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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.

Submission date
10/05/2024

Recruitment status
Recruiting

Registration date
30/07/2024

Overall study status
Ongoing

Last Edited
10/11/2025

Condition category
Injury, Occupational Diseases, Poisoning

[X] Prospectively registered
[_] Protocol
[_] Statistical analysis plan
[_] Results
[_] Individual participant data
[X] Record updated in last year

Plain English summary of protocol

Background and study aims
People have an increased risk of blood clots when they have a leg injury treated with a plaster cast or a splint, which happens to over 70,000 people every year in the UK. Blood clots can cause long term problems in the legs and can also move to the lungs, causing serious illness and occasionally death. Medicines are available to reduce the risk of blood clots, but they can also increase the risk of bleeding. In people at high risk of clots, most hospitals use the recommended daily injections which can be uncomfortable and sometimes difficult to give. Tablets are available that reduce the risk of blood clots in other groups, but we don't know if tablets work as well as the injections for people with a leg injury. We also don't know whether people at low risk of blood clots may benefit from any medication.

Our study has two aims - to determine whether giving tablets to people at high risk of clots after a leg injury is as good as injections, and whether giving any medication is better than standard care (advice only) for people at low risk of clots. TiLLI is two linked studies designed to answer these aims.

Who can participate?
Patients aged 16 years or older, placed in temporary lower limb immobilisation (rigid cast or brace) as a result of an injury that occurred within the last 7 days.

What does the study involve?
Participants will be invited who have been placed in a plaster cast or splint after injury and are being assessed for clot risk. People who agree and are at high risk of clots will have either tablets or injections to reduce their risk; those at low risk will receive tablets, injections, or no medication. Patients and doctors will know what medication they are taking. All patients will be provided with written guidance on the signs and symptoms of blood clots and advice on managing their medication.

What are the possible benefits and risks of participating?
Benefits:
Not provided at time of registration
Risks:
TiLLI-Low: the standard of care for participants considered to be low risk for VTE receive no pharmacological prophylaxis. In TiLLI-Low, participants may be randomised to receive routine care (no prophylaxis), Direct Oral AntiCoagulant (DOAC), or Low Molecular Weight Heparin (LWMH). Administration of anticoagulants may induce a propensity for increased bleeding, which may lead to several complications, including: haematuria, melena or haematochezia, pronounced ecchymosis, prolonged episodes of epistaxis, gingival bleeding, haematemesis or haemoptysis, menorrhagia. Major bleeding events and clinically-relevant bleeding events will be monitored throughout the study.

Within the LMWH cohort requiring self-injection, risks such as cutaneous ecchymosis a or irritation at the injection site.

TiLLI-high: the standard of care for participants considered to be high risk for VTE is pharmacological prophylaxis in the form of LMWH. In TiLLI-high, participants will be randomised to receive either routine care (LMWH) or DOAC. Use of DOACs are contraindicated in pregnancy and breast feeding, as such we will exclude participants who are pregnant, actively seeking pregnancy, or breast feeding from the study.

Where is the study run from?
Queen Mary University of London (UK)

When is the study starting and how long is it expected to run for?
May 2024 to April 2028

Who is funding the study?
National Institute for Health and Care Research (NIHR) (UK).

Who is the main contact?
tilli-bjh@qmul.ac.uk
Dr Xavier Griffin, x.griffin@qmul.ac.uk

Contact information

Type(s)
Scientific

Contact name
Dr - TiLLI study team

Contact details
Queen Mary University of London, Mile End Road
London
United Kingdom
E1 4UJ
+44 20 7882 5555
tilli-bjh@qmul.ac.uk

Type(s)
Principal investigator

Contact name
Prof Xavier Griffin

Contact details
4 Newark Street
London
United Kingdom
E1 2AT
+44 7983829494
x.griffin@qmul.ac.uk

Type(s)
Principal investigator

Contact name
Prof Daniel Horner

Contact details
Northern Care Alliance NHS Foundation Trust, Salford Royal, Stott Lane
Salford
United Kingdom
M6 8HD
-
Daniel.horner@srft.nhs.uk

Additional identifiers

Clinical Trials Information System (CTIS)
Nil known

Integrated Research Application System (IRAS)
1009305

ClinicalTrials.gov (NCT)
NCT06370273

Protocol serial number
V1.0-26/04/24, IRAS 1009305, CPMS 62644

Study information

Scientific 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.

Acronym
TiLLI

Study objectives
Primary objective:
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.

Secondary objectives:
1. To compare all individual components of the primary composite outcome between treatment groups within 42 and 90 days from randomisation
2. 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
3. To report adherence to each therapy
4. To estimate and draw inferences on the acceptability of different prophylactic anticoagulants using the Anti Clot Treatment Scale (ACTS)
5. 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
6. To estimate and draw inferences on the difference in hospital readmission/reattendance and medication use (specific to VTE and bleeding) between treatment groups within the first 90 days
7. To estimate the health and social care resource use and costs and the relative cost effectiveness between arms
8. 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

Ethics approval required
Ethics approval required

Ethics approval(s)
approved 22/07/2024, North West – Liverpool Central Research Ethics Committee (2 Redman Place, Stratford, London, E20 1JQ, United Kingdom; +44 207 104 8340; liverpoolcentral.rec@hra.nhs.uk), ref: 24/NW/0166

Study design
Interventional randomized parallel-group controlled trial

Primary study design
Interventional

Study type(s)
Efficacy, Safety

Health condition(s) or problem(s) studied
Venous thromboembolism (VTE) in population with temporary lower limb immobilisation following injury

Interventions
TiLLI study consists of 2 linked randomised controlled trials: TiLLI-High and TiLLI-Low. Participants suitability for TiLLI-High and TiLLI-Low will be established during screening, participants will be randomised using Sealed Envelope. 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). Site teams are permitted to choose which IMP within the treatment group to use. Drug treatments will be provided for the duration of immobilisation or up to 42 days (whichever is earlier).

a) Parenteral drug treatment
• Enoxaparin 40mg once daily via subcutaneous injection
• Tinzaparin 4500 IU once daily via subcutaneous injection
• Dalteparin 5000 IU once daily via subcutaneous injection
• Fondaparinux 2.5mg once daily via subcutaneous injection
b) Oral drug treatment
• Rivaroxaban 10mg OD via oral ingestion
• Apixaban 2.5mg BD via oral ingestion
c) No drug prophylaxis (TiLLI-Low only)

Intervention Type
Drug

Phase
Phase III

Drug/device/biological/vaccine name(s)
Rivaroxaban, apixaban, enoxaparin sodium, tinzaparin sodium, dalteparin sodium, fondaparinux sodium

Primary outcome(s)
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’ of none of the events occurred).

Key secondary outcome(s))
1. 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
2. Patient satisfaction regarding the burdens and benefits of anticoagulation, using the validated Anti-Clot Treatment Scale (ACTS) for patients allocated to drug treatments, measured 42 days after randomisation

3. 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
4. Medication adherence: monitor participant adherence to allocated anti-coagulant verified through a digital response system, measured at 7 days, 14 days, 21 days, 28 days, 35 days, and 42 days after randomisation
5. Complications including clinically relevant non-major bleeding and surgical site bleeding, objectively defined by ISTH criteria, reported throughout up until 42 days after randomisation
6. Hospital readmission/reattendance using bespoke Case report forms and review of EHR, research staff to collect information on resources required to deliver subsequent care reviews (including scheduled clinic and unscheduled hospital attendance), and investigations within the first 90 days after randomisation
7. 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 within the first 90 days after randomisation
8. Patient longer-term outcome VTE and bleeding data, using an existing VTE model with risk-adjusted, population-specific effect estimates from this study, informed by directly measured events up to 90 days after randomisation

Completion date
30/04/2028

Eligibility

Key inclusion criteria
Current key inclusion criteria as of 10/11/2025:

1. Age >=16 years
2. Acute lower limb injury
3. Clinical decision to manage injury in temporary lower limb immobilisation (rigid cast or brace)

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Previous key 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

Participant type(s)
Patient

Healthy volunteers allowed
No

Age group
Adult

Lower age limit
16 years

Sex
All

Key exclusion criteria
Current key exclusion criteria as of 10/11/2025:

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/1.73m2), 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 >5 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 >5 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

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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

Date of first enrolment

01/10/2024

Date of final enrolment
31/01/2028

Locations

Countries of recruitment
United Kingdom

England

Scotland

Wales

Study participating centre
The Royal London Hospital
The Royal London Hospital
Alexandra House
London
United Kingdom
E1 1BB

Study participating centre
Newham University Hospital NHS Trust
Newham General Hospital
Glen Road
London
United Kingdom
E13 8SL

Study participating centre
Epsom Hospital
Epsom General Hospital
Dorking Road
Epsom
United Kingdom
KT18 7EG

Study participating centre
St Helier Hospital
Wrythe Lane

Carshalton
United Kingdom
SM5 1AA

Study participating centre
Hull Royal Infirmary
Anlaby Road
Hull
United Kingdom
HU3 2JZ

Study participating centre
Kings College Hospital
Mapother House
De Crespigny Park
Denmark Hill
London
United Kingdom
SE5 8AB

Study participating centre
Leeds General Infirmary
Great George Street
Leeds
United Kingdom
LS1 3EX

Study participating centre
Manchester Royal Infirmary
Cobbett House
Oxford Road
Manchester
United Kingdom
M13 9WL

Study participating centre
Aberdeen Royal Infirmary
Foresterhill Road
Aberdeen
United Kingdom
AB25 2ZN

Study participating centre
Royal Alexandra Hospital
Marine Drive
Rhyl
United Kingdom
LL18 3AS

Study participating centre
Queen Elizabeth University Hospital
1345 Govan Road
Glasgow
United Kingdom
G51 4TF

Study participating centre
Royal Infirmary of Edinburgh
51 Little France Crescent
Old Dalkeith Road
Edinburgh
Lothian
United Kingdom
EH16 4SA

Study participating centre
Southmead Hospital
Southmead Road
Westbury-on-trym
Bristol
United Kingdom
BS10 5NB

Study participating centre
Salford Care Organisation
Northern Care Alliance NHS Foundation Trust
Salford Royal
Stott Lane
Salford
United Kingdom
M6 8HD

Study participating centre
John Radcliffe Hospital
Headley Way
Headington
Oxford
United Kingdom
OX3 9DU

Study participating centre
Uclh
250 Euston Road
London
United Kingdom
NW1 2PQ

Study participating centre
Royal Oldham Hospital
Rochdale Road
Oldham
United Kingdom
OL1 2JH

Study participating centre
St James' S University Hospital
Beckett Street
Leeds
United Kingdom
LS9 7TF

Study participating centre
Milton Keynes University Hospital
Milton Keynes Hospital
Standing Way
Eaglestone
Milton Keynes
United Kingdom
MK6 5LD

Study participating centre

Derriford Hospital
Derriford Road
Derriford
Plymouth
United Kingdom
PL6 8DH

Study participating centre
Aintree University Hospital
Lower Lane
Liverpool
United Kingdom
L9 7AL

Study participating centre
Royal Liverpool University Hospital
Prescot Street
Liverpool
United Kingdom
L7 8XP

Study participating centre
South Tyneside District Hospital
Harton Lane
South Shields
United Kingdom
NE34 0PL

Study participating centre
Sunderland Royal Hospital
Kayll Road
Sunderland
United Kingdom
SR4 7TP

Study participating centre
Royal Derby Hospital
Uttoxeter Road
Derby
United Kingdom
DE22 3NE

Study participating centre
Burton Hospital
Queens Hospital
Belvedere Road
Burton-on-trent
United Kingdom
DE13 0RB

Sponsor information

Organisation
Queen Mary University of London

ROR
https://ror.org/026zzn846

Funder(s)

Funder type
Government

Funder Name
National Institute for Health and Care Research

Alternative Name(s)
National Institute for Health Research, NIHR Research, NIHRresearch, NIHR - National Institute for Health Research, NIHR (The National Institute for Health and Care Research), NIHR

Funding Body Type
Government organisation

Funding Body Subtype
National government

Location
United Kingdom

Results and Publications

Individual participant data (IPD) sharing plan

Data will be collected in the OpenClinica4 study database and extracted to the BCC Data Safe Haven (DSH). The BCC DSH is accessible upon request to individuals with a proven and approved requirement for access (i.e., study statistician, study health economist). Raw data will not be made publicly accessible. Study data will be pseudo-anonymised using unique participant ID's, it is prohibited to attempt to identify participants from the participant ID. Participant consent will be in place for collecting study data.

IPD sharing plan summary

Not expected to be made available

Study outputs

Output type	Details	Date created	Date added	Peer reviewed?	Patient-facing?
Study website	Study website	11/11/2025	11/11/2025	No	Yes