) is a major global health burden with a background incidence of 1-2 per 1000 individuals in the general population.[1,2] VTE is associated with a 30-day and one year case fatality rate of 10.6% and 23.0% respectively; costing the NHS an estimated £640 million in initial, direct healthcare costs alone.[3] Many people who survive an episode of VTE also suffer from longer term complications, such as post thrombotic syndrome, pulmonary hypertension or psychological sequelae.[4]

Temporary lower limb immobilisation (plaster cast, walking boot or rigid splint) and injury are combined risk factors for VTE (hazard ratio of 6.31 (95%CI: 5.30-7.52).[5] Approximately 70,000 people are immobilised after injury every year in the UK. VTE in this setting is potentially preventable, through risk assessment and appropriate prophylaxis with medication. However, there are risks of bleeding and other adverse events associated with drug prophylaxis. The variety of modern methods of lower limb immobilisation and early weight bearing regimens also contribute to the highly variable VTE risk in this population.[6, 7]

There is extensive variation in the current standard of care for risk assessment and drug prescribing in this group of people. International guidelines offer conflicting advice; widespread implementation of one specific risk assessment model has to date been limited by a lack of validation data.[8-11] In the UK, the National Institute for Health and Care Excellence (NICE) guidance and quality standards support the use of drug prophylaxis for people prescribed immobilization who are at risk of VTE.[10, 12] However, an audit by the Royal College of Emergency Medicine (RCEM) and survey of emergency departments report risk assessment occurring in less than half of immobilised patients and highly variable prescribing with parenteral (by injection) and oral drugs.[13, 14]

How the evidence supports this proposal

We explored the cost effectiveness of risk assessment and different drug thromboprophylaxis for this patient group in a systematic review, network meta-analysis and decision analysis model (NIHR 15/187/06).[11] Our decision model showed that drug prophylaxis for all patients had a 76% probability of being cost effective across the NHS, at a conventional threshold of £20,000 per QALY. However, a sensitivity analysis showed that risk-based prophylaxis strategies could be more cost effective, using a validated and highly sensitive (84-89%) tool.

Since our review, a risk assessment tool has been derived for this patient group using a large thrombosis dataset and expert consensus methodology.[15] This tool has since been validated in a prospective trial cohort and recently completed cluster randomised trial, including more than 5000 participants.[16, 17] At a threshold of >/= 6, this tool delivers the optimal trade-off between sensitivity and specificity identified by our decision analysis model (sensitivity 85.7%, specificity 32.2%, negative predictive value 99.3%) and is highly likely to outperform other strategies. Recent external validation in the UK also suggests improved performance over alternative current tools.[18] Validation of this tool allows objective and

reliable VTE risk stratification in patients with lower limb immobilisation, and helps tailor research questions to populations with different baseline VTE risks.

Our decision analysis model also showed that parenteral drug thromboprophylaxis reduces the risk of VTE compared with no prophylaxis, but found no data evaluating Direct Oral AntiCoagulants (DOACs) in this setting.[19] A sensitivity analysis using our decision model suggested that DOACs would be more cost-effective given the reduced drug costs, if similarly effective to parenteral therapy. A subsequent Bayesian network meta-analysis reached similar conclusions, reporting DOAC use to have the highest likelihood of optimal performance regarding net clinical benefit in patients with lower limb immobilisation having non-major orthopaedic surgery.[20] Patient groups have also highlighted their preference for oral therapies in this setting, both within our evidence synthesis and other similar projects.[11, 21]

1.2 Rationale for study design

This topic has been identified as a top 20 research priority by three James Lind Alliance priority setting partnerships and proposed as a research recommendation within NICE guidance (NG89) and an NIHR evidence synthesis.[10, 11, 22-24]

Additionally, we recently conducted a national survey of practice through RCEM, the British Orthopaedic Association (BOA) and the Orthopaedic Trauma Society (OTS).[13] We received responses from 116 out of 167 UK hospitals with type 1 emergency departments (70%) demonstrating marked variation in care. Most hospitals reported using a risk assessment pathway for patients managed in a lower limb rigid cast, but only 53% did so for people treated with a walking boot and <25% for those placed in knee splints, despite NICE guidance.[9] There was also variation in the choice of risk assessment tools and first-line thromboprophylaxis drug. Hospitals reported using a 'locally developed tool' for VTE risk stratification (31%), NICE guidance for hospitalised inpatients (25%), or were uncertain what method was used (22%). The vast majority of responding sites (70%) reported using low molecular weight heparin (LMWH) injections as thromboprophylaxis, in accordance with NICE guidelines. However, 30% sites reported already using unlicensed Direct Oral AntiCoagulants (DOACs) or other alternatives. These data highlight the ongoing uncertainty for clinicians and unwarranted national variation in patient care.

Our proposal directly addresses these key research recommendations and the original research brief for this commissioned call. We propose two, linked randomised trials depending on initial assessment of VTE risk, to generate robust, generalisable evidence on the clinical and cost effectiveness of pharmacological thromboprophylaxis for patients with temporary lower limb immobilisation after injury.

1.3 Assessment and management of risk

All patients who agree to participate in the study will be provided with standard verbal and written guidance regarding VTE risk following lower limb immobilisation, in keeping with NICE guidance and routine care.[10] This advice will include the importance of hydration, mobilisation, and compliance with any prescribed medication. We will allow sites to use existing guidance leaflets populated with local detail where applicable. We will also work with our stakeholder representatives to create additional guidance resources relevant to lower limb immobilisation, which will act as a potential longer-term resource and be hosted online by the national charity Thrombosis UK. This information will be complemented by existing free online material, including information on the signs and symptoms of VTE and bleeding, and when to seek help/medical review.

Participants in TiLLI-High will be allocated to either drug treatments (a) or (b). Participants in TiLLI-Low will be allocated to drug treatments (a) or (b) or no drug prophylaxis (c). Drug treatments will be provided for the duration of immobilisation or up to 42 days (whichever is earlier), in accordance with current NICE guidance.[10]

a) *Parenteral drug therapy, with low molecular weight heparin (LMWH) or fondaparinux, provided and dosed according to local policy and licensed indication.*

NICE currently recommend the use of either LMWH or fondaparinux for this indication.[10] LMWH agents are porcine derivative medications and can rarely be declined on religious or ethical grounds.[25] Data on the numerous LMWH agents available (dalteparin, tinzaparin, enoxaparin etc.) and fondaparinux suggest relative bioequivalence.[26] As such, we will allow the use of any NHS trust approved LMWH or fondaparinux in the parenteral prophylaxis group to increase generalisability, address health inequalities and support practice in keeping with national guidance. We will allow prescribing as per local policy but collect data on agent and dosing strategy (including adjustments for weight and renal function) to facilitate subgroup analyses.

b) *Oral drug therapy with DOAC medications.*

The use of DOACs in this setting is outside of licensed indications but is a common off-label use in current practice. Our recent survey suggests 30% of NHS trusts are already using DOACs for this indication with local approvals. We will allow use of either fixed dose rivaroxaban (10mg once daily) or apixaban (2.5mg twice daily) dosed according to local policy for orthopaedic prophylaxis. This decision is in keeping with NICE guidance on VTE prevention in orthopaedics and will facilitate standardised exclusion criteria, body mass dosing regimes and management of perioperative care/bleeding complications.[10, 27-31]

c) *No drug prophylaxis.*

This trial is categorised as:

Type A = No higher than the risk of standard medical care (studies are those testing authorised medicinal products in accordance with the marketing authorisation in an EU member state).

As such, we will take a risk adapted approach throughout the protocol and replace an investigator brochure (IB) with the summary of product characteristics (SmPC) for each potential agent, in accordance with national guidance.[32]

2.0 Trial objectives

2.1 Primary objective(s)

- To estimate and draw inferences on the difference in a composite outcome of net clinical benefit, including symptomatic VTE events (any deep vein thrombosis or pulmonary embolism), major bleeding or cause-specific mortality (death from either pulmonary embolus or major bleeding) between treatment groups within 90 days of randomisation.

2.2 Secondary objective(s)

- To compare all individual components of the primary composite outcome between treatment groups within 42 and 90 days from randomisation.
- To estimate and draw inferences on the difference in complications (including clinically relevant non-major bleeding and surgical site bleeding) between treatment groups within 42 days from randomisation.
- To report adherence to each therapy.
- To estimate and draw inferences on the acceptability of different prophylactic anticoagulants using the Anti Clot Treatment Scale (ACTS).[33]
- To estimate and draw inferences on differences in quality-of-life measures, including quality of life-adjusted survival, between treatment groups, up to 90 days post randomisation.
- To estimate and draw inferences on the difference in hospital readmission/reattendance and anticoagulant medication use (specific to VTE and bleeding) between treatment groups within the first 90 days.
- To estimate the health and social care resource use and costs and the relative cost effectiveness between treatment groups within the first 90 days.
- To estimate longer term outcomes, such as post thrombotic syndrome, chronic thromboembolic pulmonary hypertension and bleeding complications and draw inferences on cost effectiveness, by using a previously developed decision analytic model, informed by directly measured events up to 90 days.

2.3 Endpoints

2.3.1 Primary endpoint(s)

- The composite primary outcome of net clinical benefit will include symptomatic VTE events (any deep vein thrombosis or pulmonary embolism), major bleeding or cause-specific mortality (death from either pulmonary embolus or major bleeding). All individual outcomes contributing to the composite will be reported in accordance with consensus definitions published by the International Society of Thrombosis and Haemostasis (ISTH).[34-36]

2.3.2 Secondary endpoint(s)

All individual components of the composite outcome as binary variables (‘1’ if any event occurred, ‘0’ if no event occurred) of an event happening within 42 days from randomisation

for a) major bleeding events and within 90 days from randomisation for b) symptomatic pulmonary embolism or symptomatic deep vein thrombosis and c) cause-specific mortality. This will allow characterisation of the net clinical benefit and facilitate additional analyses. Endpoints are described further in section 2.5 below.

Patient satisfaction regarding the burdens and benefits of anticoagulation, using the validated Anti-Clot Treatment Scale (ACTS) for patients allocated to drug treatments. This scale is a 15-item patient-reported instrument of satisfaction with anticoagulation treatment, with separate internal measures of burden and benefits. This scale has reliability and validity across multiple language datasets and indications for anticoagulation and will provide contextual data on medication acceptability between treatment groups.[33, 37]

Health utility (EQ-5D-5L): differences in EQ-5D-5L QoL utility at 7 days, 42 days and 90 days after randomisation compared to a retrospective baseline and QALYs within 90 days of randomisation between treatment groups.

Medication adherence: monitor participant adherence to allocated anticoagulant verified through a digital response system.[6]

Complications including clinically relevant non-major bleeding and surgical site bleeding, objectively defined by ISTH criteria.[38]

NHS and social care resource use: Readmission/reattendance data, including hospital admissions and outpatient visits, primary care contacts, and use of key medication classes.

2.4 Exploratory or tertiary endpoints

There are no exploratory or tertiary endpoints for this study.

1.5 Objectives and endpoints summary

Primary Objective	**Primary Endpoint**
To estimate and draw inferences on the difference in a composite outcome of net clinical benefit, between treatment groups within 90 days of randomisation.	A composite primary outcome of net clinical benefit, comprising symptomatic VTE events (any deep vein thrombosis or pulmonary embolism), major bleeding or cause-specific mortality (death from either pulmonary embolus or major bleeding) within 90 days used as a binary variable (‘1’ if any event occurred, ‘0’ if none of the events occurred).
Secondary Objective	**Secondary Endpoint**
To compare all individual components of the primary composite outcome between treatment groups within 42 days and 90 days from randomisation.	***All individual components*** of the composite outcome as binary variables (‘1’ if any event occurred, ‘0’ if no event occurred) of an event happening within 42 days of randomisation for a) major bleeding events and within 90 days for b) symptomatic pulmonary embolism or

	symptomatic deep vein thrombosis and c) cause-specific mortality.
To estimate and draw inferences on the difference in complications (including clinically relevant non-major bleeding and surgical site bleeding) between treatment groups within 42 days from randomisation.	***Other adverse and serious adverse events*** including clinically relevant non-major bleeding and surgical site bleeding, objectively defined by ISTH criteria.[38]
To report adherence to each therapy.	***Medication adherence*** verified through digital response system.[6]
To estimate and draw inferences on differences in quality-of-life measures between treatment groups, up to 90 days post randomisation.	***Health utility (EQ-5D-5L):*** The EuroQol 5 Dimensions 5 Level (EQ-5D-5L) is a validated instrument comprising a self-rated health VAS and a five-domain health status questionnaire related to daily activities.[39] Collected for 4 timepoints: pre-injury (completed retrospectively within 7 days following randomisation), 7 days following randomisation, 42 days following randomisation, and 90 days following randomisation.
To estimate and draw inferences on the acceptability of different prophylactic anticoagulants using the Anti Clot Treatment Scale (ACTS).	***Patient satisfaction regarding the burdens and benefits of anticoagulation***, using the validated Anti-Clot Treatment Scale (ACTS) for patients allocated to drug treatments, collected within 42 days following randomisation.
To estimate the health and social care resource use and costs and the relative cost effectiveness between treatment groups within the first 90 days	***Health and social care resource use****,* using bespoke Case Report Forms and review of EHR, research staff to collect information on health and social care resource use.
To estimate longer term outcomes, such as post thrombotic syndrome, chronic thromboembolic pulmonary hypertension and bleeding complications and draw inferences on cost effectiveness, by using a previously developed decision analytic model, informed by directly measured events up to 90 days.	***Patient longer term outcome VTE and bleeding data,*** using an existing VTE model with risk-adjusted, population-specific 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 detailed long-term follow-up of participants would be worthwhile.

3.0 Study Design

3.1 Methodology

A pragmatic, multicentre, open-label, linked pair of randomised controlled trials with common outcomes and parallel economic analysis each with internal pilot phases:

- ***TiLLI-High****:* a non-inferiority trial in people with temporary lower limb immobilisation at high risk of VTE comparing DOACs (intervention) to parenteral prophylaxis (routine care).
- ***TiLLI-Low***: a superiority trial in people with temporary lower limb immobilisation at low risk of VTE comparing parenteral prophylaxis (intervention) or DOACs (intervention) to no drug prophylaxis (routine care).

The TRiP (cast) score will stratify patients into a high-risk group, for whom existing evidence suggests thromboprophylaxis is clinically and cost effective, and a low-risk group, with a risk of VTE of ≤1%, where existing evidence suggests the benefits of thromboprophylaxis may not justify the risks and costs. The key question for the high-risk group is whether DOACs, which are cheaper and easier to administer, but currently lack evidence for this indication, are non-inferior to parenteral options. The key question in the low-risk group is whether any pharmacological thromboprophylaxis is superior to routine care (no prophylaxis) in an appropriately selected population.

Participants

Participation will be offered to people aged 16 years and above who have sustained a lower limb injury within the last 7 days and require temporary lower limb immobilisation as part of their clinical treatment. Participants being managed as an outpatient in any lower limb *rigid* cast or brace, with or without plantar support, following acute injury, will be included to align with the inclusive definition of lower limb immobilisation in NICE NG89.[10] This approach is also supported by a recently published orthopaedic international consensus meeting on VTE.[9] People who undergo a short immediate period of hospitalisation for social reasons (< 2 calendar days), receive thromboprophylaxis for < 3 calendar days prior to approach or those who undergo planned day case surgery in the days to weeks following immobilisation will be eligible to participate. To mitigate stakeholder concerns about the potential impact of using DOACs on perioperative planning, our co-applicant (RS, representing the PeriOperative Medicine Clinical Trials Network) will lead on dissemination of evidence-based study materials for best practice perioperative management of anticoagulation.

VTE risk stratification

TiLLI's Patient Advisory Group (PAG) felt that a threshold to define VTE risk in this setting should be agreed by experts, be objective, consistent, and easily reproducible. TILLI's stakeholder group felt that any tool used would need to include domains for anatomical injury, method of immobilisation and personal VTE risk.

In recognition of the limited evidence base and variable scenarios requiring risk stratification for VTE, national guidance currently recommends the use of any published risk assessment model.[10] The Department of Health VTE risk assessment tool only applies to patients admitted to hospital; we are recruiting patients discharged from a hospital setting, so this tool is inappropriate and not validated. The widespread use of locally developed risk stratification methods for this cohort reflects the lack, until recently, of a recognised and well validated tool.

We have worked with international experts to review risk assessment tools developed for this specific clinical scenario and identified the TRiP(cast) score at a threshold of ≥6 to align closest to patient expectations, stakeholder preferences and optimal performance estimates from our previous evidence synthesis.[15] This score has been externally validated within the POT-CAST and recent CASTING studies (>5000 prospectively recruited participants).[15-17]

The score can be objectively calculated via online application and is already widely used in Europe. Sites will be trained on the use of this score at site initiation visits and investigator meetings. Recent evidence suggests this score will result in approximately 1/3rd of eligible patients being allocated to the high-risk strata.[16, 18, 40]

In light of feedback from sites and the NIHR funding committee, additional allocation to the high-risk strata will be allowed if the local treating clinician feels this is indicted on an individual participant basis. This approach is pragmatic, will increase proportional representation of high-risk patients within the eligible pool irrespective of TRIP(Cast) score (such as Achilles tendon rupture) and will also address local concerns on equipoise. This approach will also offer an efficiency gain within the trial, reducing the likelihood of clinical teams excluding patients from the trial based on their personal risk thresholds. TRiP(Cast) score data will be collected for all participants prior to allocation, to facilitate sensitivity analyses at future time points.

Treatment Allocation

Each of the linked trials will have a separate randomisation sequence. A secure web-based randomisation service with 24-hour availability will be used for the randomisation of consented participants on a 1:1 basis for *TiLLI-High (DOAC: parenteral)* and 2:1:1 (*routine care (no drug prophylaxis): DOAC: parenteral*) basis for *TiLLI-Low*. Appropriately GCP trained and delegated staff (as per the study delegation log) will access the secure website and will confirm eligibility before proceeding to randomisation. The system will provide an immediate allocation. Study treatment must be commenced within 48h from randomisation, failure to commence treatment within 48h from randomisation will result in a protocol deviation.

Internal pilot

The pilot will take place at 10 or more hospitals over 12 months. The aim of the pilot will be to determine feasibility of completing main phase recruitment to time and within the planned research resource, according to Red-Amber-Green criteria. The Data Monitoring and Ethics Committee (DMEC) and Trial Steering Committees (TSC) will monitor recruitment during the pilot phase and make a recommendation regarding continued progress of the trial against pre-specified Red-Amber-Green (RAG) criteria. If the trial is stopped, all participants will be followed up per protocol. If the trial continues to the main phase, pilot participants will be included in the final analysis.

Main RCT

During main phase recruitment, participants will be recruited for a further 32 months from a minimum of 30 UK Trusts/Healthboards. All participants will be followed up directly for 90 days from the point of randomisation, the conventional end point for the definition of hospital-acquired thrombosis.

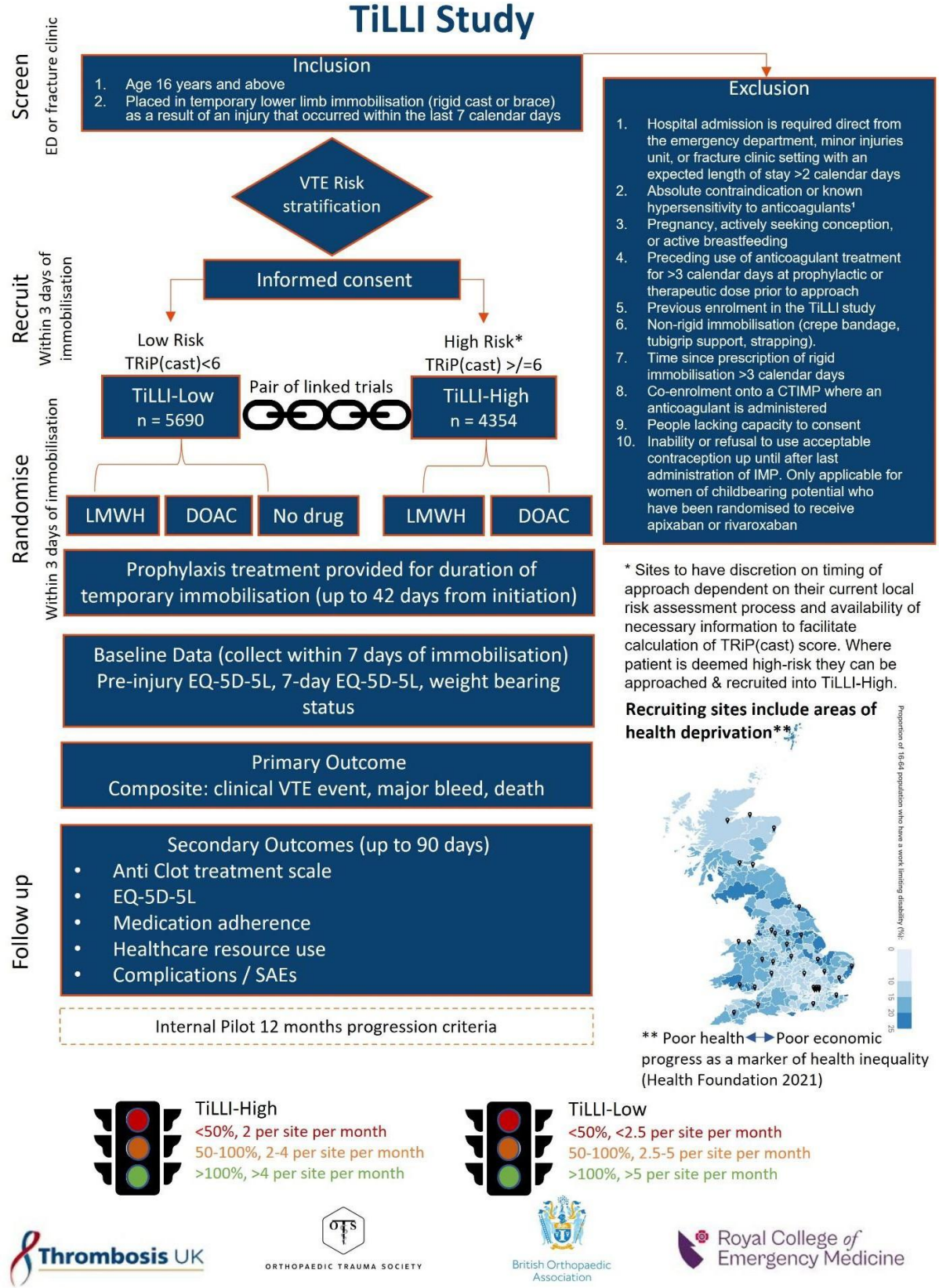
Modelling and long-term follow-up

The existing VTE decision model will be updated with risk-adjusted, population-specific effect estimates and baseline risk estimates from this study. These will include treatment effects for symptomatic VTE (including fatal pulmonary embolism) and treatment effects for major bleeding events (including fatal major bleeds) for each risk group (high-risk and low-risk). This will allow efficient, value for money inferences to be made about long-term

sequelae of VTE events and determine whether detailed long-term follow-up of participants would be worthwhile in either or both populations.

All participants will be approached to consent at enrolment for 5-year follow-up and access to their data collected within hospitals' electronic health record as well as national routinely-collected administrative datasets such as Hospital Episode Statistics and Scottish Morbidity Record (SMR01). This will facilitate efficient short and longer term clinical and cost effectiveness studies.

3.2 Study Flow Diagram



[1] Including history of end stage renal failure (eGFR <20ml/min/1.73m^2), hepatic failure or use of concomitant systemic treatment with azole-antimycotics (such as ketoconazole, itraconazole, voriconazole and posaconazole), HIV protease inhibitors (e.g., ritonavir) or active substances strongly inhibiting elimination pathways such as CYP3A4 or P-gp (such as clarithromycin, erythromycin or dronaderone) or a history of heparin induced thrombocytopenia

3.3 Study setting

UK NHS Trusts with type 1 emergency departments (ED) and acute fracture clinic outpatient facilities. Participants will be approached by delegated individuals within a secondary care setting, from an emergency medicine or orthopaedic background, either at the time of initial hospital attendance or within a subsequent outpatient setting within 3 calendar days of immobilisation. Usual care pathways for the relevant condition will be unaffected by the trial.

The study is supported by the Royal College of Emergency Medicine (RCEM), Orthopaedic Trauma Society (OTS), British Orthopaedic Association (BOA), PeriOperative Medicine Clinical Trials Network (POMCTN), VTE exemplar network and the patient charity Thrombosis UK, demonstrating multidisciplinary and multi-agency support for the study. Each network has been instrumental in the delivery and completion of several national randomised controlled trials conducted within an emergency care setting.[6, 7, 41]

4.0 Patient Evaluability and Replacement

4.1 Target Accrual

The target accrual for TiLLI-High is 4354 participants.

The target accrual for TiLLI-Low is 5690 participants.

4.2 Participant identification and recruitment

To raise awareness, study posters will be displayed in participating ED site waiting areas and outpatient fracture clinics. Each study poster will contain a QR code that directs individuals to the study website, allowing them to learn more about the study, and will have local contact details to prompt further discussion at patient request.

Potential participants will be identified and initially approached by a member of the clinical team during their ED attendance or subsequent outpatient fracture clinic appointment. Deferred approach is permitted up to a maximum of 3 calendar days from prescription of immobilisation. Prescription of thromboprophylaxis within the context of routine care will not be an exclusion criteria during this period, to allow extended consideration of participation and in accordance with previous recent trial designs.[30] This approach aligns with current clinical pathways for fracture management, risk assessment, thromboprophylaxis prescribing and clinical follow up. Initial approach will consist of verbal discussion and signposting to brief audiovisual study summary materials, developed with support of our PPIE group.

Appropriately trained and delegated members of the local research and clinical teams, including the PI, sub-investigators, and research nurses, will work together to confirm the eligibility of the individual patient to participate. People identified as potentially eligible for the study will be risk stratified using the TRiP (cast) score with supporting subjective clinical assessment and invited to participate in one of the two trials. Participants identified at high risk of VTE (TRiP (cast) ≥6 or local clinical judgement of high risk) will be invited to

participate in *TiLLI-High*; those identified at low risk of VTE (TRiP (cast) <6) will be invited to participate in *TiLLI-Low.*

An appropriately trained and delegated clinician and/or research nurse will conduct an informed consent discussion and gain consent once the person has had sufficient time to consider visual, verbal and written trial information. Research nurses with adequate consent training will be permitted to obtain consent in accordance with local policies.

Screening logs will be kept electronically in the study database to determine the number of patients assessed for eligibility and reasons for exclusion. In addition, the participant identification and recruitment process will be clearly documented by local research and clinical teams in participant medical records.

Research staff participating in patient identification should be a part of the clinical team responsible for or contributing to the patient's care. If research staff are not considered to be part of the direct care team locally, activities carried out prior to consent (including identification and introduction to the study) will be carried out by a member of the direct care team. Where research staff are not considered to be part of the care team, the research team should ask a member of the direct care team to identify suitable patients and ask permission from the patient to be approached by the research nurse to discuss participation.

5.0 Informed consent procedures

First approach will occur within existing clinical contact settings up to 3 calendar days from immobilisation, either during the initial emergency department attendance, virtual review (telephone contact), or fracture clinic appointment.

Informed consent from the participants will be obtained by an appropriately trained and delegated member of the research team. Potential participants will be provided with a localised patient information sheet (PIS) and details of the study specific website, containing video and infographic explanation of the study process. The PIS will be made available in different translations as outlined in section 5.2.

Consent may be completed on the same day that the participant was approached, as long as the participant has been given enough time to consider the study, had the opportunity to ask questions, and is willing to consent at that point in time. Consent within the same day as approach is in accordance with study delivery in an acute care setting. Electronic consent will be available to encourage participation. If first approach is remote, participants must be given adequate time to consider the study and ask questions before being directed to the eConsent module.

Where the participant has capacity but is unable to indicate their consent by signing (either by wet-ink or electronic signature) or marking a document then their consent may be given orally in the presence of at least one witness and recorded in writing on the relevant consent form. The witness must ensure that the verbal information given correlates to that written on the information sheet and must sign the consent form as witness to the process. Details of the witness (full name, relationship to participant, date they witnessed informed consent) must be documented in the participant's medical records.

Informed consent will be obtained prior to the participant undergoing procedures that are specifically for the purposes of the study and are outside standard, routine care at participating sites. This includes collection of identifiable participant data.

Remote follow up options will be available to encourage participation. Participants will be approached to consent for multimodal follow up contact during the study (including by email, telephone, or face-to-face hospital follow up). Consent for long-term follow up will be sought at the point of inclusion. If justified following primary analysis, future funding will be applied for to process linked hospital data to validate and compare longer term outcomes in this context. The Principal Investigator (PI) has overall responsibility for the informed consent of participants at their site and will ensure that any person delegated responsibility to participate in the informed consent process is duly authorised, trained, and competent to participate according to the ethically approved protocol, principles of Good Clinical Practice (GCP), and Declaration of Helsinki. If delegation of consent occurs, then details will be provided in the site delegation log.

During the consent process, participants will be informed that they can withdraw from any or all aspects of the study at any point without giving reason and without prejudicing their medical care. The right of a participant to refuse participation without giving reasons will be respected. The participant will remain free to withdraw at any time from the study without giving reasons and without prejudicing their further treatment and will be provided with a contact point where they may obtain further information about the study. Where a participant is required to re-consent (for example if new Research Safety Information becomes available during the study, or following an amendment that affects the participant, or new information needs to be provided to a participant) it is the responsibility of the PI to ensure this is done in a timely manner, prior to the next dose of IMP (where applicable), and documented in the participant's medical records.

Any new information that arises during the trial that may affect participants' willingness to take part will be reviewed by the trial steering committee (TSC), and if necessary, communicated to participants. A revised consent form will be completed if necessary. It will be clearly stated that the participant is free to withdraw from the study at any time without prejudice to future care or obligation to give reasons for withdrawal.

5.1 Vulnerable participant considerations

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

5.2 Writing, reading, and translation considerations

Understandable electronic patient facing materials will be hosted on a project website reviewed by our Patient Advisory Group (PAG). Our PAG will ensure that the relevant information is appropriately created for a lay audience, outlining the background, objectives, potential risks and alternatives to taking part in the study. Collaboration with wider representative patient groups at RCEM and Thrombosis UK will help to understand and mitigate potential barriers to recruitment in the acute setting.

The materials will be prepared in English and several 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, with options for additional translation. Arrangements for further detailed face to face discussions about the study, the consent or follow up process in additional languages will be led by local NHS care teams using locally available interpretation services.

5.3 Participants lacking capacity

Participants who do not have the capacity to provide informed consent will not be included in the trial.

If the participant loses capacity after consent is obtained, no further trial-specific assessments will be conducted. The analysis will utilise data collected up until the point where capacity loss, supplemented by any further data gathered through routine clinical practices.

Assessment of capacity will be completed by appropriately trained clinicians and research nurses. The capacity assessment must be completed following local policy and must be clearly documented in the participants medical records.

5.4 Minors

The Medicines for Human Use (Clinical Trials) Regulations define a minor in a CTIMP as 15 years or below. Participants under the age of 16 will not be included in the study.

6.0 Participant allocation

Each of the linked trials will have a separate randomisation sequence. Participants are assigned to TiLLI-High if their TRiP(cast) score is ≥6 or to TiLLI-Low if their TRiP(cast) score is <6. A secure web-based randomisation service with 24-hour availability will be used for the randomisation of consented participants within 3 calendar days of prescription of immobilisation on a 1:1 (DOAC: parenteral) basis for *TiLLI-High* and 2:1:1 (routine care (no drug prophylaxis): DOAC: parenteral) basis for *TiLLI-Low*. Trained staff will access the secure website and will confirm eligibility before proceeding to randomisation. The system will provide an immediate allocation. Participants must commence their treatment allocation within 48 hours of randomisation allocation, if treatment is not commenced within 48 hours a deviation must be logged.

7.0 Participant eligibility criteria

7.1 Inclusion criteria

1. Age ≥16 years
2. Placed in temporary lower limb immobilisation (rigid cast or brace) as a result of an injury that occurred within the last 7 calendar days

7.2 Exclusion criteria

1. Hospital admission is required direct from the emergency department, minor injuries unit, or fracture clinic setting with an expected length of stay >2 calendar days.

2. Absolute contraindication or known hypersensitivity to anticoagulants, including history of end stage renal failure (eGFR <20ml/min/1.73m^2), hepatic failure or use of concomitant systemic treatment with azole-antimycotics (such as ketoconazole, itraconazole, voriconazole and posaconazole), HIV protease inhibitors (e.g. ritonavir) or active substances strongly inhibiting elimination pathways such as CYP3A4 or P-gp (such as clarithromycin, erythromycin or dronaderone) or a history of heparin induced thrombocytopenia.
3. Pregnancy, actively seeking conception, or active breastfeeding.
4. Preceding use of anticoagulant treatment for >3 calendar days at prophylactic or therapeutic dose
5. Previous enrolment in the TiLLI study.
6. Non-rigid immobilisation (crepe bandage, tubigrip support, strapping).
7. Time since prescription of rigid immobilisation >3 calendar days.
8. Co-enrolment onto a CTIMP where an anticoagulant is administered.
9. People lacking the capacity to consent.
10. Inability or refusal to use acceptable contraception* up until after the last administration of IMP. Only applicable for women of childbearing potential who have been randomised to receive apixaban or rivaroxaban

* The Acceptable methods of contraception are as follows:

- Combined (oestrogen and progestogen containing) hormonal contraception associated with inhibition of ovulation, via oral, intravaginal or transdermal route.
- Progestogen-only hormonal contraception associated with inhibition of ovulation via oral, injectable or implantable route.
- Intrauterine device
- Intrauterine hormone releasing system
- Bilateral tubal occlusion
- Vasectomised partner
- Sexual abstinence
- Male or female condom with or without spermicide
- Cap diaphragm or sponge with spermicide

8.0 Study Schedule

8.1 Schedule of treatment for each visit

All aspects of orthopaedic and emergency care will be in accordance with routine practice. In particular, investigation and management of VTE will be conducted as outlined in current NICE guidance (NG158), a contractual standard for all UK NHS trusts.[42] Investigation and management of bleeding, including any reversal of drug interventions, will be conducted in accordance with local guidance and captured on case report forms within the primary outcome definition (for major events) or as complications (for clinically relevant non-major events).

8.2 Schedule of assessment

	Study period								
			Follow-up (days) from randomisation						
	Enrolment (day 0-3 from immobilisation)	Allocation (day 0-3 from immobilisation)	7	14	21	28	35	42	90
ENROLMENT									
Eligibility screening[1]	X								
Informed consent	X								
INTERVENTIONS[2,3]									
DOAC medication[7]		X							
Parenteral medication		X							
No medication		X							
ASSESSMENTS[3]									
Participant demographics[4]	X								
Baseline data	X								
Retrospective pre-injury EQ-5D-5L[4]			X						
EQ-5D-5L[4]			X					X	X
Adherence monitoring[4,6]			X	X	X	X	X	X	
Weight bearing status[4]			X	X	X	X	X	X	
ACTS questionnaire[4,5]								X	
Bleeding outcomes data									X
VTE outcomes data									X
Complications[6]									X
Resource use data[4]								X	X

1 Participant study ID will be issued automatically by the study database upon record creation

2 Participants must commence their allocated treatment within 48 hours of randomisation, a protocol deviation must be reported if time to commence study treatment exceeds 48 hours after randomisation.

3 Informed consent must be in place prior to intervention being allocated and assessments being completed.

4 Assessment may be participant-reported.

5 Assessment is not required for TiLLI-Low participants allocated to the no drug prophylaxis arm.

6 Complications are adverse events that are expected within the study. Complications are defined in section 13.6.

7 Comprehensive medical history (including last menses, sexual history, and current contraception methods) must be obtained by the site team prior to prescribing DOAC medication, supplemented by urine pregnancy testing as required, in accordance with routine NHS practice.

8.3 Randomisation method

Individual participant randomisation using simple randomisation (i.e., no stratification or blocking) in both *TiLLI-High* and *TiLLI-Low.* An allocation ratio of 1:1 (*DOAC: parenteral*) is used for *TiLLI-High* and a ratio of 2:1:1 (routine care (no drug prophylaxis): DOAC: parenteral) for *TiLLI-Low*.

8.4 Randomisation procedure

Sealed Envelope™, an online electronic data capture (EDC) randomisation tool will be used for this trial. The randomisation tool will be available to appropriately trained and delegated investigation site team members and the Pragmatic Clinical Trials Unit (PCTU) coordinating team.

CRFs 'Eligibility', 'VTE risk assessment'', and Participation' must be completed prior to randomisation, participants will be randomised prior to commencement of IMP.

Participants must commence their allocated treatment within 48 hours of the randomisation outcome, if treatment is not commenced within 48 hours a deviation must be logged.

8.5 Blinding

This is an open-label study so it will not be possible to mask the interventions in this study; the trials are designed to be pragmatic and aim to evaluate the effectiveness and adherence in usual NHS practice. Details of statistician and health economist blinding will be detailed in the SAP and health economist report.

8.6 Study assessments

Please refer to 8.2 schedule of assessments (in diagrammatic form) for assessment schedule.

Eligibility screening: participant eligibility for TiLLI-High and TiLLI-Low will be assessed by local research and treating clinical team individuals who have been appropriately trained and delegated as per the site's delegation log. Screening data should be entered into the study database, the participants study ID will be autogenerated upon record creation. Screening data includes eligibility criteria and VTE risk assessment.

Informed consent: details of informed consent may be found in section 5.0.

Participant demographics: participant demographic data will be collected at the point of inclusion to the study. Demographic data, including participant contact details, will be used to facilitate remote follow-up and NHS data linkage.

Baseline data: baseline data, including medical history and medication use, will be collected at the point of inclusion to the study.

Weight bearing status: data on weight bearing status (whether in cast or otherwise) will be collected at baseline, 7-days after randomisation, 14-days after randomisation, 21-days after randomisation, 35-days after randomisation, and 42-days after randomisation, or until the participant can fully weight bear, whichever occurs first. Weight bearing status will be collected by remote messaging supplemented by telephone follow up of non-responders.

Retrospective and prospective EQ-5D-5L: a retrospective pre-injury EQ-5D-5L will be collected within 7 days from randomisation. EQ-5D-5L will then be collected prospectively at

3 timepoints throughout the study: 7-day from randomisation, 42-day from randomisation, and 90-day from randomisation. The EQ-5D-5L will be collected using remote messaging supplemented by telephone follow up of non-responders.

Anti-Clot Treatment Scale (ACTS): will be collected 42-day from randomisation using remote messaging supplemented by telephone follow-up of non-responders.

Hospital attendance/admission, Bleeding outcomes, VTE outcomes, Complications, and Resource use: Prospective follow-up data and questionnaire completion during the next 90 days will be collected primarily through remote methods including Electronic Health Record (eHR) review and participant questionnaire. Participant questionnaires will be collected using remote messaging supplemented by telephone follow-up of non-responders. Telephone interviews may be required for outcome clarification. Follow up will include questions on investigation and diagnosis of VTE, significant bleeding events, orthopaedic surgical intervention, discontinuation of lower limb immobilisation, weight bearing status (in cast and out of cast), patient satisfaction, medication use, and downstream healthcare resource use (including hospital attendance, admission, readmission or primary care attendance).

8.7 Follow up procedures

Trial assessments completed during the follow up attendance as shown in 8.2 Schedule of assessments in diagrammatic form and are listed in section 8.6 Study Assessments.

Outcome and baseline data will be augmented by accessing national routinely-collected administrative datasets to determine health resource use and diagnoses to maximise capture for new VTE and bleeding events.

9.0 Participant, Study, and Site discontinuation

It is always within the remit of the responsible physician to withdraw the participant from the study for appropriate medical reasons. This can be (but is not limited to) individual adverse events or toxicities, new information gained about a treatment, patient withdrawal of consent, serious violation of the study protocol, or if it is felt to be in the participant's best interest. If a participant is withdrawn from the study, the appropriate eCRF must be completed in full in the study database.

Participants will have the option to partially or fully withdraw from the study. In the event of a full withdrawal request, all trial medication will be discontinued, and decisions regarding anticoagulant prophylaxis will be deferred to the treating clinical team. For those choosing partial withdrawal, they will withdraw from specific aspects of the study while continuing participation in all other aspects. Information on key reasons for complete or partial withdrawal will be captured in the eCRF to facilitate description in the final CONSORT flow chart. All data collected up until the point of withdrawal will be retained and analysed.

The principal risk of all study medications within this trial is that of bleeding. We have included consensus standardised definitions of bleeding within our primary and secondary outcomes and will capture minor bleeding episodes through adverse event reporting. As such, bleeding will be a recognised and anticipated issue within this pragmatic trial, which will not necessitate withdrawal, although it may result in pragmatic discontinuation of the IMP at clinical discretion.

Sites teams must inform the central trial team of all participant withdrawals by emailing tilli-bjh@qmul.ac.uk.

10.0 Laboratories and samples

Any blood samples sent during delivery of the trial will be within the remit of standard care and processed accordingly within local NHS systems.

10.1 Central laboratories

There are no central laboratories directly involved in the trial.

10.2 Local laboratories

There are no local laboratories directly involved in the trial.

10.3 Sample collection, labelling, and logging

No research samples will be taken within this trial. See section 10.0.

10.4 Sample transfer, chain of custody, and accountability

No research samples will be taken within this trial. See section 10.0.

10.5 Sample analysis procedures

No research samples will be taken within this trial. See section 10.0.

10.6 Sample Storage Procedures

No research samples will be taken within this trial. See section 10.0.

10.7 Sample and result recording and reporting

No research samples will be taken within this trial. See section 10.0.

10.8 Sample Management at End of study

No research samples will be taken within this trial. See section 10.0.

11.0 Study medication

Participants in TiLLI-High will be allocated to either parenteral drug treatment (a) or oral drug treatment (b). Participants in TiLLI-Low will be allocated to treatment (a) or (b), or no drug prophylaxis (c). Drug treatments will be prescribed for the duration of immobilisation or up to 42 days (whichever is earlier), in accordance with current NICE guidance.[10] In rare cases of ongoing lower limb immobilisation >42 days, further thromboprophylaxis can be prescribed in line with senior decision making and local guidance, at the discretion of treating teams. We will collect data on the frequency of longer term thromboprophylaxis in order to enable transparent reporting. See relevant sections for a detailed description of drug treatments (section 11.1), dosing regimes (section 12.11), allowable adjustments (section 12.12), and prescribing details (section 12.8).

All drugs used within this study are routinely prescribed by clinical teams as part of standard medical care, outside the purpose of research, and will be prescribed and administered in accordance with international guidelines, NHS advice and local policy.[13, 43, 44] Any risks from the study interventions are therefore principally associated with additional monitoring and data collection processes. Additional safety aspects of the IMPs described below will be monitored within the context of this study, providing further information on use.

11.1 Name and description of Investigational Medicinal Product(s) (IMP)

The following Direct Oral Anticoagulation (DOAC) and parenteral Low Molecular Weight Heparin (LMWH) medications are regarded as Investigative Medicinal Products (IMP) for the purposes of this study:

Rivaroxaban 10mg once daily via oral ingestion.

Rivaroxaban (Xarelto, Bayer HealthCare) is an anticoagulant that directly inhibits activated factor X (factor Xa). Inhibiting factor Xa interrupts the pathway of the blood coagulation cascade, inhibiting both thrombin formation and development of thrombi. Rivaroxaban has a marketing authorisation for the prevention of venous thromboembolism (VTE) in adult patients undergoing elective Orthopaedic hip or knee replacement surgery.

Apixaban 2.5mg twice daily via oral ingestion.

Apixaban (Eliquis, Bristol-Myers Squibb and Pfizer, and generic) is an anticoagulant that affects the blood coagulation cascade by directly inhibiting activated factor X (factor Xa), so inhibiting thrombin formation and the development of thrombi. Apixaban has a marketing authorisation for the prevention of venous thromboembolic events (VTE) in adult patients who have undergone elective orthopaedic hip or knee replacement surgery.

Enoxaparin 40mg once daily via subcutaneous injection.

Enoxaparin (Clexane, Sanofi) is a LMWH with a high anti-Xa activity (approximately 100 IU/mg) and low anti-IIa or anti thrombin activity (approximately 28 IU/mg), with a ratio of 3.6. These anticoagulant activities are mediated through anti-thrombin III (ATIII) resulting in anti-thrombotic activities in humans. Beyond its anti-Xa/IIa activity, further antithrombotic and anti-inflammatory properties of enoxaparin have been identified in healthy subjects and patients as well as in non-clinical models. These include ATIII-dependent inhibition of other coagulation factors like factor VIIa, induction of endogenous Tissue Factor Pathway Inhibitor (TFPI)

release as well as a reduced release of von Willebrand factor (vWF) from the vascular endothelium into the blood circulation.

Tinzaparin 4500 IU once daily via subcutaneous injection.

Tinzaparin sodium (Innohep, Leo laboratories) is an antithrombotic agent. It potentiates the inhibition of several activated coagulation factors, especially Factor Xa, its activity being mediated via antithrombin III.

Dalteparin 5000 IU once daily via subcutaneous injection.

Dalteparin sodium (Fragmin, Pfizer) is an antithrombotic agent, which acts mainly through its ability to potentiate the inhibition of Factor Xa and thrombin by antithrombin. It has a relatively higher ability to potentiate Factor Xa inhibition than to prolong plasma clotting time (APTT).

Fondaparinux 2.5mg once daily via subcutaneous injection.

Fondaparinux (Atrixa, Mylan) is a synthetic and selective inhibitor of activated Factor X (Xa). The antithrombotic activity of fondaparinux is the result of antithrombin III (ATIII) mediated selective inhibition of Factor Xa. By binding selectively to ATIII, fondaparinux potentiates (about 300 times) the innate neutralization of Factor Xa by ATIII. Neutralisation of Factor Xa interrupts the blood coagulation cascade and inhibits both thrombin formation and thrombus development.

All IMPs described are commercially available and licensed for postoperative orthopaedic VTE prophylaxis. In addition, all parenteral medications are recommended for this specific indication in NICE guidance and licensed for use.[10] Despite a lack of specific licensing, DOAC agents are in current use by approximately 30% of NHS trusts for the specific indication of lower limb immobilisation, with the remainder of patients prescribed parenteral drug therapy receiving the agents described above.[13] As such, and given type A study categorisation, all IMP management including storage, prescribing, dispensing, labelling and administration, must be in accordance with normal local practice and as dictated by SmPC guidance.[45, 46] In accordance with the low risk status of the study, MHRA guidance, and the pragmatic trial design[32], no additional drug monitoring or produce specific trial labelling will be required.

12.0 Legal status of IMP

All IMPs under consideration in this trial are licensed for use of thromboprophylaxis in the context of orthopaedic surgery and for prevention of thrombosis in patients at risk.

12.1 Name and description of each Non-Investigational Medicinal Product (NIMP)

There are no NIMPs within this trial.

12.2 Legal Status of NIMP

There are no NIMPs within this trial.

12.3 IMP Manufacturer(s) and supply arrangements

IMPs as described above will be manufactured, supplied and stored in accordance with manufacturer recommendations and local site practice, in accordance with the Summary of Product Characteristics (SmPC) for each agent.

IMP use will be drawn from hospital stock and ring fenced for the study; any licensed brand of each preparation is permitted on study.

SmPC are available for each IMP at the following web address:
https://www.medicines.org.uk/emc

12.4 Packaging and labelling of IMP(s), placebo(s), and NIMP(s)

Study medication will be prescribed and dispensed in accordance with usual local site prescription practice and the SmPC for the drug. There will be no variation in preparation, storage, packaging or labelling outside the usual practice at local sites, for reasons as outlined above.

Communication will be given between the research and clinical teams as to which arm of the trial a patient has been randomised to, treatment allocation will be recorded in the participants health records and clinical notes.

12.5 Accountability

There will be no additional records of accountability for supply, administration or destruction of study medications outside the standard clinical practice for these products at the local hospital site.

12.6 Assessment of compliance

Adherence to allocated therapy will be monitored to assess the fidelity of the interventions. Participants will receive weekly adherence monitoring messages at a rate of one every 7 days from randomisation up to week 6 from randomisation. Non-responders will be followed up by either a telephone call or email to prompt completion.

Participants without access to a smartphone or computer will be contacted by telephone by members of the research team.

Adherence data will be monitored centrally by the trial team, missing data, data abnormalities, and/or inconsistencies will be raised with the site team for investigation.

12.7 Drug storage

Storage arrangements, conditions, supply and chain of custody arrangements will be achieved in accordance with routine practice as guided by the Summary of Product Characteristics (SmPC) for each agent.

12.8 Prescription and Dispensing of IMP(s), placebo(s), and NIMP(s)

All members of the study team delegated to prescribe will receive appropriate training and oversight from pharmacy colleagues, local principal investigators and the trial team.

Site pharmacies are responsible for dispensing in line with their local dispensing procedures and excursion management normal practices.

12.9 Administration of IMP(s), placebo(s), and NIMP(s)

Administration and dosing schedule of all IMPs will be delivered in accordance with standard practice, licensing agreements and as guided by the Summary of Product Characteristics (SmPC) for each agent.

12.10 Destruction, return, and recall of IMP(s) and placebo(s)

Destruction, return and/or recall of all IMPs will be delivered in accordance with standard local site procedures, licensing agreements and as guided by the Summary of Product Characteristics (SmPC) for each agent.

12.11 Dosage schedules

Rivaroxaban will be administered in keeping with the SmPC recommendations for prophylaxis following orthopaedic surgery:

- Once daily, taken at 18:00 hours
- 10mg standard dose
- Duration of treatment up to 42 days
- Treatment breaks not permitted within the study protocol; compliance will be assessed as described in section 12.6.

Apixaban will be administered in keeping with the SmPC recommendations for prophylaxis following orthopaedic surgery:

- Twice daily, taken at 06:00 and 18:00
- Morning and evening
- 2.5mg standard dose
- Duration of treatment up to 42 days
- Treatment breaks not permitted within the study protocol; compliance will be assessed as described in section 12.6.

Enoxaparin will be administered in keeping with the SmPC recommendations for prophylaxis following orthopaedic surgery:

- Once daily, taken at 18:00 hours
- 40mg standard dose
- Methods for individualized doses (according to weight and/or renal function) will be in accordance with local practice.
- Duration of treatment up to 42 days
- Treatment breaks not permitted within the study protocol; compliance will be assessed as described in section 12.6.

Tinzaparin will be administered in keeping with the SmPC recommendations for prophylaxis following orthopaedic surgery:

- Once daily, taken at 18:00 hours
- 4500 IU standard dose

- Methods for individualized doses (according to weight and/or renal function) will be in accordance with local practice.
- Duration of treatment up to 42 days
- Treatment breaks not permitted within the study protocol; compliance will be assessed as described in section 12.6.

Dalteparin will be administered in keeping with the SmPC recommendations for prophylaxis following orthopaedic surgery:

- Once daily, taken at 18:00 hours
- 5000 IU standard dose
- Methods for individualized doses (according to weight and/or renal function) will be in accordance with local practice.
- Duration of treatment up to 42 days
- Treatment breaks not permitted within the study protocol; compliance will be assessed as described in section 12.6.

Fondaparinux will be administered in keeping with the SmPC recommendations for prophylaxis following orthopaedic surgery:

- Once daily, taken at 18:00 hours
- 2.5mg standard dose
- Methods for individualized doses (according to weight and/or renal function) will be in accordance with local practice.
- Duration of treatment up to 42 days
- Treatment breaks not permitted within the study protocol; compliance will be assessed as described in section 12.6.

12.12 Dosage modifications and delays

Dose modifications will be permitted in accordance with local practice and as guided by the Summary of Product Characteristics (SmPC) for each parenteral agent. We do not recommend dose adjustment for any DOAC medication based on height or weight, in accordance with the updated ISTH subcommittee statement on use of direct oral anticoagulants in patients with obesity for treatment and prevention of VTE.[47] Additional guidance for site teams, perioperative clinicians, and participants on dosing in the event of a planned invasive procedure or surgical intervention will be produced by our trial team and disseminated to sites prior to green light. In rare cases of ongoing lower limb immobilisation >42 days, further thromboprophylaxis can be prescribed in line with senior decision making and local guidance, at their discretion of treating teams. We will collect data on the frequency of longer term thromboprophylaxis in order to enable transparent reporting.

12.13 Management of IMP specific adverse events

Bleeding complications are expected within the study and will be managed in accordance with local clinical practice and international guidance on reversal of anticoagulant medications in an emergency setting.[48]

Reporting of complications is described in section 14.16 Adverse events that are expected within the study.

12.14 Known drug reactions and interventions with other therapies

The use of rivaroxaban or apixaban is not recommended in patients receiving concomitant systemic treatment with azole-antimycotics (such as ketoconazole, itraconazole, voriconazole and posaconazole) or HIV protease inhibitors (e.g., ritonavir). These active substances are strong inhibitors of both CYP3A4 and P-gp and therefore may increase plasma concentrations to a clinically relevant degree (2.6-fold on average) which may lead to an increased bleeding risk. Similarly, the use of rivaroxaban or apixaban needs to be avoided for patients undergoing treatment with strong CYP3A4 and P-gp inducers (e.g., rifampicin, phenytoin, carbamazepine, phenobarbital, St John's Wort), as these substances can significantly reduce the plasma concentrations and, therefore, the efficacy of rivaroxaban and apixaban. Care is to be taken if patients are treated concomitantly with medicinal products affecting haemostasis such as non-steroidal anti-inflammatory medicinal products (NSAIDs), acetylsalicylic acid (ASA) and platelet aggregation inhibitors or selective serotonin reuptake inhibitors (SSRIs), and serotonin norepinephrine reuptake inhibitors (SNRIs). For patients at risk of ulcerative gastrointestinal disease an appropriate prophylactic treatment may be considered.

Hypersensitivity to low molecular weight heparins and/or heparins can occur e.g., history of confirmed or suspected immunologically mediated heparin induced thrombocytopenia (type II). Such cases should be managed in accordance with routine NHS care. Bleeding is the principal side effect of concern with LMWH use which will be monitored throughout the trial both as a variable within the composite outcome, and through adverse events.

12.15 Recommended concurrent treatment

There are no recommended concurrent treatments for participants for receiving IMP.

12.16 Prohibited medication

See section 12.13 and 12.14.

The use of preceding or ongoing anticoagulant therapy at prophylactic or therapeutic dose for any alternative reason for >3 calendar days is a noted exclusion criteria to participation in the trial. Use of antiplatelet agents do not exclude patients from use of additional pharmacological thromboprophylaxis, as per NICE guidance.

12.17 Study restrictions

There are no restrictions recommended whilst on the active phase of the study.

12.18 Management of overdose

Overdose should be managed in accordance with standard clinical practice and as advised within the SmPC for each agent.

12.19 Precautions regarding women of child-bearing potential

A woman is considered of childbearing potential (WOCBP), i.e. fertile, following menarche and until becoming post-menopausal unless permanently sterile. Permanent sterilisation methods include hysterectomy, bilateral salpingectomy and bilateral oophorectomy. A postmenopausal state is defined as no menses for 12 months without an alternative medical cause. A high follicle stimulating hormone (FSH) level in the postmenopausal range may be used to confirm a postmenopausal state in women not using hormonal contraception or hormonal replacement therapy. However, in the absence of 12 months of amenorrhea, a single FSH measurement is insufficient[62].

Apixaban is not recommended for use in pregnancy and rivaroxaban is contraindicated.[49, 50,60,61] As such, pregnancy, actively seeking conception, and the inability to use an acceptable effective contraceptive measure during the period of IMP use are listed as explicit exclusion criteria to participation in the trial. These issues will be highlighted to potential participants during initial consent discussions and within the participant information sheets. A trial visit note will be also recorded at the time of consent to confirm all inclusion / exclusion criteria.

For WOCBP who agree to participate in the study, a comprehensive medical history (including last menses, sexual history, and current contraception methods) must be obtained by the site team prior to prescribing any trial medication, supplemented by a urine pregnancy test as necessary in accordance with current international guidance.[43, 44, 51] Based on the comprehensive medical history, some participants such as those who are in same-sex relationships, those who practice true abstinence (defined as refraining from heterosexual intercourse), or those who have completed high sensitivity urine or serum pregnancy test within the last 7 days may be exempt from further urine pregnancy testing and/or contraception counselling. Evidence of the comprehensive medical history, pregnancy testing, and contraceptive counselling must be documented in the participant's medical records prior to commencement of any DOAC medication, in accordance with international guideline recommendations from the specialist subcommittee of the International Society for Thrombosis and Haemostasis.[44]

This trial involves authorised IMPs, as such the SmPC for each relevant IMP has been reviewed by the CIs with regards to contraceptive recommendations. Parenteral thromboprophylaxis agents such as dalteparin, enoxaparin, tinzaparin, and fondaparinux are licensed for use in pregnancy/breastfeeding and recommended for use in UK international guidance.[52],[63-66] Although animal studies have shown reproductive toxicity with rivaroxaban related to haemorrhagic complications, a recent extensive review of 614 unique cases of DOAC exposure (predominately rivaroxaban use) in pregnancy reported a rate of birth defects and miscarriages in keeping with unexposed pregnancies.[53] Given this evidence for lack of risk based on human data, counselling on contraception should advocate the use of an acceptable effective contraceptive measure throughout the study intervention period. Acceptable methods of contraception are listed as follows:

- Combined (oestrogen and progestogen containing) hormonal contraception associated with inhibition of ovulation, via oral, intravaginal or transdermal route.
- Progestogen-only hormonal contraception associated with inhibition of ovulation via oral, injectable or implantable route.
- Intrauterine device
- Intrauterine hormone releasing system

- Bilateral tubal occlusion
- Vasectomised partner
- Sexual abstinence
- Male or female condom with or without spermicide
- Cap diaphragm or sponge with spermicide

Please see section 14.10 Pregnancy for additional information.

12.20 Arrangements for post-study access to IMP and care

All study drugs will be provided through local NHS sources and clinical trial pharmacists for the duration of immobilisation or up to 42 days, whichever is earlier. After cessation of 42 follow up, any need for medication will fall outside the scope of routine thromboprophylaxis and thus be prescribed and supplied at the discretion of treating teams, as detailed in section 12.12.

13.0 Equipment and Devices

Site teams may be provided with one tablet per Trust to facilitate access to the study database and the randomisation service.

The tablet provided to site teams will be, when not in use, securely stored in designated areas within the Trust premises, preferably in locked cabinets or rooms to prevent unauthorised access. Access to the tablets will be limited to authorised personnel involved in the study. The tablets will be password protected and restricted, allowing access to only study-related systems. Study systems, including the study database and randomisation service, will require unique login credentials which will be issued only to appropriately trained and delegated site team personnel. In the event that the tablet is lost or stolen, immediate action will be taken to mitigate risk to patient data. This would include reporting the loss or theft within 24 hours to the central trial team and appropriate authorities. The central trial team will remotely lock the device. In cases where the tablet is not available or operational, site team personnel may access study-related systems using a computer to complete the same tasks.

14.0 Pharmacovigilance

14.1 General definitions

Term	Definition
Adverse Event (AE)	Any untoward medical occurrence in a participant to whom a medicinal product has been administered, including occurrences which are not necessarily caused by or related to that product.
Adverse Reaction (AR)	An untoward and unintended response in a participant to an investigational medicinal product which is related to any dose administered to that participant. The phrase "*response to an investigational medicinal product*" means that a causal relationship between a study medication and an AE is at least a reasonable possibility, i.e., the relationship cannot be ruled out. All cases judged by either the reporting medically qualified professional or the sponsor as having a reasonable suspected causal relationship to the study medication qualify as adverse reactions.

Serious Adverse Event (SAE)	A serious adverse event is any untoward medical occurrence that: • Results in death. • Is life-threatening. • Requires hospitalisation or prolongation of existing hospitalisation. • Results in persistent or significant disability/incapacity. • Consists of a congenital anomaly or birth defect. Other 'important medical events' may also be considered serious if they jeopardise the participant or require an intervention to prevent one of the above consequences. NOTE: The term "life-threatening" in the definition of "serious" refers to an event in which the participant was at risk of death at the time of the event; it does not refer to an event which hypothetically might have caused death if it were more severe.
Serious Adverse Reaction (SAR)	An adverse event that is both serious and, in the opinion of the reporting Investigator or medical assessor, believed with reasonable probability to be due to one of the study treatments, based on the information provided.
Suspected Unexpected Serious Adverse Reaction (SUSAR)	A serious adverse reaction, the nature and severity of which is not consistent with the information about the medicinal product in question set out in the Reference Safety Information (RSI): • In the case of a product with a marketing authorisation, in the summary of product characteristics (SmPC) for that product. • In the case of any other investigational medicinal product, in the investigator's brochure (IB) relating to the study in question.
Complication	An adverse event that is expected within the study as defined by section 14.6.
Major bleeding event	A major bleeding event meets one or more of the following criteria: • Fatal bleeding • Bleeding that is symptomatic and occurs at a critical area or organ such as intracranial, intraspinal, intraocular, retroperitoneal, pericardial, in a non-operated joint, or intramuscular with compartment syndrome • Extrasurgical site bleeding causing a fall in haemoglobin level of 20g L^{-1} (1.24 mmol L^{-1}) or more, or leading to transfusion of 2 or more units of whole blood or red cells, with temporal association within 24–48 h to the bleeding • Surgical site bleeding that requires a second intervention -open, arthroscopic, endovascular – or a haemarthrosis of sufficient size as to interfere with rehabilitation by delaying mobilisation or delayed wound healing, resulting in prolonger hospitalisation or a deep wound infection • Surgical site bleeding that is unexpected and prolonged and/or sufficiently large to cause hemodynamic instability, as assessed by a surgeon. There should be an associate fall in haemoglobin level of at least 20 g L^{-1} (1.24 mmol L^{-1}), or transfusion, indicated by the bleeding, of at least two units of whole blood or red cells, with temporal association within 24 h to the bleeding.
Clinically relevant non-major bleeding event	A clinically relevant non-major bleeding event is defined as: Any sign or symptom of haemorrhage (e.g., more bleeding than would be expected for a clinical circumstance, including bleeding found by imaging alone) that does not fit the criteria for the definition of major bleeding but does meet at least one of the following criteria:

	• Requires medical intervention by a healthcare professional; • leads to hospitalisation or increased level of care; • Prompts a face to face (i.e., not just a telephone or electronic communication) evaluation.

14.2 Site investigator assessment

The Principal Investigator is responsible for the care of the participant, or in their absence an authorised medic within the research team is responsible for assessment of any event that is deemed not a complication for:

- **Seriousness**
  Assessing whether the event is serious according to the definitions given in 14.1 general definitions.
- **Causality**
  Assessing the causality of all serious adverse events/reactions in relation to the study treatment according to the definition given. If the SAE is assessed as having a reasonable causal relationship, then it is defined as a SAR.
- **Expectedness**
  Assessing the expectedness of all SARs according to the definition given. If the SAR is unexpected (as per the RSI), then it is a SUSAR.
- **Severity**
  Assessing the severity of the event according to the following terms and assessments. The intensity of an event should not be confused with the term “serious” which is a regulatory definition based on participant/event endpoint criteria.
  - **Mild**: Some discomfort noted but without disruption of daily life
  - **Moderate**: Discomfort enough to affect/reduce normal activity
  - **Severe**: Complete inability to perform daily activities and lead a normal life

14.3 Reference Safety Information (RSI)

Reference Safety Information (RSI) is the information used for assessing whether an adverse reaction is expected. For each IMP we will use the SmPC as RSI, the central trial team will conduct annual reviews to ensure the trial literature is up-to-date and implement any necessary updates throughout the duration of the study.

14.4 Notification and recording of Adverse Events (AEs) or Reactions (ARs)

All AE and AR’s are to be documented in the participants’ medical notes or other source data documents. AE and AR’s should be reported and classified using medDRA version 27.
Once assessed, if the AE is not defined as SERIOUS or a complication (as defined in section 14.6 adverse events that do not require reporting), no further reporting is required.

14.5 Notification of AEs of Special Interest (AESIs)

No AESIs have been identified for prioritised reporting within this study.

14.6 Adverse events that are expected within the study

Complications are adverse events that are expected within the study. As such, they are excluded from adverse reporting obligations and follow a different reporting pathway. Complications should be reported in the participants medical notes, and/or other source data documents, and the eCRF Complication Log.

The following events are complications:

- Bleeding events: bleeding events, including clinically relevant non-major bleeding events and major events, are expected in low frequency within this study, defined using international consensus definitions and are part of the composite net clinical benefit outcome.

- VTE events: VTE events, including symptomatic distal DVT, proximal DVT, pulmonary embolism, and death attributed to VTE, are expected in low frequency within this study, defined using international consensus definitions and are part of the composite net clinical benefit outcome.

- Hospitalisation events related to any operative intervention/surgical management of the index injury are expected within the study.

- Death as a result of disease progression or death from other events that are primary or secondary endpoint measures are not considered to be SAEs and should be reported in the eCRF Complications Log and eCRF Death.

14.7 Notification and reporting of Serious Adverse Events (SAEs) and Suspected Unexpected Serious Adverse Reactions (SUSARs)

Any events that are not exempt from reporting (as outlined in section 14.6) and are considered a Serious Adverse Event (SAEs) or Suspected Unexpected Serious Adverse Reactions (SUSARs) will be recorded in the participants' notes, the eCRF SAE Log, and reported to the sponsor using the Sponsor SAE form within 24 hours of the site becoming aware of the event, unless the event is specifically exempted from reporting in the protocol.

Nominated co-investigators (as listed by the delegation log) will be authorised to sign the SAE forms in the absence of the PI at the participating sites.

14.8 Sponsor medical assessment

Sponsor has delegated the responsibility for oversight of IMP safety profile and medical assessment of AEs, ARs, SAEs and SUSARs to the CI as medical assessor. The CI must review all SAEs within 72 hours of receipt. In instances where the CI is not available, an appropriately trained and delegated clinician will review received SAEs. The SAE review should encompass seriousness, relatedness, and expectedness. Day 0 for all SUSARs is when the SAE/SUSAR is received by the CI and/or coordinating team and/or sponsor (whichever is first).

It is noted that the CI cannot downgrade the PI assessment of an event's causality. If there is disagreement between CI and PI assessment, no pressure should be placed on the PI to alter their assessment, but the CI can liaise with the site PI before the CI's final decision. The CI and PI assessment can differ.

14.9 Urgent safety measures

The CI may take urgent safety measures to ensure the safety and protection of the clinical study participants from any immediate hazard to their health and safety, in accordance with Regulation 30 of the Medicines for Human Use (Clinical Trials) regulations. The measures should be taken immediately. In this instance, the approval of the Competent Authority prior to implementing these safety measures is not required.

The CI has an obligation to inform both the MHRA and Research Ethics Committee in writing **within 3 days** of implementing the Urgent Safety Measure. They must also submit a substantial amendment documenting the changes within 14 days of implementing the urgent safety measure. The JRMO must be sent a copy of the correspondence with regards to this matter as soon as it is sent.

14.10 Pregnancy and Breast Feeding

If a participant becomes pregnant whilst involved in a CTIMP, it is not considered to be an SAE or an AE. However, it is an event that requires reporting, monitoring and follow up. If a participant or participant's partner becomes pregnant whilst or after taking an IMP contraindicated during pregnancy, the sponsor should be notified immediately (within 24 hours of site becoming aware of the pregnancy) using the Sponsor pregnancy form. The pregnancy reporting procedure will be the same as the SAE reporting route.

DOAC therapy is either contraindicated[60] or should be avoided[61] in pregnancy, depending on drug type.[49, 50] Therefore, pregnancy or actively seeking conception is an exclusion criterion for this study. If accidental pregnancy occurs during the trial intervention period, site clinical teams must immediately cease DOAC therapy. Ongoing VTE risk should be managed in accordance with routine NHS care for the remainder of the period of lower limb immobilisation. Any deviation from the protocol, such as discontinuing DOAC therapy due to accidental pregnancy and starting an alternative anticoagulant, must be documented as a protocol deviation in the eCRF Protocol Deviation Log and the participant's medical records. Follow-up and reporting will continue as per protocol requirements. Participants in the no drug prophylaxis or LMWH arm will continue on study without interruption.

In the event of accidental pregnancy during the trial intervention period, the CI (in conjunction with the site PI) should determine if the foetus has been exposed to an IMP contraindicated during pregnancy. The PI has the responsibility to ensure that the pregnancy form is completed and sent to the sponsor within the agreed timelines. The initial report should be sent within 24 hours of the PI or co-investigator becoming aware of the event and follow up information submitted as and when it becomes available up to agreed follow up time after birth.

The sponsor will arrange for a review of the pregnancy report by an appropriate expert medic (usually a consultant obstetrician). The study team must follow all instructions provided by the sponsor's expert.

Rivaroxaban is contraindicated during breastfeeding[60], it is unknown whether apixaban or its metabolites are excreted in human milk[61]. If a participant taking a DOAC decides to start breastfeeding during the study, site clinical teams should advise immediate cessation of DOAC therapy. Ongoing VTE risk should be managed in accordance with routine NHS care for the remainder of the period of lower limb immobilisation. Any deviation from the protocol, such as discontinuing DOAC therapy due to initiation of breastfeeding and starting an alternative anticoagulant, must be documented as a protocol deviation in the eCRF Protocol

Deviation Log and the participant's medical records. Follow-up and reporting will continue as per protocol requirements. Participants in the no drug prophylaxis or LMWH arm will continue on study without interruption.

15.0 Annual reporting

15.1 Development Safety Update Report (DSUR)

The DSUR will be written by the CI (following Sponsor procedures) and submitted to the sponsor for review prior to submission to the MHRA. The DSUR is due for submission within 60 days of the end of the reporting period. The reporting period is annually from the date on the "*Notice of acceptance letter*" from the MHRA. The sponsor's delegated Medical Assessor, usually the CI, will carry out a risk benefit analysis of the IMPs encompassing all events having arisen on the study. REC will be sent a copy of the DSUR.

15.2 Annual Progress Report (APR)

The APR will be written by the CI (using the HRA's template) and submitted to the sponsor for review prior to submission to the REC. The APR is due within 30 days of the anniversary date of the "favourable opinion" letter from the REC.

16.0 Statistical and data analysis

16.1 Sample size calculation

Sample sizes for the two linked trials using the composite primary outcomes as a binary variable and absolute risk differences as treatment effect estimates are described below.

TiLLI-High

We expect the event risk for the primary outcome for this trial to be driven by symptomatic VTE and estimate the risk of a composite outcome at 1.8 to 2.5% in patients with a TRiP(cast) score of >/=6 treated with LMWH.[15, 16, 30] We will assume a control (LMWH) event risk of 2% and use an absolute risk difference of 1.5% (risk ratio 1.75) to define the non-inferiority margin for DOAC agents compared to LMWH, in line with feedback from our patient group and stakeholders. This is consistent with previous VTE research in similar, orthopaedic populations (risk ratio <2) and the proposed design of the RIVACAST study.[27, 29, 54] The absolute risk margin reflects the benefits of avoiding the suffering and specific complications of parenteral therapy, such as pain, injection site haematoma, exacerbation of needle phobia, sharps disposal, clinic or district nurse attendance with impact on quality of life, and heparin induced thrombocytopenia.

Using the Farrington-Manning score test, if there is truly no difference between LMWH and DOAC, we estimate that 3918 patients are needed for 90% chance of detecting that DOAC therapy is non-inferior to LMWH therapy, based on the upper limit of a two-sided 95% confidence interval excluding an absolute difference >1.5% in favour of LMWH. We will inflate the sample size by 10% to account for attrition and treatment crossover. The projected final sample size is 4354 participants.

TiLLI-Low

We estimate the risk of a composite outcome at 0.5 to 1.1% in patients with a TRiP(cast) score of <6.[15, 16] Again, we expect the event risk to be driven by symptomatic VTE and therefore estimate the absolute risk difference of the composite outcome between no drug prophylaxis and LMWH or DOACs to be between 0.25% and 0.9%.[19, 30] Given the low absolute risk, our patient panel report that willingness to participate in this trial would be dependent on expectation of a sizeable relative risk reduction. In keeping with this opinion and in the interests of deliverability, we will assume an event rate of 0.25% with any drug and 1% with no medication, i.e., a risk difference of 0.75% we wish to be able to detect. With sample size inflation of 10.4% to afford futility analyses at 50 and 75% information time points, we estimate that 5120 patients are needed for 90% power to detect that pharmacological thromboprophylaxis is superior to standard care, using a two-group two-sided test with alpha = 5%. We will aim to increase the sample size by 10% for

attrition, including medication crossover. The projected final sample size is 5690 participants.

The above calculation is based on randomising in a 2:1:1 ratio for routine care (no prophylaxis); LMWH; DOAC to enable most efficient testing of the primary hypothesis.

16.2 Planned recruitment rate

There are 167 type 1 emergency departments in the UK. Our recent survey reported >60 sites had an interest in participating in future research on this topic. Recently funded and recruiting trials in emergency care have engaged between 25-65 sites for project delivery.[41, 55, 56]

It is estimated that 670 potentially eligible patients per year will attend each emergency department.[18] Following exclusions, 500 patients are estimated to be eligible for recruitment/site/year, of which 20-50% will be eligible for *TiLLI-High* and 50-80% for *TiLLI-Low.* Recruitment rate is estimated to be 3-5 and 4-6 patients/month/site respectively, representing approximately 20% of those eligible for recruitment. The TiLLI trial will be delivered across 30 NHS sites to facilitate completion within a 5-year study period.

Internal pilot progression criteria

Individual pilot phases with interim assessment will be conducted for each trial after 12 months of active recruitment. Separate stop/go criteria for each trial have been established so that one trial could continue if feasibility is not demonstrated for both. Robust progression criteria have been set, including staggered site set up prior to pilot commencement, negligible lag phase and 10% of total recruitment in <30% total recruitment window.

TiLLI-High pilot recruitment phase: 12 months			
Red/Amber/Green thresholds	<50%	50-100%	>100%
Average recruitment rate/site/month	<2	2-4	>4
Number of sites opened	<10	10-20	>20
Total number of participants recruited	<335	335 - 670	>670
Action	Recruitment not feasible; consider stopping the trial	Review recruitment strategies Report to TSC; continue but monitor closely	Recruitment feasible; proceed with study
TiLLI-Low pilot recruitment phase: 12 months			
Red/Amber/Green thresholds	<50%	50-100%	>100%
Average recruitment rate/site/month	<2.5	2.5-5.0	>5.0
Number of sites opened	<10	10 - 20	>10
Total number of participants recruited	<420	420-840	>840
Action	Recruitment not feasible; consider stopping the trial	Review recruitment strategies Report to TSC; continue but monitor closely	Recruitment feasible; proceed with study

Stopping rules

Two futility interim analyses when 50% and 75% of the primary outcome data has been obtained have been incorporated in the design of TiLLI-Low. Futility stopping boundaries are set to correspond to predictive power of 20% at both analyses, that is, the trial is stopped for futility if predictive power is below 20% at the respective time point, starting with an initial non-informative prior. Constant predictive power boundaries have been indicated to be a near optimal criterion in terms of minimizing the average expected sample size if there truly is no treatment effect between groups.[57] Earlier interim looks were considered but would require a sample size inflation that was deemed unreasonable. The sample size has been inflated by 10.4% to allow for the two interim looks whilst maintaining 90% power. The average expected sample size that will be needed for TiLLI-Low if there is in fact no difference between groups is 57.5% of the total recruitment target. A nonbinding futility analysis approach has been chosen. Futility boundaries are regarded as guidelines and any decision to stop the trial would only be made following recommendations of the oversight committees taking into account all accruing data.

16.3. End of trial (EOT) definition

The end of trial will occur when the 90-day follow-up data for the final participant recruited has been entered on the study database. Site teams will have up to 6-weeks to enter the last participants 90-day follow-up data into the study database.

The CI is delegated the responsibility of submitting the EOT notification to REC and MHRA once reviewed by the sponsor. The EOT notification must be received by the REC and MHRA within 90 days of the end of the study. If the study is ended prematurely, the Chief Investigator will notify the Sponsor, REC, and MHRA within 15 days, including the reasons for the premature termination.

16.4 Statistical Analysis

Reporting of the results and flow of participants through the trial will be in accordance with the CONSORT statement and relevant extensions.[58, 59] Baseline demographic data will be summarised by treatment arm and overall using suitable measures of central tendencies; for continuous data (means and medians), variability (standard deviation (SD) and IQR); for categorical data (frequencies and proportions).

The primary analysis in both trials assesses the difference between treatment groups in the proportion of participants experiencing an event in terms of the composite net clinical benefit outcome defined in 5.12.1. If any of the individual component events is experienced within 90 days from randomization the primary outcome is ‘yes’, otherwise it is ‘no’.

The primary analysis in TiLLI-High will be a non-inferiority test of DOAC vs LMWH in the intention-to-treat population. Non-inferiority is declared if the upper limit of a two-sided 95% Farrington-Manning confidence interval for the risk difference lies below the non-inferiority margin. The Farrington-Manning method is preferred over the

conventional Wald confidence interval in a non-inferiority design.[60] A subsequent superiority interpretation will be made should non-inferiority be declared. A compliance adjusted per-protocol analysis using inverse probability weighting will be conducted as a supplementary analysis to assess non-inferiority in terms of treatment efficacy. Precise adherence criteria for the per-protocol population will be pre-specified in the study protocol.

The primary analysis for TiLLI-Low will be a two-group risk difference comparison of any pharmacological prophylaxis (DOAC or LMWH) compared to no pharmacological prophylaxis on an intention-to-treat basis. If a significant difference between prophylaxis and no medication can be declared, individual comparison of DOAC and LMWH vs control will be made using a Dunnett test like procedure for binary outcomes based on the Newcombe's hybrid score confidence interval.[61]

Individual components of the primary outcome will be analysed as binary variables using the same approach as the aforementioned primary analyses. Additionally, these variables will be analysed as time to event outcomes with log rank test and Kaplan-Meier curves. Further secondary endpoints will be summarised and analysed using appropriate techniques (corresponding to the primary outcome analysis) according to whether the variable is binary, categorical, continuous or time-to-event. Exploratory subgroup analyses will be conducted for gender, ethnicity, age, injury type and method of immobilisation.

A detailed statistical analysis plan (SAP) with all proposed statistical analyses will be drafted early in the trial and finalised prior to the first data extraction from the database. The SAP will explain all analysis models, model checks to be performed and any (multiple) imputation methods used. The SAP will be reviewed by oversight committees prior to sign off. Formal interim analyses other than futility analysis in TiLLI-Low are not planned and will be performed only where requested by the DMC.

16.5 Summary of baseline data and flow of participants

Data will be collected using a standardised electronic case report form (eCRF) hosted within a secure server, managed by the Pragmatic Clinical Trials Unit. Baseline data including demographics and risk factors for VTE/bleeding will be collected at the point of inclusion into the study. Weight bearing status (whether in cast or otherwise) will be collected at baseline and throughout the study period, to capture progression and facilitate future sub-group analyses. A retrospective, pre-injury baseline measure of EQ-5D-5L will be collected within 7 days of randomisation using remote messaging supplemented by telephone follow up of non-responders.

Prospective follow-up data and questionnaire completion during the next 90 days will be collected primarily through remote methods including Electronic Health Record (eHR) review, remote messaging and contact with secondary care teams. Use of postal/telephone interviews may be deployed if electronic methods are unsuccessful or for outcome clarification as required. Follow up will include questions on investigation and diagnosis of VTE, significant bleeding events, orthopaedic surgical intervention, discontinuation of lower limb immobilisation, weight bearing status (in

cast and out of cast), patient satisfaction, EQ-5D-5L measures, anticlotting scale measure, medication use, and downstream healthcare resource use (including hospital attendance, admission, readmission or primary care attendance). Any direct follow up and questionnaire completion required will coincide with routine orthopaedic review where feasible (recognising these reviews may be delivered virtually and at inconsistent timepoints), to mitigate direct research burden to participants.

Table of baseline data variables:

Variable	Defined as	Form	Reported as
Age	Participants age	Digit	Years
Biological sex	Participants biological sex	Category	Female Male
Gender	Participants gender as defined by Diversity and Inclusion Survey (DAISY)	Category	Man Woman Non-binary Prefer to self-describe Prefer not to say
Ethnicity	Participants ethnicity as defined by Diversity and Inclusion Survey (DAISY)	Category	Asian/Asian British • Bangladeshi • Chinese • Indian • Pakistani • Any other Asian background Black/African/Caribbean/Black British • African • Caribbean • Any other black/African/Caribbean background White • English / Welsh / Scottish / Northern Irish / British • Gypsy or Irish Traveller • Irish • Roma • Any other White background Any other ethnic group • Arab • Hispanic • Latina/Latino/Latinx • Any other ethnic group
Height	Participants height	Digit	Centimetres / Feet and Inches
Weight	Participants weight	Digit	Kg / stone and pounds
BMI	(Participant weight) / (participant height)^2	Digit	1 Decimal Place

Index of multiple deprivation rank	Ordinal variable	Digit	1-32,844
Comorbidities			
Prior VTE	Prior confirmed diagnosis of VTE event requiring treatment for a period of 3 months or longer	Category	No Yes
Known major thrombophilia	Confirmed diagnosis of a disorder which causes major thrombophilia such as Antiphospholipid Syndrome (Hughes syndrome)	Category	No Yes
Family history of VTE	First degree relative	Category	No Yes
Cancer diagnosis	Diagnosis of cancer in last 5 years	Category	No Yes
Immobilisation within last 3 months	Participant was admitted to hospital, underwent surgery, bedbound, went on a long-haul flight >6h, or experienced lower limb paralysis in the last 3 months	Category	Recent hospital admission Bedbound Long-haul flight >6h Paralysis Surgery in last 3 months
Other known comorbidities	Prior confirmed diagnosis of heart failure, rheumatoid arthritis, chronic kidney disease, COPD, inflammatory bowel disease, or venous insufficiency (varicose veins)	Category	Heart failure Rheumatoid arthritis Chronic kidney disease (Chronic eGFR <30 or RRT) COPD Inflammatory bowel disease Venous insufficiency Stroke
Smoking status	Participants current smoking status (cigarettes, cigars, chewing tobacco)	Category	Current Smoker Ex-Smoker Never smoked
Diabetes	Prior confirmed diagnosis of type 1 or type 2 diabetes	Category	Type 1 Type 2 requiring insulin Type 2 managed by diet Not diabetic
Medication use			
Antiplatelets	Ongoing use of aspirin, clopidogrel, dipyridamole, ticagrelor, prasugrel.	Category	Aspirin Clopidogrel Dipyridamole Prasugrel

			Ticagrelor Other None of the above
Proton Pump Inhibitor	Ongoing use of omeprazole, lansoprazole, pantoprazole, rabeprazole, or ranitidine	Category	Omeprazole Lansoprazole Pantoprazole Rabeprazole Ranitidine Other None of the above
Non-steroidal anti-inflammatory drugs (NSAIDs)	Ongoing use of ibuprofen, naproxen, diclofenac, ketorolac, indomethacin, meloxicam, or piroxicam	Category	Ibuprofen Naproxen Diclofenac Ketorolac Indomethacin Meloxicam Piroxicam Other None of the above
Type of Injury			
Type of Injury	Most serious injury	Category	Tibia and/or fibular shaft fracture Tibial plateau fracture Achilles tendon rupture Bi/tri malleolar ankle fracture Unimalleolar ankle fracture Patella fracture Ankle dislocation Lisfranc injury Severe knee sprain (grade 3) Severe ankle sprain (grade 3) Patellar dislocation Metatarsal or forefoot fracture Non severe knee or ankle sprain (grade 1 or 2) Significant muscle injury Other
Type of immobilisation			
Degree of immobilisation	Method of immobilisation of index injury	Category	Upper-leg cast (above the knee) Lower-leg cast (below the knee) Foot cast (ankle free) Rigid soled shoe Rigid knee brace without plantar support (cricket pad splint) Rigid ankle brace with plantar support (aircast or tenor boot) Ankle stirrup
Weight Bearing Status			

Weight bearing assessment	Weight bearing at initial ED discharge	Category	Full weight bearing Weight bearing as tolerated Partial weight bearing Toe touch weight bearing Non-weight bearing
TRiP (Cast) Score at point of screening			
TRiP (Cast) score	Ordinal variable	Digit	1-17

16.6 Analysis of participant populations

An intention to treat analysis will be used as the primary analysis. A per protocol analysis and several pre-defined sensitivity analyses will also be conducted, excluding those patients allocated to a risk strata outside TRIP(Cast) score.

16.7 Primary endpoint analysis

The primary analysis in TiLLI-High will be a non-inferiority test of DOAC vs LMWH in the intention-to-treat population. Non-inferiority is declared if the upper limit of a two-sided 95% Farrington-Manning confidence interval for the risk difference lies below the non-inferiority margin. The Farrington-Manning method is preferred over the conventional Wald confidence interval in a non-inferiority design.[60] A subsequent superiority interpretation will be made should non-inferiority be declared. A compliance adjusted per protocol analysis using inverse probability weighting will be conducted as a supplementary analysis to assess non-inferiority in terms of treatment efficacy. Precise adherence criteria for the per-protocol population will be pre-specified in the statistical analysis plan.

The primary analysis for TiLLI-Low will be a two-group risk difference comparison of any pharmacological prophylaxis (DOAC or LMWH) compared to no medication on intention-to-treat basis. If a significant difference between prophylaxis and no medication can be declared, individual comparisons of DOAC and LMWH vs control will be made using a Dunnett test like procedure for binary outcomes based on the Newcombe's hybrid score confidence interval.[61]

16.8 Secondary endpoint analysis

Individual components of the primary outcome will be analysed as binary variables using the same approach as the aforementioned primary analyses. Additionally, these variables will be analysed as time to event outcomes with log rank test and Kaplan-Meier curves. Further secondary endpoints will be summarised and analysed using appropriate techniques (corresponding to the primary outcome analysis) according to whether the variable is binary, categorical, continuous or time-to-event.

A detailed statistical analysis plan (SAP) with all proposed statistical analyses will be drafted early in the trial and finalised prior to the first data extraction from the database. The SAP will explain all analysis models, model checks to be performed and any (multiple) imputation methods used. The SAP will be reviewed by oversight committees prior to sign off. Formal

interim analyses other than futility analysis in TiLLI-Low are not planned and will be performed only where requested by the DMEC.

Modelling of long-term events

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 inform our existing model with population-specific effect estimates from TiLLI. 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 follow-up participants and measure long-term health outcomes, such as the incidence and severity of PTS.
We will evaluate the impact on downstream adverse events >90 days (including PTS) using our previously developed decision analytic model funded by NIHR, which estimates the cumulative incidence of PTS and chronic pulmonary hypertension in the years following VTE.[11] We will update this model with recent evidence suggesting the longer-term impact of even small isolated VTE events has been underestimated, in addition to other relevant evidence following stakeholder review.[62] Model structure is described below and in detail at https://www.journalslibrary.nihr.ac.uk/hta/hta23630.

16.9 Safety analysis

Our composite primary outcome of net clinical benefit includes major bleeding or cause-specific mortality (death from either pulmonary embolus or major bleeding). All individual outcomes contributing to the composite will be confirmed using consensus definitions published by the International Society of Thrombosis and Haemostasis (ISTH).[34-36]

Serious adverse events will be collected throughout the study and reported as themes.

16.10 Subgroup analyses

Exploratory subgroup analyses will be conducted for gender, ethnicity, age, injury type and method of immobilisation.

16.11 Adjusted analysis

The primary outcome analysis is unadjusted. Adjusted analyses are planned accounting for known likely prognostic variables to assess robustness of effect estimates.

Recruiting centre and TRiP(Cast) score have been identified as variables that will be adjusted for in this analysis.

16.12 Interim analysis and criteria for the premature termination of the study

An Independent Data Monitoring and Ethics Committee (DMEC) and an independent Trial Steering Committee (TSC) will oversee the individual pilot phase with interim assessment after 12 months of active recruitment for each trial. Separate stop/go criteria (described previously) have been proposed for each trial so that one trial could continue in the event

that feasibility is not demonstrated for both. Robust progression criteria have been set, including staggered site set up prior to pilot commencement, negligible lag phase and 10% of total recruitment in <30% total recruitment window.

Stopping rules

Two futility interim analyses when 50% and 75% of the primary outcome data has been obtained have been incorporated in the design of TiLLI-Low. Futility stopping boundaries are set to correspond to predictive power of 20% at both analyses, that is, the trial is stopped for futility if predictive power is below 20% at the respective time point, starting with an initial non-informative prior. Constant predictive power boundaries have been indicated to be a near optimal criterion in terms of minimizing the average expected sample size if there truly is no treatment effect between groups.[57] Earlier interim looks were considered but would require a sample size inflation that was deemed unreasonable. The sample size has been inflated by 10.4% to allow for the two interim looks whilst maintaining 90% power. The average expected sample size that will be needed for TiLLI-Low if there is in fact no difference between groups is 57.5% of the total recruitment target. A nonbinding futility analysis approach has been chosen. Futility boundaries are regarded as guidelines and any decision to stop the trial would only be made following recommendations of the oversight committees taking into account all accruing data.

16.13 Procedure(s) to account for missing or spurious data

The primary analysis of all outcomes will be by intention to treat (ITT), in the sample of participants with a non-missing outcome. Performing an intention-to-treat analysis does not mean that the outcome must have been collected for all participants, though it does assume that every effort has been made to do so. For the primary outcome, missing data is not possible due to the definition of the outcome, unless (known) administrative or IT errors lead to absence of participant records. In this case multiple imputation would be used for efficiency gain, otherwise the available data will be analysed. For the secondary outcomes, for which there are participants with missing outcomes, we will conduct analyses with multiple imputation under missing-at-random assumption using a pattern mixture modelling approach.

16.14 Economic evaluation

Within-trial economic evaluations will be conducted over the 90 days duration as well as long-term modelling using our previously developed model from the perspective of NHS health and social care services.

Within trial Health Economic Analysis

The EuroQol 5 Dimensions 5 Level (EQ-5D-5L) is a validated instrument comprising a self-rated health VAS and a five-domain health status questionnaire related to daily activities.[39] Responses are converted into an overall score using a published utility algorithm for the UK population. A retrospective EQ-5D-5L questionnaire will be administered 7 days from randomisation to capture baseline prior to injury, EQ-5D-5L will be administered 7 days following randomisation, 42 days following randomisation, and 90 days following randomisation. Utility scores for the UK population, as recommended by NICE, will be used, together with patient survival data, to derive quality-adjusted life years (QALYs) during the

90 days follow-up using the area under the curve method. We will report differences in EQ-5D-5L QoL utility at 90 days and QALYs within 90 days between treatment groups.

In a review of secondary care Electronic Health Records (EHR), research staff will collect information on resources required to deliver subsequent care reviews (including scheduled clinic and unscheduled hospital attendance), investigations, treatments or management. This will provide detailed comparative resource use. Participants will be invited to complete additional questionnaires to complement this EHR review and collect other health and social care and personal out-of-pocket expenditures, including remote hospital admissions and outpatient visits, GP & community nurse visits, and social care service provision and medications. Unit costs for health and social care resources will be derived from national sources including Unit Costs of Health and Social Care (PSSRU), NHS Reference Costs and the British National Formulary. Resources will be valued using the most up-to-date reference costs and local sources, such as hospital finance departments, for micro-costing when appropriate.

The within-trial analysis will be developed from the perspective of UK NHS over the 90-day follow-up post-randomisation. Costs assessed in the trial will include costs of treatments (LMWH, DOAC), hospital admissions and readmissions post-randomisation, other medication use, and outpatient appointments and investigations. The EQ-5D-5L questionnaire will be administered to study participants at randomisation, collecting a retrospective, pre-injury QoL measure, and at 7-days, 42-days and 90-days follow-up measures. The main health outcome measure in the within-trial analysis will be the quality adjusted life year (QALY), evaluated using the trial EQ-5D-5L measures and survival data up to 90-days in the within-trial analysis.

It is likely that, despite efforts to collect all planned study data, a degree of missing EQ-5D and resource use data will be present. Multiple imputation methods, tailored to the degree and type of missing data, will be used in the base case analyses to impute missing cost and EQ-5D data and avoid biases associated with a complete case analysis.[63]

The within-trial analysis will estimate the incremental QALYs gain, incremental cost and incremental cost effectiveness ratio (ICER) for allocation to DOAC therapy compared to LMWH in TiLLI-High and for allocation to any DOAC/LMWH compared to no pharmacological prophylaxis treatment in TiLLI-Low. We will also undertake a full incremental cost-effectiveness analysis between DOACs, LMWH and no treatment in low-risk patients. We will present our results in terms of net monetary benefits using the range of willingness to pay thresholds from £0 to £30,000/QALY to facilitate appropriate comparisons between the interventions. We will use the non-parametric bootstrap approach to assess the parameter uncertainty in cost-effectiveness results, sampling with replacement from the respective study arms, and present cost-effectiveness acceptability curves. A detailed health economic analysis plan (HEAP) with full details of all analyses will be finalised prior to primary outcome analysis.

Long term Health Economic Analysis

In further economic analyses we will use our previously developed decision analytic model to evaluate the expected life-time costs and QALYs for the alternative treatment options in high and low risk populations. The model structure has been developed in consultation with clinical experts. A short-term decision tree model (6 months), informed by key effectiveness and safety outcomes observed in the trial, will be combined with a long-term Markov model. The Markov model is used to quantify the QALY losses from any deaths and any ongoing morbidity from bleeding complications in the short-term model. It also captures the costs and QALY losses over a life-time horizon attributable to PTS or chronic pulmonary hypertension occurring

after VTE. The long-term modelling will be informed by published literature on epidemiology, resource use and quality of life and outcomes will be discounted at 3.5% per annum.

16.15 Data linkage for routinely collected participant-level data

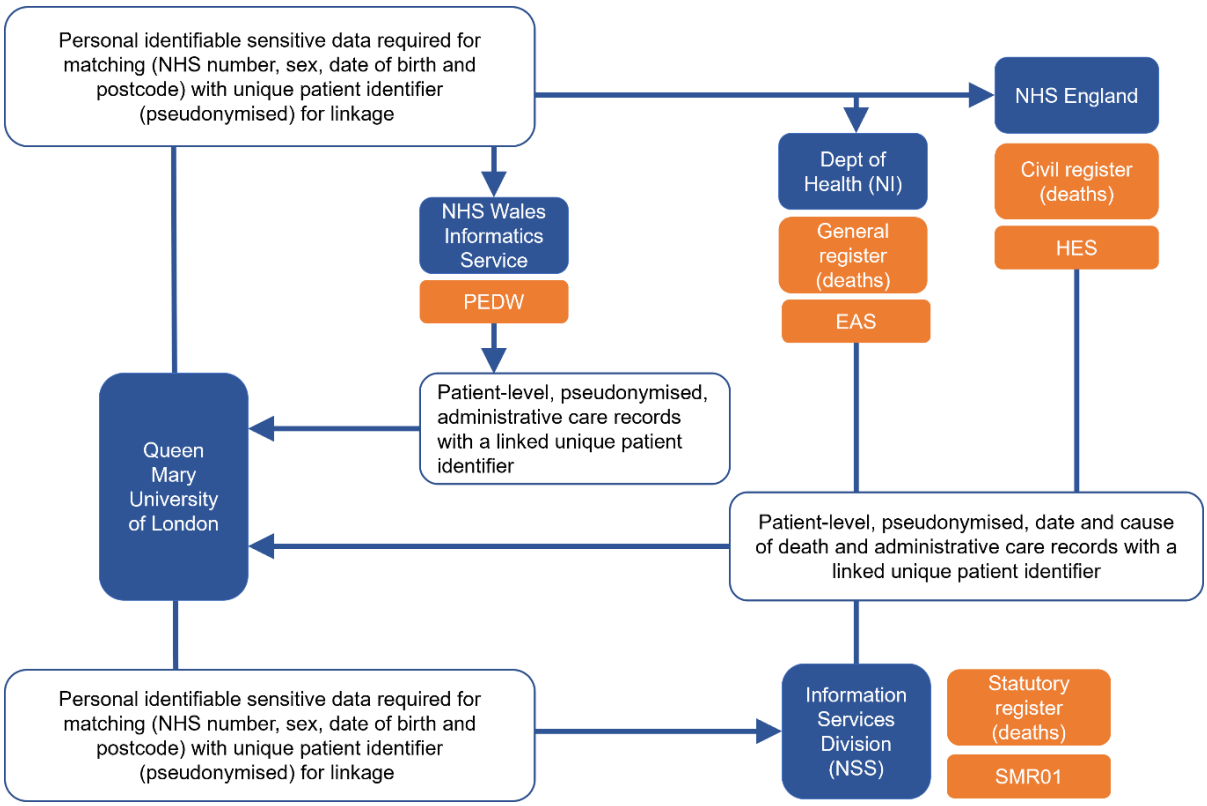
Data linkage for routinely collected patient-level data

Consent will be sought from participants to access their patient-level routinely collected data captured by the various UK data warehouses, including diagnostic and procedural codes relevant to hospitalisations and/or outpatient attendances for participants treated in NHS hospitals in order to provide a measure of long-term outcomes and NHS resource use.

For participants treated in England, linkages will be sought with the admitted patient care, emergency care, outpatient care and critical care datasets within the Hospital Episode Statistics (HES) database; in Wales, the Patient Episode Database for Wales (PEDW) derived from the Admitted Patient Care dataset; in Scotland, The Scottish Morbidity Register – General/Acute Inpatient and Day Case (SMR01). In addition, linkages will also be sought with the relevant registers of deaths and the causes of deaths in each jurisdiction. Civil Registration (deaths) provides a complete register of date and cause of death in England and Wales and is administered by NHS Digital; the General Register Office for Northern Ireland records deaths in this jurisdiction; the Statutory Registers of Births, Deaths and Marriages in Scotland is administered by the National Records of Scotland.

For the purposes of the data analyses, the research team will only process linked, de-identified data. In order that this dataset can be created, identifiable data will be provided to each data controller for the purpose of the linkage. A bespoke cohort will be generated from the TiLLI database and sent to each data controller containing participant health service number, date of birth, sex and postcode as well as a unique identifier for linkage. The trusted third parties will link the cohort to the relevant civil register of deaths and administrative databases in their jurisdiction and return the relevant variables.

Data flow



Identifiable data from the bespoke cohort will be provided to NHS Digital, Dept. of Health (Northern Ireland) and NHS Wales Informatics Service for data linkage. Queen Mary University of London will send the health service number, date of birth, sex and postcode as well as a unique patient identifier (de-identified) for linkage. The legal basis for Queen Mary University of London to collect and transfer these personal data to the trusted third parties is participant consent (section 261.2(c) of the Health and Social Care Act 2012).

NHS Digital will link Civil Registration (deaths) date and cause of death and HES data with the unique identifier. Queen Mary University of London will receive from NHS Digital patient-level de-identified data only, i.e., the linked date and cause of death as well as HES data with the unique patient identifier. The legal basis for Queen Mary University of London to receive and process data from NHS Digital is Articles 6 and 9 of the General Data Protection Regulations (GDPR).

Department of Health (Northern Ireland) will link General Register Office for Northern Ireland date and cause of death and EAS data with the unique identifier. Queen Mary University of London will receive from Department of Health (Northern Ireland) patient-level de-identified data only, i.e., the linked date and cause of death as well as EAS data with the unique patient identifier. The legal basis for Queen Mary University of London to receive data from NHS Digital is the Health and Social Care Act 2012.

NHS Wales Informatics Services will link PEDW data with the unique identifier. Queen Mary University of London will receive from NHS Wales Informatics Services patient-level de-identified data only, i.e., the linked PEDW data with the unique patient identifier. The legal

basis for Queen Mary University of London to receive data from NHS Digital is the Health and Social Care Act 2012.

Queen Mary University of London will aggregate these datasets for each participant using the unique patient identifier (de-identified) to create a research dataset for the processing purposes described within the statistical analyses and health economics analyses contained within the protocol.

Description of analysis methods

Where applicable, linked routinely collected data will be received at episode level (period of time a patient is under the care of a consultant), from which spells of continuous care will be built and combined with mortality data from the national registries.

For each randomised comparison, statistical models will be estimated to investigate the association between treatment and categorical variables based upon events identified through International Classification of Diseases (ICD; diagnostic), Office of Population Censuses and Surveys (OPCS; procedure) codes, and deaths. The specific events of interest will be described in each of the appendices.

Where applicable, sensitivity analyses will be conducted comparing the in-trial analyses based upon bespoke CRF data with those based on the linked administrative data to provide context for the long-term analyses.

In addition, participant-level profiles of resource use associated with linked hospital episodes encompassing inpatient admission, outpatient visits and emergency department attendances will be costed using NHS Reference Costs.

16.16 Other statistical considerations

Long-term outcome analyses based upon routinely-collected data from hospital EHRs as well as national healthcare sources such as PEDW, SMR01 and HES, for which explicit consent for follow-up 5 years after study inclusion is sought at enrolment, will be planned contingent on successful future funding. Full statistical and economic analysis plans will be developed and made publicly available for any future such analyses at that time.

17.0 Data handling and record keeping

17.1 Source data and source documents

Source data is defined by ICH GCP section 1.51, as "all information in original records and certified copies of original records of clinical findings, observations, or other activities in a clinical trial necessary for the reconstruction and evaluation of the trial. Source data are contained in source documents (original records or certified copies)."

Source documents are defined as "Original documents, data and records (e.g., hospital records, clinical and office charts, laboratory notes, memoranda, subjects' diaries of evaluation checklists, pharmacy dispensing records, recorded data from automated instruments, copies or transcriptions certified after verification as being accurate and complete, microfiches,

photographic negatives, microfilm or magnetic media, x-rays, subject files, and records kept at the pharmacy, at the laboratories, and at medico-technical departments involved in the clinical trial)." [ICH E6 1.52]. Source documents will likely contain participant identifiable data and therefore will be stored securely at investigative sites and will not leave Trust premises. All documents will be stored safely in confidential conditions.

To enable review, monitoring, audit and/or inspection of study source data, the PI must agree to keep records of all participants. Trial data will be captured in source documents such as (but not limited to) participant medical records/clinical notes, original consent forms, questionnaires, trial specific source document worksheets, and evaluation checklists.

Sites that use electronic source (e-source) data should ensure to provide access to e-source systems and database(s) to the TiLLI Trial Manager and Monitor (and all other authorised personnel) at onsite visits. It is the site's responsibility to maintain these e-source databases, to ensure that they are GCP and MHRA guidelines compliant and provide a suitable audit trail, and that systems are in place to demonstrate that the PI at site has clinical oversight of e-source data. Printouts from e-source data must be documented to be verified copies, dated and signed.

A source data location document will be in place for each site that will detail where the source data will be located locally and what documents comprise the source documents.

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

17.2 Case Report Forms (CRFs)

An electronic case report form (eCRF) is a form on which individual participant data that are required by the study protocol are recorded. The eCRF is used to collect the data that will be used to perform statistical or health economical analyses. eCRFs must:

- Ensure that all required data is captured.
- Ensure that no superfluous data is captured (which can make data capture unnecessarily complicated, make data extraction and analysis difficult, and potentially breach the Data Protection Act).
- Ensure that paper trails are maintained to demonstrate the validity of the study (both during and after the study).

eCRF entries may be source data if the eCRF is the site of the original recording (i.e., there is no other written or electronic record of data, e.g., questionnaires completed by participants such as the EQ-5D-5L questionnaire and ACTS questionnaire). If the eCRF contains source data and is sent to the sponsor, the study site must retain a copy to ensure that the Principal Investigator can provide access to the source documents to a monitor, auditor, or regulatory agency. Additional information can be found in ICH E6, section 6.4.9.

eCRFs will be completed throughout the course of the study by appropriately trained and delegated site personnel or study participants. Study participants will receive appropriate training from site team personnel. Data must be entered into the eCRF within 5 working days of collection.

Trial data will be captured electronically in an OpenClinica4 database system. The database will be designed and developed by PCTU in accordance with its own SOPs and the Sponsor's SOP 38b "Trial Data Management Systems", with input from the CI and study team.

Participant identifiable data that is required for remote follow-up and data linkage will be entered directly into the secure OpenClinica4 database on an eCRF separate to all other study data. Access to the eCRF storing participant contact details will be provided to authorised team members with a demonstrated need to do so.

17.3 Data capture

Data will be recorded from a variety of sources including, but not limited to, participant-reported information, site proformas, printouts from equipment, recording results from electronic displays, laboratory reports, validated questionnaires, and electronic health records.

All efforts will be made to maximise completeness of data, as such flexibility has been introduced to facilitate the participants' preference for mode of data collection e.g., direct contact, remote contact via SMS, and remote contact via email. In instances missing data persists, tactics including telephoning subjects to obtain missing data may be deployed.

All interactions with participants will be documented (including telephone conversations and emails). Validated questionnaires (such as EQ-5D-5L and ACTs) will be completed by participants at site attendances or remotely via electronic link. The PI/delegate will keep records of all participants to allow sufficient information to enable link of de-identifiable data back to the participants records e.g., eCRFs, hospital records and samples), all original signed informed consent forms and copies of the eCRF pages.

Access to the database will be by password-protected user accounts to prevent unauthorised access, and the database will be encrypted at rest. The CI will have overall responsibility for the data stored within the database. Data will be entered into the eCRF by delegated trial site team members. Further detail on data management may be found in the trial data management manual.

17.4 Transferring and transporting data

All data will be handled in accordance with the Data Protection Act (2018).

Site team personnel will be reminded that participant identifiable information must not be stored or transported on any portable device (e.g., laptops, memory sticks, CD / DVDs) unless it is encrypted. Where trial data needs to be transferred and stored outside of sites, no participant identifiable data (PID) will be used; only the participant ID will be used.

17.5 Data Management

Data management will be undertaken by PCTU at Queen Mary. Standard operating procedures will be in place for the collection and handling of data received at the Unit. All trial data will be entered into a database by appropriately trained staff with restricted access. Data collected on the eCRFs will be stored in an electronic database housed in OpenClinica4. The database validity and quality can be ensured and monitored by validation and audit trails.

Once data has been entered by site personnel on the eCRF, the data will be reviewed and checked for error and inconsistencies by the TiLLI trial manager or other authorised members of the trial team. Once the patient is 'off-study' and all data has been entered onto their record, the Principal Investigator or delegate must provide an electronic sign-off to authorise the complete subject eCRF. By authorising the eCRF the principal investigator is confirming that all data entered is accurate and reliable.

A central statistical monitoring plan and data management plan will be developed to detail the trial specific procedures for data accuracy and quality check processes that will be completed on the study data periodically throughout the course of the study.

Source data verification will be performed by authorised members of the Investigator team as per local SOPs. Further details on source data verification and monitoring may be found in the trial monitoring plan.

Further details on data management may be found in the trial data management plan.

18.0 Confidentiality

The Chief Investigator will be the data custodian for all data generated during the study. The Chief Investigator and the study team will ensure that all participants' identities are protected at every stage of the study. To ensure this, each participant will be allocated a unique study number before undergoing any screening procedures.

Information regarding study participants will be kept confidential and managed in accordance with the Data Protection Act (2018), the UK Policy Framework for Health and Social Care and Research Ethics Committee approval. All study data will be stored in line with the Medicines for Human Use (Clinical Trials) Regulations 2004 and subsequent amendments and the Data Protection Act. Study data will be archived in line with the Medicines for Human Use (Clinical Trials) Regulations 2004 and all subsequent amendments, and as defined in the JRMO SOP 20 Archiving. The participants' full name, date of birth, NHS number, telephone number, and address will be collected to allow for follow-up. The participant identifiable data collected will be regarded as confidential and stored in an eCRF independent from other study data. All other study data will be pseudonymised with use of the study ID number.

The Principal Investigator is responsible for protecting the identity of participants at their site. Participants will be referred to only by their unique study identifier whenever data is transferred outside of the site, and in all correspondence between the site and the coordinating centre, co-investigators, sponsor, or anyone associated with the study.

No participants will be individually identifiable from any publications resulting from the study.

18.1 De-identification of participants

Participant Identifiable Data (PID) will be stored on participant consent forms, screening logs and Participant Identifiable Data eCRF. All trial documents (apart from those aforementioned and source data which by default may contain identifying data) will be labelled with the participant ID only.

A screening log will be maintained throughout the study to allow participant identification by relevant site staff. A unique participant ID will be allocated to each participant that enters

screening, if the participant progresses through the trial they will maintain the same unique participant ID.

Full participant identifiable data will be collected to perform long term flagging with Hospital Episode Statistics (HES) as outlined in the study objectives.

The following participant identifiable data will be collected in the Participant Identifiable data eCRF to allow long-term flagging with HES and remote follow-up:

- Participant name (forename and surname)
- Participant date of birth
- Participant telephone number
- Participant address and postcode
- Participant NHS number

PID will be entered into the eCRF PID by site team personnel. No PID will be sent to the central trial team by email or fax. Any study data sent to the central trial team must be de-identified before it is used or sent / transferred from the site.

19.0 Monitoring, Audit, and Inspection

19.1 Monitoring

A Trial Monitoring Plan will be developed and agreed by the sponsor, Chief Investigator, PCTU Trial Manager, and PCTU QA manager based on the sponsor's risk assessment, which will include on site monitoring. Monitoring procedures are detailed in the Trial Monitoring Plan.

19.2 Auditing

The sponsor retains the right to audit any aspect of the study, study sites, or central facilities. In addition, any part of the study may be inspected by the regulatory bodies, and funders where applicable.
All sites and vendors are asked to inform the sponsor if notified of any Audit or inspection affecting this study
.

20.0 Compliance

The CI will ensure that the protocol and study is conducted in compliance with the principles outlined in the Medicines for Human Use (Clinical Trials) Regulations 2004 and subsequent amendments, current UK Policy Framework for Social and health care research (2017), GCP guidelines, the World Medical Association Declaration of Helsinki, the Sponsor's and study specific SOPs, and other regulatory requirements.

The study will not commence until sponsor permission to activate sites is received.

Sites will be individually activated by the CI and team; this will not occur until site approval is granted.

20.1 Non-Compliance

Accidental protocol deviations can happen at any time. They must be adequately documented on the protocol deviation log eCRF. The CI and the PCTU coordinating team will assess non-compliances and action a timeframe in which they need to be dealt with (this assessment should include the need to escalate to the Sponsor where applicable). Corrective and preventative actions (CAPAs) will be assigned (where applicable), and each action will be given a different timeframe dependent on the severity.

Any event with the potential to affect participant safety or data integrity should be reported to the Sponsor and PCTU Information Governance team within 24 hours of the coordinating team becoming aware. Prospective, planned deviations or waivers to the protocol are not allowed under the UK regulations on Clinical Trials and must not be used (i.e., it is not acceptable to enroll a participant if they do not meet the eligibility criteria or restrictions specified in the study protocol). Deviations from the protocol which are found to frequently recur are not acceptable, will require immediate action and could potentially be classified as a serious breach. Systematic failure of both the CI and the study staff adhering to SOPs, protocol, ICH GCP or UK regulations, which leads to prolonged collection of deviations, may constitute breaches or suspected fraud.

Non-compliances may be captured from a variety of different sources including monitoring visits, eCRFs, communications and updates. The sponsor will maintain a log of non-compliances to ascertain if there are any trends developing which need to be escalated.

20.2 Notification of Serious Breaches to GCP and/or the protocol

A 'serious breach' is a breach which is likely to affect to a significant degree:

- The safety or physical or mental integrity of the participants of the study; or
- The scientific value of the study.

The site Principal investigator is responsible for reporting any potential serious breaches to the sponsor (research.safety@qmul.ac.uk), copying in tili-bjh@qmul.ac.uk within **24 hours** of becoming aware of the event.

The Chief Investigator is responsible for reporting any potential serious breaches to the JRMO **within 24 hours** of becoming aware of the event.

The sponsor is responsible for determining whether a potential serious breach constitutes a serious breach and will work with the CI to investigate and notify and report to the MHRA and REC (as applicable) within 7 working days of becoming aware of the serious breach.

21.0 Declaration of interests

The CI, PIs at each site, and committee members for the overall study management, will provide the following declarations of interest:

- All competing interests.
- Ownership interests that may be related to products, services, or interventions considered for use in the study or that may be significantly affected by the study.
- Commercial ties (e.g. pharmaceutical, behaviour modification, and/or technology companies).
- Non-commercial potential conflicts (e.g. professional collaborations that may impact on academic promotion).

These will be held within the Trial master file. Please address enquiries to Tilli-bjh@qmul.ac.uk

22.0 Peer review

All CTIMP studies sponsored by the JRMO will undergo scientific peer reviewed by two independent experts in the field (independent of Queen Mary and Barts Health). The study will also be reviewed by the CI's Institute or Clinical Board prior to sponsorship in principle being given by the JRMO as per the procedure outlined in JRMO SOP 14 Peer Review.

23.0 Public and Patient Involvement (PPI)

This study addresses multiple specialty James Lind Alliance priority setting partnership recommendations from the last 5 years, developed by patients, service users and carers.

We have built on prior collaborations to form a diverse patient advisory group (PAG) – 2 white men, 2 white women, 2 Bangladeshi women, 1 black woman, age range 30-70 with significant lived experience of emergency care and VTE. Our group includes patients with recent experience of participating and completing NIHR funded research on VTE, those who have directly suffered VTE after lower limb immobilisation, people who have cared for someone with VTE and the director of the charity Thrombosis UK. We have held multiple guided focus groups throughout the development of stage 1 and stage 2 applications. This group have challenged our methods and reasoning through the design stages and ensured we have kept a clear focus on the outcomes most important to patients.

24.0 Indemnity/ Insurance

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 non-negligent harm.

25.0 Study committees

For this trial there will be three overall committees: A Trial Steering Committee (TSC), a Data Monitoring and Ethics Committee (DMEC) and a Trial Management Group (TMG) overseeing the trial throughout the duration of study.

The Data Monitoring and Ethics Committee (DMEC) has been appointed in accordance with NIHR recommendations, is fully independent of the trial and operates without any conflicts of interest with the Sponsor. Further details on the membership and full remit of these committees may be found in the TSC, DMEC and TMG Charters.

25.1 Trial Management Group (TMG)

The Trial Management Group (TMG) is mandatory for all MHRA regulated trials. The TMG should meet regularly to ensure all aspects of the study are progressing and working well, and everyone within the study is aware of their required actions. The TMG will operate under the following terms and be responsible for the following actions:

- Initial monthly meetings, organised through virtual teleconference, with the potential to step down to quarterly meetings later in the project.
- The TMG will comprise the lead and all co-applicants for the study, the trial manager and invited site representatives at discretion.
- The TMG will have authority to terminate / prematurely discontinue the study.

25.2 Trial Steering Committee (TSC)

An independent TSC will provide overall supervision for the trial and will report to the Sponsor. Members of the TMG and PCTU coordinating team will be invited to the meeting. Representatives of the Sponsor and funder may also attend. The frequency of TSC meetings will be (a minimum of) once a year. An emergency meeting may be convened if a significant issue is identified. The TSC will not have the authority to terminate / prematurely discontinue the study, but may advise the TMG to do so. The TSC will include members that are both independent and associated with the research team, comprising of an independent chair, independent statistician, at least one public member, and others with relevant clinical experience.

25.3 Data monitoring and Ethics committee (DMEC)

The DMEC will monitor participant safety and review unblinded trial data whilst the trial is ongoing. The frequency of DMEC meetings will be (a minimum of) once a year. An emergency meeting may also be convened if a safety issue is identified. The DMEC will report directly to the TSC, who will make recommendations to the Sponsor. The DMEC may consider recommending the discontinuation of the trial if the recruitment rate or data quality are unacceptable or if any issues are identified which may compromise participant safety, or if, in the DMEC's view, the interim results showed differences between treatments that were deemed to be convincing to the clinical community.

26.0 Publication and dissemination policy

26.1 Publication

We intend to publish the trial protocol and statistical and health economic analysis plans during the initial phases of the trial. At the end of the main phase, we will publish two main results papers (clinical effectiveness and economic evaluation reports) and a final publication on longer term outcomes using the decision analysis model. In order to reach a wider audience, we will develop videos to disseminate the results. These will be shared on our stakeholder social media channels in addition to the study website. The videos will facilitate dissemination to audiences who do not speak English as their first language with the use of animations and infographics to facilitate knowledge transfer. We will also promote study outputs at multiple international conferences in the field of orthopaedics, trauma and emergency care.

It is the CIs responsibility to ensure they meet all requirements laid out by The International Committee of Medical Journal Editors (ICMJE) (http://www.icmje.org/). All publications will be sent to the JRMO prior to publication.

Responsibility for ensuring accuracy of any publication from this study is delegated to the Chief Investigator. All publications should acknowledge the Sponsor. The correct designation for the sponsor is “Queen Mary University of London”.

The full study report will be accessible via EudraCT or other suitable public website within one year of the End of the Trial Notification.

26.2 Dissemination policy

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.

Patients, patient advocacy groups & members of the public. The trial team in line with the Queen Mary’s Communications and Marketing policy 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. The combined Twitter audience of our trial team and related organisations is ~200,000 followers, so we will regularly provide project updates and findings via Twitter. We will work with the Patient, Carer and Public Involvement and Engagement (PCPIE) Group of the Royal College of Emergency Medicine throughout the trial will ensure that the results of the study are disseminated to patients and the public. The TiLLI study website will also include dedicated pages for members of the public. We will hold open days in some of the hospital departments participating in the study where members of the public will be invited to find out about the study.

Healthcare providers. We have costed the application to include 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 (e.g., Emergency Medicine Journal, Journal of Thrombosis and Haemostasis, Bone & Joint Journal). 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.

National guidelines and policy makers. We will use our established network involvement (UK POMCTN, VTE Exemplar Network, BOA, RCEM) 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 College of Surgeons and RCEM to TiLLI results. and submit suggested updates to the British Orthopaedic Foot and Ankle Society (BOFAS), to facilitate updates of their guidance in light of TiLLI findings.

TiLLI will be due to report in 2028 and inform the update to NICE Guidance NG89 "Venous thromboembolism in over 16s: reducing the risk of hospital-acquired deep vein thrombosis or pulmonary embolism". TiLLI is highly likely to be the largest, most applicable trial addressing the research question and will therefore directly influence national clinical practice within five years. These outputs would be expected to directly benefit patients, healthcare staff and the NHS by decreasing uncertainty, allowing standardisation of care and promoting the development of pathways for better care.

We do not expect any requirement for specific additional funding for the NHS. All health technologies under investigation are in current use within an NHS setting and either freely available or routinely stocked at NHS list prices. We will therefore work closely with the specialty associations supporting the study (RCEM, Thrombosis UK, BOA, OTS, POMCTN and the VTE Exemplar network) to ensure rapid translation of the study results to daily clinical practice. We will ask our PAG for advice on dissemination to what to expect as best care through public charities, support organisations, local networks and advocacy groups.

26.3 Access to the final study dataset

The CI, TSC and DMEC will have access to the final trial dataset.

27.0 Archiving

Archiving is only permitted once close-out visits have been performed and all action points completed. Permission to archive will be given to sites in writing by the Clinical Trial Manager once permission has been given by the Sponsor.
During the course of the research, all records are the responsibility of the Chief Investigator and will be kept in secure conditions. When the research study is complete, it is a requirement of the Barts Health and Queen Mary, University of London Policy that the records are kept for a further 25 years as per sponsor archiving SOP.

Site files from other sites must be archived for 25 years at the external site and will not be stored at the Barts Health Modern Records Centre or within Queen Mary.

Destruction of essential documents will require authorisation from the Sponsor.

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This protocol is based on JRMO Protocol template for MHRA Regulated Studies; SOP 11a Associated Document 2 v8.0 07.04.2022 FINAL