FULL TRIAL TITLE:

A randomised controlled trial of the effectiveness of intermittent surface neuromuscular stimulation using the geko™ device compared with intermittent pneumatic compression to prevent venous thromboembolism in immobile acute stroke patients

SHORT TRIAL TITLE:

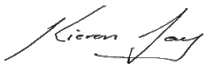
GEKO Venous Thromboembolism Prevention Study

PROTOCOL NUMBER:	FSK-VTE-001
PROTOCOL VERSION NUMBER AND DATE:	3.0, 14 NOVEMBER 2023
IRAS ID:	315387
ISRCTN NUMBER:	ISRCTN11175235
CLINICAL TRIALS.GOV REF:	NCT05476913
SPONSOR:	Firstkind Ltd
FUNDER:	NIHR i4i Programme Grant

PROTOCOL APPROVAL SIGNATURES

The undersigned confirm that this protocol has been reviewed and agree that it contains all relevant information to conduct the trial in compliance to the principles outlined in the Declaration of Helsinki, the Sponsor's SOPs, Good Clinical Practice (ISO 14155:2020) and other regulatory requirements as applicable.

For and on behalf of the Trial Sponsor:

Signature:  Date: 02-Feb-2024

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Name (please print): Kieron Day

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Position: Head of Clinical Affairs

.....

Chief Investigator:

Signature: 

Date: 02-Feb-2024

..../...../.....

Name: (please print): C. Roffe

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Position: Professor of Stroke Medicine

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INVESTIGATOR SIGNATURE PAGE

I have read the protocol specified above and agree to participate in and comply with the procedures, as outlined herein for the conduct of this clinical trial. I also agree to comply with the Investigational Research Ethics Committee (EC) requirements for testing on human patients. I agree to ensure that the requirements for obtaining informed consent are met.

Signature:
.....

Date:
...../...../.....

Name: (please print):
.....

Position:
.....

Site Name:
.....

Site Number:
.....

i. KEY TRIAL CONTACTS

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Patient and Public Involvement	Mr Brin Helliwell Birmingham Email: brin.helliwell@googlemail.com
Health Economics	Mr Andrew Thelwell Firstkind Ltd Email: andrew.thelwell@firstkindmedical.com
Committees	Trial Management Group / Data Monitoring Committee / Trial Steering Committee: Names and addresses of members are included in the trial master file

ii. TABLE OF CONTENTS

iii. LIST OF ABBREVIATIONS

ADE	Adverse Device Effect
AE	Adverse Event
CI	Chief Investigator
CIP	Clinical Investigation Plan
CMP	Clinical Monitoring Plan
Co-I	Co-Investigator
CRF	Case Report Form
CRO	Contract Research Organisation
CTPA	Computer Tomography Pulmonary Angiogram
CTU	Clinical Trials Unit
DD	Device Deficiency
DMC	Data Monitoring Committee
DVT	Deep Vein Thrombosis
EC	Ethics Committee
eCRFs	Electronic Case Report Forms
EDC	Electronic Data Capture
EQ-5D-5L	EuroQOL quality of life assessment tool
GCP	Good Clinical Practice
GMP	Good Manufacturing Practice
HR	Hazard Ratio
IB	Investigator Brochure
ICF	Informed Consent Form
ICH	International Conference on Harmonisation
IEC	Independent Ethics Committee
IFU	Instructions for Use
IMD	Investigational Medical Device
ISF	Investigator Site File
IPC	Intermittent Pneumatic Compression
ISRCTN	International Standard Randomised Controlled Trials Number
MA	Marketing Authorisation
mCIA	Model Clinical Investigation Agreement

MHRA	Medicines and Healthcare products Regulatory Agency
mRS	Modified Rankin Scale
NICE	National Institute for Health and Care Excellence
NIHSS	National Institutes for Health Stroke Scale
NHS R&D	National Health Service Research & Development
NMES	Neuromuscular Electrostimulation
NRS	Numerical Rating Scale
PCPIE	Patient, Carer, Public Involvement and Engagement
PE	Pulmonary Embolism
PI	Principal Investigator
PIC	Participant Identification Centre
PIS	Participant Information Sheet
QA	Quality Assurance
QC	Quality Control
RA	Regulatory Authority
RCT	Randomised Control Trial
REC	Research Ethics Committee
SADE	Serious Adverse Device Effect
SAE	Serious Adverse Event
SDV	Source Data Verification
SOP	Standard Operating Procedure
TMF	Trial Master File
TMG	Trial Management Group
TSC	Trial Steering Committee
VAS	Visual Analogue Scale
VTE	Venous Thromboembolism

iv. TRIAL SUMMARY

Trial Title	A randomised controlled trial of the effectiveness of intermittent surface neuromuscular stimulation using the geko™ device compared with intermittent pneumatic compression to prevent venous thromboembolism in immobile acute stroke patients	
Internal ref. no. (or short title)	GEKO Venous Thromboembolism Prevention Study	
Trial Design	Prospective, multicentre, randomised controlled trial	
Trial Participants	Age 18 years or older Clinical diagnosis of acute stroke (WHO criteria) Within 36 hours of symptom onset Not able to get up from a chair/out of bed and walk to the toilet without the help of another person	
Planned Sample Size	At least 1200	
Treatment duration	30 days or until the patient is independently mobile or discharged into the community, whichever is the earliest	
Follow up duration	3 months	
Planned Trial Period	01Dec 2022-30 Nov 2025	
Inclusion/Exclusion Criteria	Inclusion Criteria: 1. Age 18 years or older 2. Clinical diagnosis of acute stroke (WHO criteria) 3. Within 36 hours of symptom onset 4. Not able to get up from a chair/out of bed and walk to the toilet without the help of another person	Exclusion Criteria: 1. Inability to gain consent from the patient, or a declaration from a Personal Consultee or Nominated Consultee 2. Unwitnessed onset with a long lie on the floor before admission 3. Clinically apparent deep vein thrombosis at screening 4. Patient is expected to require palliative care within 14 days 5. Patient does not live in the local catchment area and is expected to be transferred to their local hospital for on-going care. 6. Patient has recently been involved in or is currently involved in a clinical trial for either a medical device or medicinal product, within the past 3 months, with the exception: if co-enrolment is not considered to impact adverse events or outcomes in the opinion of the Chief Investigator. (A live document containing a list of approved studies will be included in a reference document made available to all study sites and available upon request) 7. Contraindications for the use of the geko™ device: - Allergy to hydrogel constituents. 8. Contraindications to IPC: - Severe peripheral vascular disease - Large leg ulcers requiring extensive bandaging (small ulcers or skin breaks with flat coverings are not an exclusion) - Severe oedema.

		- Leg deformities making appropriate fitting impossible 9. Uncontrolled congestive cardiac failure 10. Pregnancy 11. Single or double leg amputations
Objectives		Outcome Measures
Primary	To determine whether the geko™ device is more effective at preventing venous thromboembolism within 30 days of randomisation than intermittent pneumatic compression in immobile patients with acute stroke.	Any symptomatic or asymptomatic deep vein thrombosis (DVT) in the calf, popliteal or femoral veins or any confirmed fatal or non-fatal pulmonary embolism (PE) within 30 days of randomisation
1.Secondary outcomes up to 30 days	To compare effectiveness and tolerability	a. Patient tolerance of the device at day 14 b. Adherence to allocated treatment to day 30 c. Death from any cause by day 30 d. Confirmed fatal or non-fatal PE to day 30 e. Any symptomatic or asymptomatic above knee DVT to day 30 f. Any symptomatic or asymptomatic DVT in popliteal or femoral veins and symptomatic calf vein DVT to day 30 g. Combined c-e
2. Secondary outcomes at 90 days	To compare survival, functional outcomes, and quality of life	a. Leg pain (NRS scale) b. Death from any cause c. Any symptomatic or asymptomatic DVT or PE occurring between randomisation and final follow-up d. Combined b and c e. Disability (modified Rankin Scale) f. Health related quality of life (EQ-5D-5L) g. Place of residence.
Exploratory and health economic outcomes	To compare exploratory and health economic outcomes	a. Early neurological recovery (difference in NIHSS between baseline and 7 days) b. Neurological recovery (difference in NIHSS between baseline and 14 days) c. Stroke recurrence up to 30 d d. Length of hospital stay at 90 days e. Home time at 90 d
Safety outcomes up to 30 days	To assess safety	a. Falls with significant injuries b. Fractures c. Skin breaks d. Adverse events (additional to those listed above)
Investigational Device	The geko™ neuromuscular electrostimulation device (Firstkind Ltd, High Wycombe, UK)	
Control	Intermittent pneumatic compression (IPC) using any NHS approved device	
Application of the device/control	geko™ therapy / IPC will be applied to both legs as soon as possible after randomisation and continued 24 hours a day until independent mobilisation/discharge into community or for a maximum of 30 days.	

v. FUNDING AND SUPPORT IN KIND

National Institute for Health Research i4i	Research grant
Firstkind Ltd, Hawk House, Peregrine Business Park, High Wycombe, HP13 7DL, UK.	Geko™ devices, device training, trial unit support, health economic assessment

vi. ROLE OF TRIAL SPONSOR AND FUNDER

The Sponsor assumes overall responsibility for the initiation and management of the trial and for adherence to ISO 14155 – good clinical practice for the design, conduct, recording and reporting of clinical investigations carried out on human subjects to assess the clinical performance or effectiveness and safety of medical devices.

The named Chief Investigator (CI) is the data custodian and takes primary responsibility for the conduct of the trial. The CI is responsible for the trial design, conduct, data analysis and interpretation, manuscript writing, and dissemination of results in consultation with the co-investigators. The CI controls the final decision regarding these aspects of the trial.

The trial is funded by NIHR i4i and an unrestricted grant from Firstkind Ltd. The funder has no input in the original design of the trial, data analysis and interpretation, or manuscript writing, and dissemination of results. However, they can refuse to support changes in the protocol that deviate from the originally funded project. They will review any outputs before dissemination.

An unmodified model clinical investigation agreement (mCIA) shall be used as clinical trial and financial agreement between the sponsor and each respective research site. The mCIA will cover all aspects of the trial and no other agreements shall be used between the sponsor and research sites.

vii. ROLES AND RESPONSIBILITIES OF TRIAL MANAGEMENT COMMITEES/GROUPS & INDIVIDUALS

vii.a. Trial Steering Committee

The independent Trial Steering Committee (TSC) will provide overall supervision of the trial on behalf of the sponsor and the funder and to ensure that the trial will be performed in accordance with the World Medical Association Declaration of Helsinki, ISO14155:2020 and all local legal and regulatory requirements. Its tasks are to approve the protocol and substantial changes, receive 12 monthly reports from the Data Monitoring Committee (DMC), provide advice and resolve problems brought to it by the Trial Management Group (TMG), and ensure publication of the results. It will report to the sponsor and the funder of the trial. It will include an independent chair, an independent statistician, an independent clinician, a patient and carer representative, the CI, and other members as determined by the chair. At least 75% of the members will be independent. It will meet before the start of the trial, and then annually until the end of the trial and publication of the key results. Minutes will be sent to TSC members, the CI, the sponsor, the funder, and filed in the trial master file.

vii.b. Data Monitoring Committee

An independent DMC will be appointed to assess the progress of the clinical trial, safety data, and the critical efficacy endpoints and to recommend whether to continue, modify or stop the trial. They will be provided with blinded, and on request, unblinded, safety reports prepared by an independent statistician every 12 months, or more frequently, if requested. A formal unblinded interim analysis of the data will not be conducted, unless requested. A DMC charter will be prepared with details of membership, terms and conditions, and trial stopping rules. The DMC will report to the independent chair of the trial steering committee, who will report to the sponsor and the funder. The DMC will include a clinician with expertise in stroke, a statistician and a member with expertise in multicentre clinical trials. The DMC will meet once a year or more frequently if required.

vii.c. Trial Management Group

The TMG is responsible for the day to day running of the trial, the overall design and conduct of the trial, analysis of the data, reporting and dissemination of results. It will report to the TSC and DMC. The TMG includes the CI, co-investigators, the clinical project manager, a patient representative, the trial statistician, a representative of the sponsor and other project staff. It will meet monthly, or more frequently if required.

viii. Investigator's Responsibilities

By agreeing to this protocol, the investigators and their institutions accept to allow monitoring, audits, Ethics Committee (EC) review, and regulatory inspections that are related to the investigation. They also agree to provide authorised individuals with direct access to source data and documentation as well as the right to copy records, provided such activities do not violate patient consent and patient data confidentiality.

A Principal Investigator should have experience in and/or will be responsible for:

- Providing signed Investigator / co-investigator(s) Agreement;
- Providing signed Financial Disclosure Form of Clinical Investigators;
- Providing appropriate Ethics Committee approved Informed Consent;
- Collection and archiving of data obtained at follow-up examinations and after the investigation has been completed;
- Strict adherence to the Clinical Investigational Plan (CIP) testing requirements to provide for optimal safety and efficacious use of the device under clinical investigation;
- Screening and selecting appropriate patients;
- Support the monitor, and auditor, if applicable, in their activities to verify compliance with the CIP, to perform source data verification and to correct the case report forms where inconsistencies or missing values are identified.

It is acceptable for the Principal Investigator to delegate one or more of the above functions to an associate or co-investigator, however, the Principal Investigator remains responsible for the proper conduct of the clinical investigation, complying with the investigational plan and collecting all required data. The investigation is not transferable to centres attended by the investigator unless prior approval is obtained from the sponsor.

In addition to the responsibilities of the investigators, the trial CI will:

- Sign off the final version of the trial protocol and after modifications to the protocol;
- Act as main contact for all trial investigators in case of medical questions related to the conduct of the trial.

ix. PROTOCOL CONTRIBUTORS

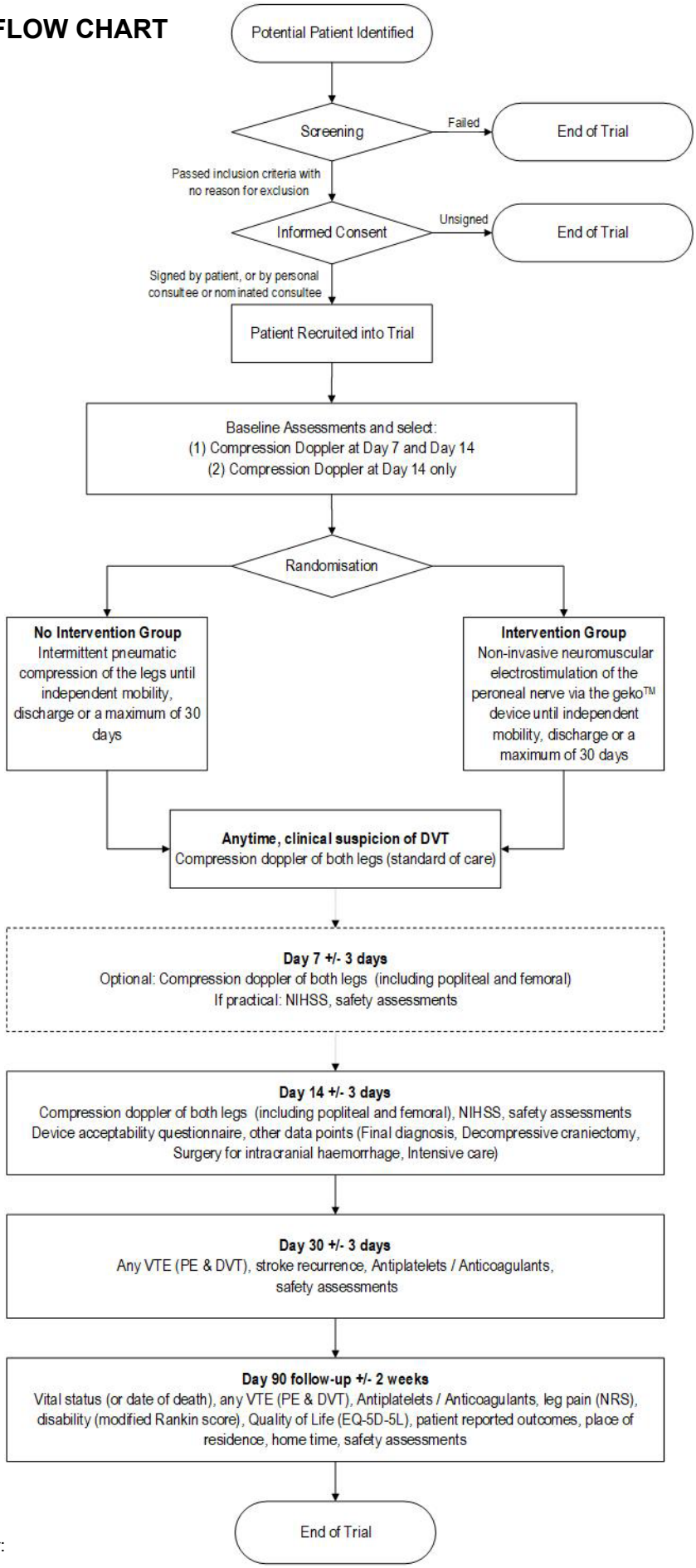
This protocol has been written by the CI and the co-investigators including a statistician, an expert in venous thromboembolism, a clinical trialist, a stroke physician, a specialist in electrical stimulation, and a patient and public representative. The protocol has also been discussed and reviewed with the Sponsor. All final decisions regarding the trial design, conduct, data analysis and interpretation, manuscript writing and dissemination of results are to be made by the CI in consultation with the co-investigators.

Patient representatives have been consulted in a focus group meeting about outcomes relevant to stroke survivors.

x. KEY WORDS

Stroke, cerebral infarct, intracerebral haemorrhage, venous thromboembolism, deep vein thrombosis, pulmonary embolism.

xi. TRIAL FLOW CHART



FULL TRIAL TITLE:

A randomised controlled trial of the effectiveness of intermittent surface neuromuscular stimulation using the geko™ device compared with intermittent pneumatic compression to prevent venous thromboembolism in immobile acute stroke patients

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GEKO Venous Thromboembolism Prevention Study

1 BACKGROUND

The Incidence and Effects of Venous Thromboembolism Globally

Venous thromboembolism (VTE) is a major health issue worldwide causing preventable death and long-term disability due to chronic leg swelling, pain, and skin changes (post-thrombotic syndrome). The Global Burden of Disease study reports an incidence rate of 115-269/100,000 and a mortality rate of 9.4-32.3/100,000 for venous thromboembolism, only slightly lower than the mortality rate for stroke, which was 42.3/100,000 in the same study.[1] The risk of VTE has been reported to be considerably higher in medical inpatients (5.5%), even with VTE prophylaxis (in 53%).[2] VTE is associated with a high incidence of long term disability and doubles the risk of permanent work-related disability.[3] This is mainly due to post-thrombotic syndrome, which has been reported to occur on 50% of cases.[4][5][6]

Venous Thromboembolism after Stroke

Stroke patients are at particular risk of VTE due to immobilisation and limb paralysis. VTE incidence varies between studies, depending on the population studied and the method of diagnosis.[7][8][9][10][11] In 2009, the Clots in Legs Or sTockings after Stroke (CLOTS) 1 trial reported an incidence of 10% for DVT diagnosed by Doppler, of which 7% were asymptomatic and 3% were symptomatic, and there was a 1% incidence of symptomatic PE[12]. The risk of VTE is highest in the first month after stroke (Hazard ratio (HR) 19.7) and declines to 10.6 between 30 and 90 days after the stroke, with roughly similar risks for DVT (HR 19.1) and pulmonary embolism (HR 20.2).[13] Prevention is therefore important. However, the options for VTE prevention are limited. The CLOTS-1 compared compressive stockings, commonly used on medical and surgical ward, found that the devices had no significant effect on VTE prevention in stroke patients. Prophylactic anticoagulation is almost universally used for VTE in medical inpatients but has no overall benefit in patients with stroke[14] and UK guidelines therefore stipulate that they should not be prescribed in this population.[15] CLOTS-3 compared IPC with no IPC and found a significant reduction in VTE and improved survival in patients with IPC.

Intermittent Pneumatic Compression

IPC is the application of controlled external pressure using compressed air and a pump, which cyclically inflates and deflates the chambers within a specially designed sleeve that envelops the leg. This cyclic inflation and deflation mimics calf muscle pump action and can promote venous return and decrease blood stasis thus potentially reducing the risk of venous thromboembolism (Fig. 1).

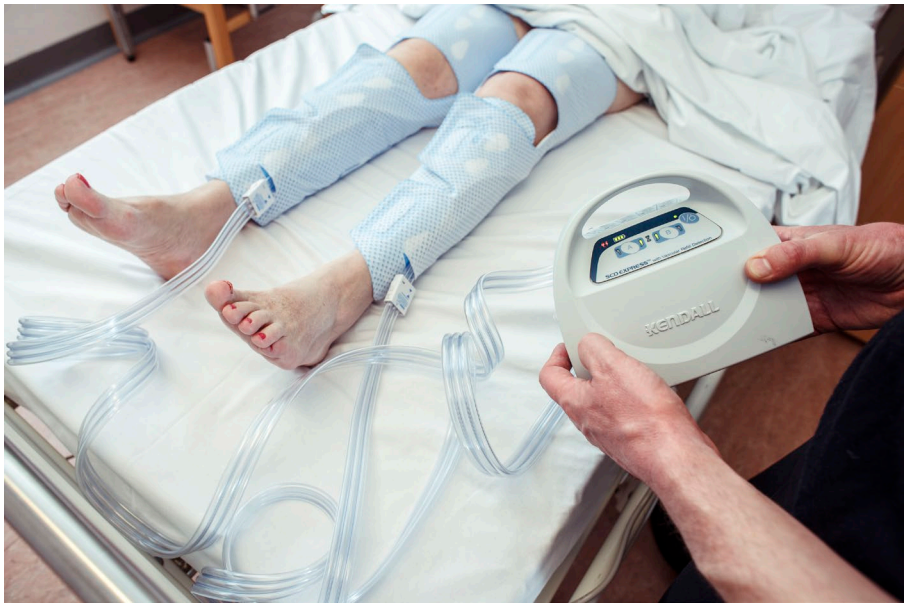

Figure 1 Intermittent Pneumatic Compression

IPC is now standard care in the UK, however, about 30% of patients have contraindications or are unable to tolerate IPC.[16] For this population there is currently no safe and evidence-based alternative.

Neuromuscular Electrostimulation for VTE Prevention

Neuromuscular electrical stimulation (NMES) has been explored as an alternative method of thrombo-prophylaxis. This technique uses electrodes attached to the skin to apply a current which stimulates the nerves or muscles underneath leading to muscle contraction. Contraction of the calf muscles in the lower limb stimulates blood flow in the underlying veins and decreases blood stasis thus potentially reducing the risk of VTE. The first reference to NMES being used for this purpose dates back to 1954,[17] with a steady level of clinical interest since the 1970s, and an increasing number of published studies in recent years. Early studies used direct stimulation of the calf muscles, and clinical use was limited by discomfort.

Geko™ Neuromuscular Electrostimulation Device

A different method of inducing calf muscle contraction via stimulation of the peroneal nerve was first described in 2010 by Tucker et al.[18] This has subsequently led to the development of the innovative geko™ neuromuscular electrostimulation device.

The geko™ device, manufactured by Firstkind Ltd (High Wycombe, United Kingdom), is a small, self-adhesive, disposable, battery powered, neuromuscular electrostimulation device designed to increase blood circulation and is indicated for the prevention and treatment of oedema, and the prevention of VTE.

See Figure 2 for an illustration of the device (front view)

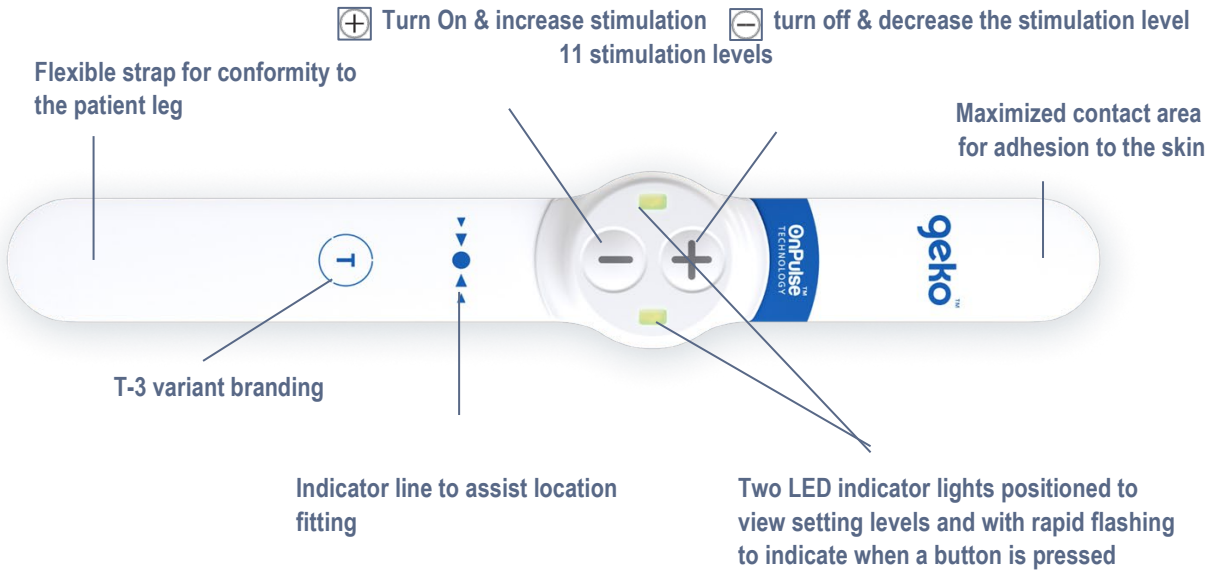

Figure 2. The geko™ T-3 device variant (front view)

The geko™ device utilises an electronically conductive skin adhesive solid hydrogel layer that adheres to the skin and when applied externally to the leg on the lateral/posterior aspect of the knee, the device will stimulate the common peroneal nerve prior to its deep-superficial branch bifurcation.

Figure 3 shows an illustration of the device (rear view) with electrodes.

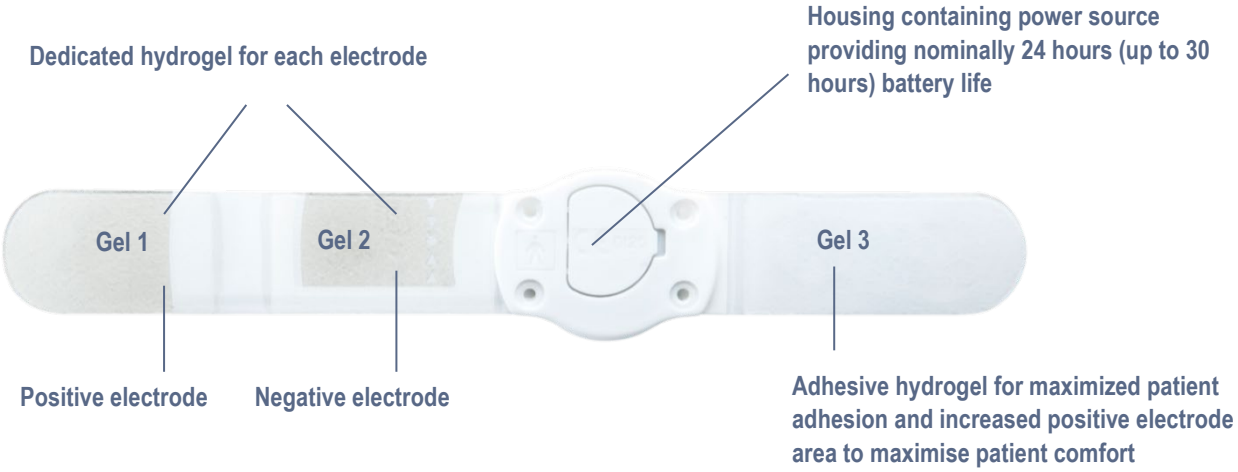

Figure 3. The geko™ T-3 device variant (rear view) with adhesive hydrogel layers and electrodes.

Subsequently, two separate and opposing complexes of muscles in the anterior and lateral muscle compartments of the lower limb will be stimulated by the device, eliciting a contraction of the lower leg muscles and activating the venous muscle pumps of the leg and foot, so increasing blood flow in the lower limb, which will boost venous return and increase blood circulation. Neither normal movement of the limb nor patient mobility are affected by the device.

Stimulation of the nerve requires less current and is considerably more comfortable than directly stimulating the muscle and achieves the same degree of muscle contraction, while utilising considerably less electrical power.

The geko™ device has up to eleven stimulation levels (pulse widths) to ensure optimal stimulation evidenced by dorsiflexion of the foot despite the individual variation in patient skin impedance. The optimal stimulation level, which may vary between patients, is achieved when a stimulus results in a visible dorsi-flexion of the foot. Dorsi-flexion may also be of benefit in counteracting the plantar-flexion associated with pyramidal lesions and may assist in the recovery of walking and improve quality of movement.

See Figure 4 for an illustration of the device fitted to the lower leg.

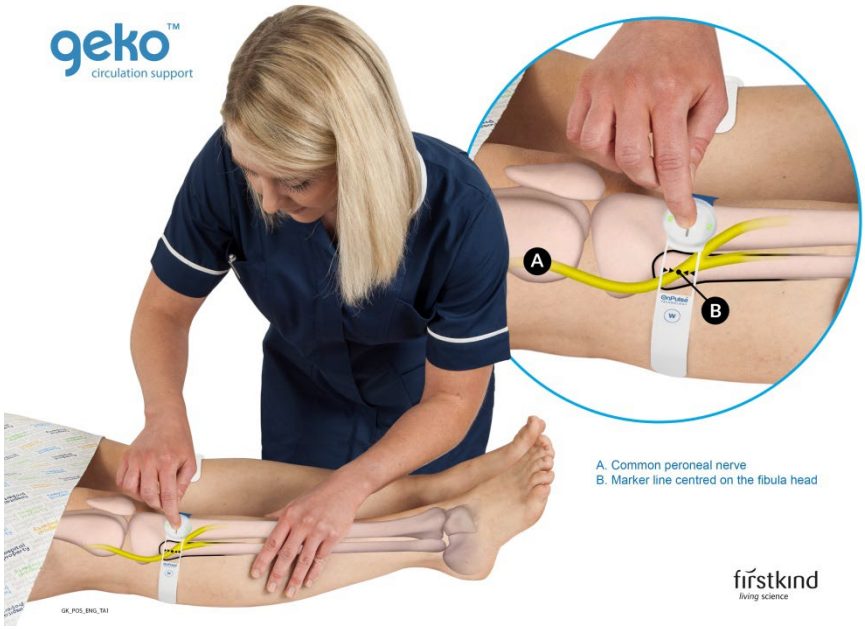

Figure 4. Administering non-invasive neuromuscular electrical stimulation via the geko™ device applied at the peroneal nerve.

The device is made from mylar (polyethylene terephthalate (PET)) and the electronic circuit is enclosed in a fully insulated polypropylene protective casing, so there is no risk of electric shock to the patient. The geko™ device also has charge-balanced waveforms that yield no build-up of charge in the patient, therefore, provided the device is used in accordance with the instructions for use, galvanic effects such as electrical burns cannot occur. The device is powered by battery and is thus totally isolated from the mains electricity supply. The primary lithium coin cell battery powering the device is removable for disposal in line with local regulations.

2 RATIONALE

VTE is a disabling and potentially fatal complication of stroke. VTE prevention is a major clinical priority throughout all specialties. The standard method of VTE prevention is prophylactic anticoagulation.[19] In stroke patient the risks of anticoagulation (bleeds) outweigh the benefits (VTE prevention), therefore this is not recommended in the UK. The use of elastic compression stockings is also not recommended.

Use of IPC is supported by grade 1 evidence and is recommended by NICE in stroke patients.[20]

NICE guideline's state that IPC can be considered for prevention in immobile patients who are admitted within three days of acute stroke. IPC should continue for 30 days or until the patient is mobile or discharged into the community, whichever is sooner. For the further 30% of patients who will have contraindications or are unable to tolerate IPC and who would otherwise receive no prophylaxis, NICE guidance[21] recommends the use of the geko™ NMES device as an alternative mechanical prophylaxis strategy for addressing circulatory stasis. Local audit data in 2000 immobile patients with acute stroke show that the device is safe and well tolerated. In contrast to IPC which tethers patients to the bed due to the pressure tubing, is hot in summer, and gets easily soiled in patients with diarrhoea, The geko™ device represents a more comfortable and less restrictive alternative.

Introduction of the geko™ device for patients not tolerating IPC led to a 46% reduction in symptomatic VTE compared to the time period before the device was used [Unpublished data].

We hypothesize that the geko™ device is more effective than (superior to) IPC at prevention of VTE in patients with acute stroke.

2.1 Risk description and minimisation

Risks
The risks involved with this investigation are similar to those associated with standard of care treatment for VTE prevention in immobile acute stroke patients. There should be no additional risks to the patients assigned to the investigation.

Benefits
Participation in this trial will not benefit participants directly but may benefit future patients being treated for VTE by adding to the treatment knowledge base.

3 OBJECTIVES AND OUTCOME MEASURES / ENDPOINTS

The aim of this trial is to compare the effectiveness of the geko™ device versus IPC on prevention of VTE in immobile patients after acute stroke.

3.1 Primary objective

To determine whether the geko™ device is more effective at preventing VTE (any symptomatic or asymptomatic DVT in the calf, popliteal or femoral veins or any pulmonary embolism (PE)) within 30 days of randomisation when compared to IPC (standard of care) in immobile patients with acute stroke.

3.2 Secondary objectives

- To compare effectiveness and tolerability
- To compare the survival, functional outcomes, and quality of life
- To compare exploratory and health economic outcomes
- To compare safety outcomes

3.3 Outcome measures / endpoints

These are listed below in detail and summarised in Table 1.

3.4 Primary endpoint / outcome

Deep vein thrombosis (DVT) is painful and can lead to fatal and disabling complications such as PE and post thrombotic syndrome with leg pains and ulcers. The primary outcome has been chosen to reflect the expected effect of the device and also relevance to the patient. The primary outcome will be:

- Any symptomatic or asymptomatic DVT in the calf, popliteal or femoral veins or any PE within 30 days of randomisation (yes or no).

Any time there is a clinical suspicion of DVT, for symptomatic below or above knee indications, compression Dopplers (Compression Duplex Ultrasound) will be conducted as per standard of care. In addition, at 7-days post-randomisation where practical and at 14-days post-randomisation (mandatory), above knee compression Dopplers will be conducted. Compression Doppler recording and imaging will be conducted following a Sponsor developed Work Instruction to ensure consistent application across study sites. Pulmonary embolism will be assessed by ventilation perfusion scan or by computer tomography pulmonary angiogram (CTPA), as indicated clinically. Other forms of imaging, diagnosis methods and post-mortem results will also be accepted to confirm a clinically indicated PE or DVT diagnosis.

The primary outcome analysis will be by logistic regression, adjusted for baseline covariates, and reported as risk estimates with 95% confidence intervals and p-values.

3.5 Secondary endpoints / outcomes

These will be assessed at 14 days, 30 days and at 90 days, when most of the patients are expected to have returned back to their primary residence. At Day-14, a questionnaire will assess the effectiveness and tolerability of the devices and the 90-day outcomes assess longer term effects on survival, functional recovery, and quality of life.

3.6 Exploratory endpoints/outcomes

These outcomes will be collected to ascertain differences in stroke severity and recovery. They are important in understanding potential differences in the primary outcome (stroke severity) and the effect on costs and the NHS (length of stay, home time i.e. when patient was discharged into the community).

3.7 Safety outcomes

These will include known adverse effects of both IPC and geko™ therapy (discomfort, skin irritation), potential adverse events (e.g. falls with significant injuries and fractures due to the effect of the devices on mobility) and other non-specified adverse events.

Table 1. Summary of Outcome Measures

Objectives	Outcome Measures	Timepoint(s) of evaluation of this outcome measure (if applicable)
Primary Objective		
To determine effectiveness for prevention of VTE	Any symptomatic or asymptomatic DVT in the calf, popliteal or femoral veins or any PE within 30 days of randomisation	Within 30 days of randomisation using leg Dopplers at 7 days where practical, and at 14 days (mandatory) for asymptomatic DVTs, plus imaging for PE when clinically indicated and leg Dopplers when clinically indicated
Secondary Objectives		
1. To compare effectiveness and tolerability	a. Patient tolerance of the device	At 14 days after randomisation
	b. Adherence to allocated treatment c. Death from any cause d. Confirmed fatal or non-fatal PE e. Any (symptomatic or asymptomatic) above knee DVT f. Any (symptomatic or asymptomatic) DVT in popliteal or femoral veins and symptomatic calf vein DVT g. Combined c-e	At 30 days after randomisation
2. To compare the effect on survival, functional outcomes, and quality of life	a. Leg pain via Numerical Rating Scale (NRS)[22] b. Death from any cause c. Any symptomatic or asymptomatic DVT or PE occurring between randomisation and final follow-up d. Combined b and c e. Disability (modified Rankin Scale)[23] f. Health related quality of life (EQ-5D-5L)[24] g. Place of residence after discharge	At 90 days after randomisation
3. To compare the effect of exploratory and health economic outcomes	a. Early neurological recovery[25] b. Neurological recovery. c. Stroke recurrence (new infarct or bleed on imaging or NIHSS increase of 8 points or more without confirmation by imaging) d. Length of hospital stay until discharge into the community e. Home time[26, 27, 28, 29]	At 7 (a), 14 (b) and 30 days (c) after randomisation and at 90 days after randomisation (d and e)
Safety Assessment		
4. To compare safety	a. Falls with significant injuries b. Fractures c. Skin breaks d. Adverse events (additional to those listed above)	Up to 30 days after randomisation or discharge, whichever comes earlier

4 TRIAL DESIGN

This is a prospective, multicentre, randomised controlled trial single blinded to the primary outcome, designed to determine whether the geko™ device is more effective at preventing VTE (any symptomatic or asymptomatic DVT in the calf, popliteal or femoral veins or any pulmonary embolism (PE)) within 30 days of randomisation when compared to standard of care (IPC) in immobile patients with acute stroke.

There are two arms in the trial consisting of:

Group	Description
No Intervention Group	IPC (standard of care)
Intervention Group	geko™ T-3 or variant (24 hours daily therapy).

The Day 7 compression Doppler is optional. The study sites can determine at baseline whether they consider it to be practical for the participants to proceed with this option. Please see Section 7.7 Trial Assessments for further details.

5 TRIAL SETTING

The trial will be run in the emergency departments and on the acute stroke unit of primary and comprehensive stroke centres on the UK.
Patient identification will follow the clinical pathway with patients arriving via the emergency department, where hyper acute stroke treatments such as thrombolysis, reversal of anticoagulation, and blood pressure management are initiated, and decisions about mechanical thrombectomy are made. After initial hyper acute stroke treatments are given, patients are admitted to the acute stroke unit, where they continue to be cared for until discharge or transfer to a rehabilitation unit. Patient enrolment will take place in the emergency department or on the acute stroke unit, after acute treatments have been given and while waiting for, or after, mechanical thrombectomy, if this is clinically indicated.
Participating sites will include the University Hospital of North Midlands NHS Trust and other acute stroke services listed in the IRAS form. Eligible sites will have to admit patients with acute stroke, have access to doctors and nurses with trial specific training, including training and experience in the use of IPC and geko™ devices in accordance with their respective instructions for use (IFU).

5.1 Trial Size and Duration

The estimated trial duration is from 1st Dec 2022 to 30th Nov 2025 (36 months) and the trial will recruit at least 1200 participants.

6 PARTICIPANT ELIGIBILITY CRITERIA

6.1 Inclusion criteria

1. Age 18 years or older
2. Clinical diagnosis of acute stroke (WHO criteria)
3. Within 36 hours of symptom onset
4. Not able to get up from a chair/out of bed and walk to the toilet without the help of another person

6.2 Exclusion criteria

1. Inability to gain consent from the patient, or a declaration from a Personal Consultee or Nominated Consultee
2. Unwitnessed onset with a long lie on the floor before admission
3. Clinically apparent deep vein thrombosis at screening
4. Patient is expected to require palliative care within 14 days
5. Patient does not live in the local catchment area and is expected to be transferred to their local hospital for on-going care.
6. Patient has recently been involved in or is currently involved in a clinical trial for either a medical device or medicinal product, within the past 3 months, with the exception: if co-enrolment is not considered to impact adverse events or outcomes in the opinion of the Chief Investigator. (A live document containing a list of approved studies will be included in a reference document made available to all study sites and available upon request).
7. Contraindications for the use of the geko™ device:[30]
   - Allergy to hydrogel constituents
8. Contraindications to IPC:[31]
   - Severe peripheral vascular disease
   - Large leg ulcers requiring extensive bandaging (small ulcers or skin breaks with flat coverings are not an exclusion)
   - Severe oedema
   - Leg deformities making appropriate fitting impossible
   - Uncontrolled congestive cardiac failure
9. Pregnancy
10. Single or double leg amputations.

Patients with pacemakers will not be excluded as there is no clinical rationale to suggest interference. The geko™ device, delivers a single pulse at a frequency of 1Hz with electrodes placed topically, close together, at the knee. The nature of the stimulation pulse, and its location make it extremely unlikely that the geko™ device could interfere with cardiac demand pacemakers.

7 TRIAL PROCEDURES

A schedule of procedures is included in Appendix 1

7.1 Recruitment

All patients due to be admitted to the acute stroke unit will be screened for inclusion. Anonymised information on participants who are not enrolled will include:

- age,
- gender,
- the reason not eligible for trial participation, or if they are eligible but declined

7.1.1 Participant identification

Target population
Adult patients admitted to hospital with an acute stroke will be recruited. There will be no upper age limit and no exclusion of patients on the grounds of frailty, dependency, sex, race, or religion.

Recruitment
As soon as possible after hospital arrival, the research team, or the emergency department will screen and approach the patient or their relative/friend. Hyperacute stroke treatments such as thrombolysis or thrombectomy

for ischemic strokes or blood pressure management patients with intracerebral haemorrhage will not be delayed for trial inclusion. For patients with wake-up stroke the time of onset will be defined by the time they wake up with symptoms.

The investigator or their nominee, e.g. from the research team or a member of the participant's usual care team, will inform the participant, their legal representative, or an independent physician will be informed of all aspects pertaining to participation in the trial. If needed, the usual hospital interpreter and translator services will be available to assist with discussion of the trial: the participant information sheets, and consent forms, will not be available printed in other languages.

It will be explained to the potential participant that entry into the trial is entirely voluntary and that their treatment and care will not be affected by their decision. It will also be explained that they can withdraw at any time. In the event of their withdrawal, it will be explained that their data collected so far cannot be erased and we will seek consent to use the data in the final analyses where appropriate.

7.1.2 Screening

Screening will be based on clinical history and exam of the patient. No blood tests, scans, or other investigations are required.

7.1.3 Payment

Travel expenses for follow-up visits will be reimbursed. No incentive payments will be made.

7.2 Consent

The process for obtaining participant informed consent or Consultee Declaration will be in accordance with the HRA REC guidance, ISO 14155 GCP and any other regulatory requirements that might be introduced. The investigator or their nominee and the participant or consultee shall sign and date the Consent Form or Declaration Form, or provide witnessed consent via the telephone, where in-person consent is not possible before the patient can participate in the trial. Consent will be sought by a member of the clinical research team trained in protocol procedures and included on the delegation log.

The decision regarding participation in the trial is entirely voluntary. Informed consent will be sought by a member of the clinical or research team trained in the trial protocol, after full and adequate oral and written information about the design and purpose of the trial, potential risks and benefits, and the right to refuse and to withdraw at any time without penalty or affecting the quality or quantity of their future medical care has been provided. No trial-specific interventions will be done before informed consent has been obtained.

Fully informed consent will be sought from patients, wherever possible. If the patient has capacity to consent but is unable to sign because of impairments, verbal consent, which is witnessed and signed by an independent observer, will be documented. Where the patient has capacity to consent but is only able to make a mark on the paper rather than sign as required, the same procedure will be followed. For participants who do not understand sufficient English to give fully informed consent, translation via a friend or family member or via the hospital translation services will be accepted. However, as we are recruiting patients with moderate to severe strokes to this trial, it is anticipated that many will be unable to give fully informed consent.

In cases where the patient does not have capacity to consent, advice will be sought from a relative, friend or professional, who is interested in that person's welfare, but is not doing so for remuneration or acting in a professional capacity (Personal Consultee). The Personal Consultee will be provided the information and asked

to sign a Declaration Form providing an opinion on the views and feelings of the potential participant. As the time frame for enrolment is short, and it is not always possible for the Personal Consultee to attend in person for the consent procedure, witnessed verbal declaration via the telephone will also be accepted. A telephone consent form is drafted for this purpose. This is particularly important if access to hospital is restricted due to Covid-19 or other emergencies. Full written declaration will be obtained from the Personal Consultee at the first available opportunity. In addition, in cases where the patient is not competent to consent themselves, there will be an option for an independent physician or medical professional (Nominated Consultee) to review the legal and medical appropriateness of enrolling the patient and consider the wishes of the patient. This option will be utilised where the Personal Consultee cannot be reached, and/or where the Personal Consultee is uncomfortable to make this decision. This option is important, as it puts less strain on potentially frail and distressed relatives and this option is supported by patient and carer views.[32] The Nominated Consultee would review the study information and consider whether it is legally and medically appropriate for the patient to participate in the study. They would then sign a Nominated Consultee Declaration Form.

In cases where a Personal Consultee could not be reached initially and the Nominated Consultee enrols the patient, further advice from the Personal Consultee will be sought. Once the Personal Consultee is reached, they should then be asked their opinion. They can decide to withdraw the patient, continue the patient in the study or they can defer to the Nominated Consultee's opinion if they are not comfortable to make the decision.

After signing the respective declaration forms, prior to completing enrolment into the study, the study staff will need to confirm that the patient did not previously opt-out from sharing their confidential information for research and planning purposes via the NHS National Data Opt-Out. If the patient had opted out, this decision will take precedence and the patient will not participate in the study. The Consultee (Personal Consultee and/or Nominated Consultee) will be informed accordingly.

Confirmation of consent will be sought in participants who were advised by a Personal Consultee or Nominated Consultee, but who regain capacity to consent prior to the end of the trial. Participants will be approached and informed on what has happened and asked if they are happy to continue in the trial. If the Participant regains capacity and is subsequently discharged, prior to the Local Research Team being made aware, all efforts will be made to obtain consent from the Participant at the next available opportunity. Should participants only be available to consent via telephone, witnessed verbal consent via the telephone will also be accepted.

If a participant loses capacity after giving consent, continuation in the study will need to be sought from a Personal Consultee or Nominated Consultee. The same process will be followed for obtaining Consultee signed declarations for enrolment: The Personal Consultee will be provided the information and asked to sign a Declaration Form if they consider the patient would wish to continue participation in the study. Due to the short time frame, and in case the Personal Consultee may not be in attendance when the patient loses capacity, witnessed verbal declaration via the telephone will also be accepted. Full written consent will be obtained from the Personal Consultee at the first available opportunity. In addition, if the Personal Consultee is not reachable or they are uncomfortable to make this decision, the decision can also be made by a Nominated Consultee (an independent physician or medical professional) to review the legal and medical appropriateness of continuing the patient in the study. In cases where a Personal Consultee could not be reached initially and the Nominated Consultee completes a declaration stating the patient can continue in the study, further advice from the Personal Consultee will be sought. Once the Personal Consultee is reached, they should then be asked their opinion. They can decide to withdraw the patient, continue the patient in the study or they can defer to the Nominated Consultee's opinion if they are not comfortable to make the decision. The NHS Opt-out is not applicable in this case, as the patient originally consented to participate in this research. If the patient regains capacity, they will be informed on the decision of the Personal Consultee or Nominated Consultee accordingly.

Informed consent or declaration will be obtained for each participant before they undergo any interventions related to the trial. The participant/Personal Consultee/Nominated Consultee will receive a copy of the signed and dated forms and the original will be retained in the Investigator Site File. A second copy will be filed or

scanned in the participant's medical notes and a signed and dated note made confirming informed consent was obtained for the trial.

Should there be any subsequent amendment to the final protocol or if new information becomes apparent, which might affect a participant's participation in the trial, continuing consent will be obtained using an amended Consent form which will be signed by the participant. If the participant does not have capacity, the Personal Consultee/Nominated Consultee will be informed and an amended Personal Consultee declaration form or amended Nominated Consultee declaration form, will be signed by the respective parties.

7.2.1 Point of enrolment

Patient consent will be the point of enrolment into the trial. Once enrolled, the patient will be assigned a trial ID code.

7.3 The randomisation scheme

Participants will be randomly assigned to treatment groups, with 1:1 ratio to receive either geko™ or IPC. The assignment will be determined by 1:1 randomisation, with three stratification variables (study site, NIHSS, stroke type) and random permuted blocks. Specifically, the allocation sequence will allow for up to 120 strata: 20 recruitment sites; three NIHSS categories (0-6, 7-15, >15), and two stroke types (ischemic, haemorrhagic). The allocation schedule for group assignment will be created by a qualified statistician from Keele University. This allocation schedule will then be uploaded into the trial specific electronic data capture (EDC) system Medrio, which will allow allocation to be administered centrally across the sites. This central remote randomisation service will be utilised to ensure allocation concealment from the recruiting study sites.

7.3.1 Method of implementing the randomisation/allocation sequence

Randomisation will be by a member of the research team and the allocated treatment will be prescribed immediately.
The CI, the local PI, and the lead research nurse will be informed by email of each randomisation.

7.4 Blinding

Participants and research staff involved in the collection of inpatient data, and the clinical teams will be aware of the treatment allocation, as the devices used for the intervention and control look, feel and sound very different.

The trial will be single blinded for the primary outcome assessment based on the compression Dopplers at Day-7 (optional) and Day-14 (mandatory). Devices will be taken off before participants have their compression Doppler procedure to blind the sonographer to the allocated treatment. Where possible single blinding will be maintained. However, for patients who have an emergency clinical investigation for DVT or PE, it may not be possible to blind the assessor (i.e. sonographer or radiographer) conducting the assessment due to the urgency of the procedure. Data on VTE will be taken by a blinded researcher using information available on hospital information systems.

The trial will be fully unblinded after the database lock, completion of the analysis plan and publication of the trial protocol.

7.5 Emergency unblinding

Not applicable, as the participant and their clinical teams will be aware of treatment allocation.

7.6 Baseline data

Baseline data will be collected before randomisation. Note, some baseline data may be taken from source data obtained during patient admittance, which may occur prior to obtaining participant consent/Consultee advice. A mismatch in dates for this reason, will not constitute a protocol deviation.
Baseline data to be collected include:

1. Date and time of symptom onset
2. Date and time of admission
3. Age
4. Sex
5. Previous DVT (number of times this occurred)
6. Previous PE (number times this occurred)
7. Known diabetes
8. Known myocardial infarction in the past
9. mRS pre-Stroke
10. EQ-5D pre-stroke
11. Place of residence
12. On antiplatelets (yes/no); if yes: aspirin, clopidogrel, dipyridamole, ticagrelor, other antiplatelet agent (specify)
13. On prophylactic dose anticoagulant (yes/no); if yes: unfractionated heparin, dalteparin, enoxaparin, other (specify)
14. On full dose anticoagulant (yes/no); if yes: warfarin, apixaban, edoxaban, rivaroxaban, dabigatran, other direct acting anticoagulant, dalteparin, enoxaparin, other low molecular weight heparin, unfractionated heparin
15. On diuretics (yes/no)
16. Covid-19 infection within the last 30 days (yes/no/unknown)
17. Covid-19 vaccination within the last 30 days (yes/no)
18. Blood pressure
19. Heart rate
20. Temperature
21. Oxygen saturation
22. Stroke pathology (cerebral infarct/ intracerebral haemorrhage)
23. National Institutes for Health Stroke Scale (NIHSS)
24. Leg swelling yes/no; if yes (one or both/ pitting or non-pitting)
25. Post-thrombotic syndrome (skin discoloration/sclerosis with change of leg shape/current or past leg ulceration)
26. Thrombolysed (yes/no)
27. Mechanical thrombectomy (yes/no)
28. Treatment with tranexamic acid for haemorrhages (yes/no)
29. Treatment with other haemostatic agents (yes/no); if yes: octaplex, FVII, platelets, vitamin K, other [specify]
30. Indicate option whether the participant will undertake the Day 7 compression Doppler if it is considered practical.

Note: if the participant is unable to answer the patient questions/questionnaires, this is not deemed as a protocol deviation.

7.7 Trial Assessments

Please refer to Appendix 1 for a schedule of procedures.

7.7.1 Day 7 (window of +/- 3 days) OR at discharge into the community if discharged before 7 days

If Investigators have decided the participant will not undergo their Day 7 compression Doppler, only clinical assessments will be completed. If the participant is discharged prior to their Day 7 follow-up, the clinical assessments will be conducted at discharge, if practical. If not practical, this will not constitute a protocol deviation - Note these clinical assessments will also be collected at Day 14.

For those patients where the Day 7 compression Doppler was chosen at baseline this becomes a required visit, inclusive of the clinical assessments. If the participant is discharged prior to their Day 7 follow-up, the compression Doppler will be conducted at their discharge, if practical. If not practical, patients who recover mobility and are discharged into the community prior to this follow-up visit will be asked to return for the above assessment within the outlined window. If this visit or any of the listed assessments are not completed, this will constitute a protocol deviation for missed data.

1. NIHSS
2. Adverse events (falls with significant injuries, fractures, skin breaks, other)
3. Optional: Compression Doppler of both legs (above knee) 30 or more minutes after removal of IPC/geko™

7.7.2 Day 14 (window of +/- 3 days)

This is a mandatory visit.

1. Compression Doppler of both legs (above knee) 30 or more minutes after removal of IPC/geko™
2. NIHSS
3. Adverse events (falls with significant injuries, fractures, skin breaks, other) since prior assessment
4. Device acceptability questionnaire (discomfort, sleep quality, no of times the device is checked and not in place/not working effectively, number of days the device was worn)
   Other data points:
5. Final diagnosis (cerebral infarct/ intracerebral haemorrhage/clinical diagnosis of stroke, no imaging done/ transient ischemic attack/not a stroke (give details of diagnosis)
6. Decompressive craniectomy (yes/no)
7. Surgery for intracranial haemorrhage (yes/no)
8. Intensive care (number of days, record “0” for no intensive care)

Note: if the participant is unable to answer the patient questions/questionnaires, this is not deemed as a protocol deviation.

Patients who recover mobility and are discharged into the community earlier than Day 14 will be asked to return for the above assessments at Day 14.

If a Day 7 compression Doppler is also to be conducted, please include a minimum of 7 days between any 2 compression Doppler assessments. For example, if a patient’s Day 7 compression Doppler cannot be scheduled until day 10 for any reason, and they are discharged into the community at Day 11, please bring them back on Day 17 for their second compression Doppler,

7.7.3 Day 30 (window of +/- 3 days)

1. DVT (list all with date of diagnosis, symptomatic or asymptomatic, leg affected (left, right, both), result (no DVT/ popliteal DVT/ below knee DVT) of any Leg Doppler done for clinical indications
2. Date and result of any VQ Scan/ CTPA/ other scan done for clinical reasons/ other mode of diagnosis (e.g. post-mortem), result (no PE, PE identified), participant was symptomatic/asymptomatic. If PE, please report as SAE.
3. Stroke recurrence (yes/no)
4. Covid-19 infection since admission (yes/no)
5. On antiplatelets yes/no if yes (aspirin, clopidogrel, dipyridamole, ticagrelor, other antiplatelet agent (specify)) during hospital stay yes/no if yes how many days
6. On prophylactic dose anticoagulant yes/no (unfractionated heparin, dalteparin, enoxaparin, other (specify)), during hospital stay yes/no, if yes how many days
7. On full dose anticoagulant yes/no (warfarin, apixaban, edoxaban, rivaroxaban, dabigatran, other direct acting anticoagulant, dalteparin, enoxaparin, other low molecular weight heparin, unfractionated heparin) during hospital stay yes/no if yes how many days.
8. On antiplatelets yes/no if yes (aspirin, clopidogrel, dipyridamole, ticagrelor, other antiplatelet agent (specify)) at hosptial discharge
9. On prophylactic dose anticoagulant yes/no (unfractionated heparin, dalteparin, enoxaparin, other (specify)) at hosptial discharge
10. On full dose anticoagulant yes/no (warfarin, apixaban, edoxaban, rivaroxaban, dabigatran, other direct acting anticoagulant, dalteparin, enoxaparin, other low molecular weight heparin, unfractionated heparin) at hosptial discharge
11. Adverse events (falls with significant injuries, fractures, skin breaks, other) since day 14 assessment.
12. Has the patient been transferred to another ward or hospital for ongoing care (yes/no). If yes, please specify date and type of facility (same hospital/another hospital) and type of care provided there (acute medical or surgical/ rehabilitation/ preparation of discharge/ palliative care/ other (specify)
13. Has the patient been discharged form hospital into the community (yes/no). If yes, give discharge date and destination (private residence/care home).

Data to be collected from the participant's medical notes and entered on the relevant eCRFs.

7.7.4 Day 90 (window of +/-2 weeks), Long-term follow-up assessments

Long-term assessment will be done by a member of the local site team at 90 days after randomisation. The assessment will be conducted via the phone, wherever possible, using the 90-day questionnaire worksheet. If the participant indicated a preference for alternative follow-up email/ text messaging/ in person visits/ mail, this will be used to complete the follow-up. Information on doctor/GP visits, hospital readmissions, potential DVT symptoms, known DVT/PE diagnoses, known antiplatelet and anticoagulation medication and place of abode will be collected from the participant. Information on length of hospital stay, antiplatelet treatment and anticoagulant treatment and if required, re-admissions and Home Time (days), can be collected from the participant's medical notes, their GP, and, where necessary from hospital episode statistics.

1. Vital status (or date and cause of death)
2. Antiplatelets (none, aspirin, clopidogrel, dipyridamole, ticagrelor, other antiplatelet agent)
3. Anticoagulants (none, warfarin, apixaban, edoxaban, rivaroxaban, dabigatran, other direct acting anticoagulant, dalteparin, enoxaparin, other low molecular weight heparin, unfractionated heparin)
4. DVT (list all with date of diagnosis, symptomatic or asymptomatic, leg affected (left, right, both)
5. PE (list all with date of diagnosis, mode of diagnosis (imaging modality, clinical, post-mortem), symptomatic or asymptomatic)
6. Leg pain (Numerical Rating Scale (NRS) for worst affected leg, one leg or both)
7. Disability (simplified modified Rankin Scale questionnaire[33])
8. Quality of life (EQ-5D-5L)
9. Leg vein-related quality of Life (VEINES-QOL and Symptom Score)[34], [35], [36]

10. Leg swelling none/same as before stroke/worse since stroke affecting one leg/both legs
11. Skin breaks on legs (no/one leg/ both legs)
12. Place of residence (private residence/care home/ still in hospital/)
13. Date of hospital discharge into the community
14. Readmissions (yes/no) if readmission give time and dates
15. Home time (days) (calculated value from discharge date, readmission, and time spent in a nursing or care home)
16. Adverse events (falls with significant injuries, fractures, skin breaks, other) via “any other health condition” question.

If it is not possible to contact the participant by phone or if the participant is unable to answer the questions / questionnaires for any reason, the alternative contact person/s provided by the participant, the GP, their carer or close relative/friend may be contacted to check the address/phone number and/or help complete the follow-up questions.

As much data is to be collected as possible. If certain data points cannot be found from any available sources, please close the data queries accordingly, this will not constitute a protocol deviation.
The sources used to collect this 90-day data will be indicated on the eCRFs.

7.8 Qualitative assessments

There will be no formal qualitative analysis. However, the device acceptability questionnaire at Day 14 will assess whether the participant finds the device acceptable or not, and if not, what aspects they disliked and or why they stopped using it. The reasons will be presented as lists and in narrative form.

7.9 Withdrawal criteria

7.9.1 Withdrawal

Participation in the trial is voluntary. Participants are free to withdraw from the trial at any time without giving a reason. However, participants will be asked whether withdrawal relates to the treatment alone, or follow-up, or to any trial-related procedure. The participant will be asked if they wish to withdraw from any or all of the following: use of the investigational medical device, follow-up with participant contact, or follow-up without participant contact. Unless the participant withdraws from follow-up, they will continue follow-up as per protocol. If the participant declines continued personal participation but allows data collection from other sources (such as the general practitioner and hospital databases) follow-up data will be collected via this route. In-person or witnessed verbal confirmation from the participant will be recorded on a specific form. If the participant is temporarily withdrawn from the trial intervention by a member of the clinical team, they may return to the trial treatment within the original timescale. Withdrawal, and the reasons for withdrawal, if given, will be documented on the relevant eCRF. Participants will be made aware that withdrawal will not affect their medical care and non-trial follow-up. Participants will be made aware (via the information sheet and consent form) that should they withdraw the data collected to date cannot be erased and may still be used in the final analysis.

The same withdrawal authorization can be given by the Personal Consultee or Nominated Consultees, in cases where the participant lacks capacity.

7.9.2 Trial treatment withdrawal due to adverse events

If a participant experiences an adverse event, the trial treatment may be withdrawn permanently or temporarily halted at the discretion of the Investigator. Should the participant not receive the complete trial intervention, they will remain in the trial and be followed up until the end of the trial, unless the participant or Investigator requests withdrawal from the study. If the participant has their trial treatment withdrawn, their study data will still be collected and still contribute to the primary endpoint, based on Intention to Treat as completeness of follow-up is essential.

7.9.3 Loss to follow-up

Every effort will be made to trace participants lost to follow-up. Hospital databases, records from the general practitioner and details of third persons given by the participant will be checked to determine whether the participant is alive, what his/her health status is, and whether there are any new contact details. Before a participant is identified as lost-to-follow up, the site should make all reasonable efforts to contact the participant. These attempts must be documented and should include at a minimum one phone call and one letter/email.

Participants will not be considered as lost to follow-up until the trial has closed. Continued attempts at finding contact details will be made. Participants who decline follow-up will not be recorded as lost to follow-up and entered as alive at the last point of contact.

7.9.4 Replacement

Enrolled participants who are not yet randomised can be replaced (though keeping their trial ID), but participants who withdraw after randomisation will not be replaced.

7.9.5 Premature Stopping of the trial

This may be necessary if the DMC identified a clear risk or overwhelming benefit associated with either treatment group which cannot be addressed by changes to the protocol.

Decisions relating to stopping the trial will be made by the TSC and the funder based on advice from the DMC. The sponsor will not have a role in stopping decisions.

7.10 End of trial

The end of the trial is when the last participant has completed the 90 day follow up.

8 TRIAL TREATMENTS

8.1 Intervention

The investigational medical device (IMD) is the geko™ T-3 device or variant. The geko™ device is CE marked (GB12/87339; SGS, United Kingdom Ltd) and has regulatory approval for use in a human patient population for multiple indications in numerous countries. The geko™ device is made from mylar (polyethylene terephthalate (PET)), it is enclosed in a polypropylene casing and a hydrogel layer will adhere the device to the skin.

The IMD will be applied bilaterally as soon as possible after randomisation and each geko™ device will be used to deliver one 24-hour dose. Devices will be worn continuously and changed every 24 hours. Treatment will be continued for 30 days or until discharge into the community, whichever comes earlier.
The IMD may be removed before the 30 days if:

- The patient becomes independently mobile
- The patient is discharged into the community
- The patient declines to have the device applied
- Adverse effects necessitate device removal

8.2 Control

Control treatment will be IPC using NHS approved devices as used for standard clinical care. They will be applied to both legs as soon as possible after randomisation. They will not be changed unless damaged or soiled. Treatment will be continued for 30 days or discharge into the community, whichever comes earlier. This is standard of care in the UK.

The IPC device may be removed before the 30 days if:

- The patient becomes independently mobile
- The patient is discharged into the community
- The patient declines to have the device applied
- Adverse effects necessitate device removal

Temporary removal of devices for procedures, investigations, and treatment

Both the geko™ device and the IPC device must be removed temporarily when the participant is having a shower or a bath, for magnetic resonance imaging (MRI), defibrillation and electroconvulsive treatment. The devices will also be removed 30 min before each leg Doppler exam. If the participant requires surgery temporary removal of the device is at the discretion of the surgeon and anaesthetist. If necessary, the IPC device can be removed for short periods (no longer than 30 minutes) to allow therapy and mobilisation.

8.3 Regulatory status of the device

The geko™ has a CE mark for use in European Economic area and is FDA approved. It will be supplied and used in its original packaging. The geko™ device will be used within its CE marked intended purpose. During the course of the trial the geko™ device will transition to UKCA Mark and will remain on label as per indications for use.

8.4 Storage and supply

The devices will be stored on the Stroke Unit at room temperature. The geko™ device will be supplied by Firstkind Ltd free of charge. The IPC devices will be taken from hospital stocks.
The use of the geko™ therapy and IPC is limited to 30 days. This is current standard of care in the UK. Continued use after the end of the trial intervention is at the discretion of the treating clinician. Both geko™ and IPC are approved for VTE prevention and available in the UK. No specific arrangement for access will be made by the sponsor.

Both medical devices are CE marked and should be used for their intended use. Device accountability will be performed for the geko™, as this is being supplied Free of Charge (FOC) solely for the use with participating patients.

8.4.1 Product Accountability

The Investigator or designee will verify the contents of each shipment against the shipping documents. Verification of the investigational device will be documented according to the Sponsor's requirements.

Accountability and Dispensing Logs will be provided to the site for use by the Investigator to maintain current and accurate inventory records (batch, expiry, and quantity) covering the receipt, dispensing and the destruction of the investigational product. The Lot number(s) information will also need to be recorded in the EDC using the relevant eCRF.

Device accountability will only be completed by trained study staff. Reconciliation will be by the number of devices remaining in the secured storage and the number of devices dispensed and if appropriate by comparing the lot number dispensed to that recorded in the eCRFs.

At the conclusion of the study the Investigator must agree to return or dispose of all investigational products as instructed by the Sponsor.

8.5 Treatment schedules

Devices will be fitted as soon as possible after randomisation and continued (with changes every 24 hours for the geko™ device) until discharge into the community or for 30 days, whatever comes earlier.

8.6 Treatment modifications

Devices will be worn 24 hours a day until discharge into the community or for a maximum of 30 days. The geko™ T3 device has 11 stimulation settings designed to enable activation of the venous muscle pumps of the calf and foot irrespective of individual patient's skin impedance and accommodating patient comfort. The optimal setting will vary between patients and is achieved when the setting selected is enough, to simultaneously activate the calf and foot muscle pumps thus initiating dorsiflexion i.e. an involuntary upward outward movement of the foot whilst remaining comfortable for the patient. The maximum stimulation setting resulting in dorsiflexion that can be comfortably tolerated by the patient should be selected.

Note:

- The T-3 device will run for 30 hours unless switched off, therefore, each device will deliver 24 hours continuous use.
- There are three possible fitting locations that will give successful activation of the peroneal nerve and initiate dorsiflexion. If fitting at the primary location on the fibular head does not initiate dorsiflexion, the alternative fitting locations should be tried (refer to Appendix 5)

The IPC sleeves come in different sizes, with the same pressure setting for all. No modifications are made.

8.7 Participants who are unresponsive or intolerant to geko™ device, or intolerant to IPC

For participants who physically seem unresponsive to geko™ i.e. show no involuntary rhythmic upward and outward movement of the foot (dorsiflexion) at the maximum tolerable device setting at any of the three device fitting locations, participants will remain in the geko™ arm of the study. The geko™ will be applied every day at the maximum tolerable device setting, until the patient regains mobility and / or is discharged into the community. Physical responsiveness to the geko™ device will be recorded on the relevant eCRF. The participant will remain in the trial and be followed up until the end of the trial and their study data will still be collected and still contribute to the primary endpoint, based on Intention to Treat, unless the participant, Personal Consultee, Nominated Consultee or Investigator requests withdrawal from the study. Any data already collected as part of this study will be retained.

If a participant is randomised to the geko™ arm, but is intolerant to the device after application, the participant will immediately be switched to following the national guidelines. The treatment will be offered to the participant again the next day, but they will not be forced or coerced into using the device if they refuse. The participant will remain in the trial and be followed up until the end of the trial and their study data will still be collected and still contribute to the primary endpoint, based on Intention to Treat, unless the participant, Personal Consultee, Nominated Consultee or Investigator requests withdrawal from the study. Any data already collected as part of this study will be retained.

For participants who are randomised to IPC, should the participant be found to be intolerant to IPC, they will also be switched to follow the national guidelines. The treatment will be offered to the participant again the next day, but they will not be forced or coerced into using the device if they refuse. They will remain in the trial and be followed up until the end of the trial and their study data will still be collected and still contribute to the primary endpoint, based on Intention to Treat, unless the participant, Personal Consultee, Nominated Consultee or Investigator requests withdrawal from the study. Any data already collected will be retained.

8.8 Known interaction with other therapies

The geko™ can produce artefactual readings (additional spikes) in the electrocardiogram (ECG). The device should be turned off during ECG recordings.
Both the geko™ device and the IPC device must be removed temporarily when the participant is having a shower or a bath, for magnetic resonance imaging (MRI), defibrillation and electroconvulsive treatment.

8.9 Concomitant medication

There are no restrictions in relation to concomitant medications or treatments. Elastic compression stockings are contraindicated in patients with acute stroke and should not be worn.

8.10 Trial restrictions

There are no specific dietary requirements or restrictions with the use of the devices.

8.11 Assessment of compliance with treatment

The investigational medical device and control device will be prescribed in the participants' drug chart and signed for on a daily basis. Reasons for non-compliance will be recorded on the drug chart and in the device acceptability questionnaire. All participants will be followed to 90 days, whether they are compliant with the treatment or not.

9 ADVERSE EVENTS, ADVERSE DEVICE EFFECTS (Definitions and Reporting)

The Investigator or duly trained designee(s) will be responsible for detecting, documenting and reporting all types of adverse events / adverse device events as defined in ISO 14155:2020 (Clinical investigation of medical devices for human subjects — Good clinical practice).

9.1 Definitions

9.1.1 Medical Device

Any instrument, apparatus, implement, machine, appliance, implant, software, material or other similar or related article intended by the manufacturer to be used, alone or in combination, for human beings for one or more of the specific purposes(s) of:

- Diagnosis, prevention, monitoring, treatments or alleviation of disease,
- Diagnosis, monitoring, treatment, alleviation of, or compensation for, an injury,
- Investigation, replacement, modification, or support of the anatomy or of a physiological process,
- Supporting or sustaining life,
- Control of conception,
- Disinfection of medical devices,
- Providing information by means of *in vitro* examination of specimens derived from the human body.

Which does not achieve its primary intended action in or on the human body by pharmacological, immunological or metabolic means, but which may be assisted in its intended function by such means.

9.1.2 Adverse Event (AE)

Any untoward medical occurrence, unintended disease or injury, or untoward clinical signs (including abnormal laboratory findings) in participants, users or other persons, whether or not related to the medical device.

This definition includes events related to the medical device or the comparator.
This definition includes events related to the procedures involved.

9.1.3 Serious Adverse Event (SAE)

An adverse event that led to:

- Death
- A serious deterioration in the health of the subject, users, or other persons as defined by one or more of the following:
  - A life-threatening illness or injury OR
  - A permanent impairment to a body structure or a body function including chronic diseases, OR
  - in-patient or prolonged hospitalization OR
  - A medical or surgical intervention to prevent life-threatening illness or injury or permanent impairment to a body structure or a body function OR
  - Foetal distress, foetal death, a congenital abnormality or birth defect including physical or mental impairment

A planned hospitalization for a pre-existing condition, or a procedure required by the protocol is not considered a serious adverse event.

9.1.4 Adverse Device Effect (ADE)

An adverse event related to the use of a medical device. This definition includes adverse events resulting from insufficient or inadequate instructions for use, deployment, implantation, installation, or operation, or any malfunction of the medical device

This definition includes any event resulting from a use error or from intentional misuse of the medical device.

9.1.5 Serious Adverse Device Effect (SADE)

Adverse device effect that has resulted in any of the consequences characteristic of a serious adverse event.

9.1.6 Unanticipated Serious Adverse Device Effect (USADE)

A serious adverse device effect which by its nature, incidence, severity or outcome has not been identified in the current version of the Instructions for Use (IFU).

9.1.7 Anticipated Serious Adverse Device Effect (ASADE)

A serious adverse device effect which by its nature, incidence, severity or outcome has been previously identified in the IFU.

Adverse event categories are summarised in the Table 2.

Table 2. Categories of Adverse Events

<table>
<tr><th>Adverse events</th><th>Non-device-related</th><th colspan="2">Device- or investigational procedure-related</th></tr>
<tr><td>Non-serious</td><td>Adverse event (AE)[a] (3.2)</td><td colspan="2">Adverse device effect (ADE)[c] (3.1)</td></tr>
<tr><td rowspan="3">Serious</td><td rowspan="3">Serious adverse event (SAE)[b] (3.45)</td><td colspan="2">Serious adverse device effect (SADE) (3.44)</td></tr>
<tr><td>Anticipated</td><td>Unanticipated</td></tr>
<tr><td>Anticipated serious adverse device effect (ASADE)[c] (3.1, Note 1 to entry)</td><td>Unanticipated serious adverse device effect (USADE) (3.51)</td></tr>
<tr><td colspan="4">[a] Includes all categories.
[b] Includes all categories that are serious.
[c] Includes all categories that are related to the device or the investigational procedure.</td></tr>
</table>

9.2 Recording and reporting adverse events, adverse device effects, serious adverse events and serious adverse device effects

Safety surveillance and reporting will be done for all participants enrolled in this trial.
Safety surveillance within this trial and the safety reporting both performed by the Investigator, starts as soon as the participant is enrolled in this trial (date of signature of the informed consent form). The safety surveillance and the safety reporting will continue until the last trial visit has been performed or the participant is deceased, or the participant concludes their participation into the trial.

- Serious Adverse Events and all Adverse Device Effects (serious or non-serious) are to be documented in the participant's medical records and electronic CRFs (eCRFs) and reported to the Sponsor a maximum 24 hours after becoming aware of the event.

- Non-serious adverse events are to be documented in in the participant's medical records and eCRFs and reported as soon as possible but not later than 72 hours after becoming aware.

Sponsor SAE Contact:
Kieron Day
Tel: +44 (0) 7921 106 253
e-mail: safety@firstkindmedical.com

All events will be reported along with the following information:

- The onset and end dates
- Whether the event is at the site of the investigational device
- Whether the event is related to the device or investigational procedure.
- The impact the event had on trial procedures will be assessed as either: none, trial treatment interrupted, trial treatment discontinued, or not applicable. The "not applicable" assessment will be used only when the participant is no longer in the treatment phase of the protocol.
- Whether treatment was given because of the event will be as either: none, medication administered, therapy administered, surgery, or other (with a specification).
- The outcome of the event will be assessed as either: resolved, resolved with sequelae, ongoing, or death. Only one AE per participant is allowed to have an outcome assessment as "death." If there are multiple causes of death for a given participant, only the primary cause of death will have an outcome of death.

Additional information may be requested by the Sponsor in order to support the reporting of AEs to regulatory authorities.
The Investigator must notify the EC / IRB, if appropriate, in accordance with national and local laws and regulations, of the AEs reported to the Sponsor

9.3 Device Deficiencies

A device deficiency (DD) is defined as an inadequacy of a medical device with respect to its identity, quality, durability, reliability, usability, safety or performance. Device deficiencies include malfunctions, use errors, and inadequacy in the information supplied by the manufacturer including labelling. This definition includes device deficiencies related to the investigational medical device or the comparator. Any device deficiency should be documented on the relevant eCRF in the EDC system and it should be determined whether the DD has resulted in a SADE and reported appropriately.

Once the investigator becomes aware of a DD, it must be reported to the sponsor within 72 hours, preferably via the trial specific EDC system. If it is not possible to report a DD via EDC, please use the contact information below.

Sponsor's DD Contact:

Wing To
Tel: +44 (0) 7827 612 109
E-mail: safety@firstkindmedical.com

9.4 Responsibilities

Trial Steering Committee (TSC):

In accordance with the Trial Terms of Reference for the TSC, periodically reviewing safety data and liaising with the DMC regarding safety issues.

Data Monitoring Committee (DMC):
In accordance with the Trial Terms of Reference for the DMC, periodically reviewing overall safety data to determine patterns and trends of events, or to identify safety issues, which would not be apparent on an individual case basis.

9.5 Notification of deaths

Notification of death should be documented in the appropriate eCRFs (AE and exit eCRFs) and include a detailed statement of the pertinent events and the eCRFs be signed by the investigator.

It is the investigator's responsibility to notify the relevant Ethics Committee as per the Ethics Committee policy. Details of death and the following information, should be provided if required in a letter to the sponsor summarising the patient's course since enrollment in the trial:

- Date and time of death.
- Place death occurred (e.g. hospital, nursing home, patient's home).
- If death was witnessed.
- Cause of death.
- Any other circumstances surrounding the death.
- Approximate time interval to death from the initiating event.
- Autopsy report (if performed).
- Whether it was device related.
- Whether it was related to the trial.
- Device configuration at the time of death.
- If available, also provide clinical notes and witness statements.

Should the participant have died during their treatment period, attempts should be made to retrieve the last used geko™ device and return to the sponsor for analysis, if practical.

It is the investigators responsibility to inform the sponsor within 24 hours of becoming aware of the death. The investigator must also inform the Ethics Committee according to their required timelines.

10 STATISTICS AND DATA ANALYSIS

10.1 Sample size calculation

The trial size is based on the hypothesis that the geko™ device is more effective than IPC at preventing VTE events. This is supported by the results of our local audit, where VTE halved after we introduced the geko™ device as an additional option for VTE prevention, and data from studies with healthy individuals, which show that the geko™ device is more effective at improving arterial and venous blood flow in the lower limbs [37].
The incidence of symptomatic or asymptomatic VTE in stroke patients treated with IPC is 17.2% at 30 days.[38] A 40% reduction of VTE can be demonstrated with 90% power and an alpha of 0.05, assuming a 5% loss to follow-up with a trial size of 1200 patients, 600 per arm.

10.2 Planned recruitment rate

It is initially planned for 10 or more centres to enrol at least 1200 participants. Based on an average of 3 patients with acute stroke admitted per day 5 days a week, enrolment of 6 (expected range 1-20) participants per month per centre is realistic and will complete enrolment within 24 months. More centres will be opened if enrolment falls below the monthly target.

10.3 Statistical analysis plan

The analysis and reporting of the trial will be in accordance with CONSORT guidelines.[39] A full Statistical Analysis Plan will be developed prior to completion of data collection and agreed with the DMC and TSC before database lock.

10.3.1 Summary of baseline data and flow of patients

Appropriate descriptive statistics (mean, standard deviation, median, lower and upper quartiles, minimum, maximum or frequencies and percentages) for the demographic and clinical outcome measures at baseline, will be used to assess balance between the randomised arms at baseline, but no formal statistical comparisons will be performed. Baseline characteristics will also be descriptively compared between those randomised and those analysed to see if the attrition has introduced any imbalances.
Flow of patients will be illustrated in a CONSORT flow diagram.

10.3.2 Primary outcome analysis

VTE will be recorded as yes/no for each patient at 30 days and will be compared between the two groups.
The primary analysis will be intention to treat (analysed according to randomised allocation, regardless of duration of interventional treatment). Note: patients who are intolerant to IPC or geko™ will follow National guidelines. The analysis will be by a logistic regression model, adjusted for treatment site, NIHSS category (NIHSS≤6,7-15,>15) and stroke type, and reported as risk estimates with 95% confidence intervals and p-values.

Sensitivity analyses will include a per protocol population (patients who have had at least 50% of the allocated treatment) and a dataset with imputed data for the primary outcome, where there is substantive and imbalanced missing data.

10.3.3 Secondary outcome analysis

Between-group comparison of secondary outcomes will be based on an appropriate regression model for the outcome (linear for continuous, generalised linear for categorical, and Cox proportional hazards for time-to-event), adjusted for treatment site, NIHSS category, stroke type and the corresponding baseline value as appropriate.

10.4 Sub-group analyses

Sub-group analyses will be specified in detail in the statistical analysis plan but will include stroke aetiology (infract/haemorrhage), stroke severity (NIHSS≤6,7-15,>15), concomitant treatments (thrombolysis/no thrombolysis, anticoagulation/no anticoagulation, thrombectomy/no thrombectomy), and infection with Covid-19 (yes/no).

10.5 Sensitivity analysis

As a sensitivity analysis, we will repeat the primary analysis by additionally adjusting for any variables with marked imbalance at baseline and for other post randomisation factors which are expected to affect outcome, e.g. thrombolysis (yes/no), mechanical thrombectomy, anticoagulation (none/ 7 days or less/ more than 7 days/ Covid-19 (yes/no).

10.6 Interim analysis and criteria for the premature termination of the trial

No interim analysis is planned. Criteria for stopping the trial will be laid out in the DMC charter.

10.7 Participant population

1. All-treated population: Any participant randomised into the trial where the treatment was applied for any period of time.
2. Protocol-compliant population: Any participant who was randomised and received at least 50% of the trial intervention.

10.8 Procedures to account for missing or spurious data

Missing data will be described, for example, by presenting the number and percentage of individuals in the missing category in total and split by study arm.

The Day 7 compression Doppler is optional, therefore missing data for this item will only be recorded as 'missing' if the investigator had opted into performing both Day 7 and Day 14 compression Dopplers.

The NIHSS at Day 7 will only be done if practical i.e. the participant is still in hospital at that time point.

All data collected on data collection forms will be used, since only essential data items will be collected. No data will be considered spurious in the analysis since all data will be checked and cleaned before analysis.

11 DATA MANAGEMENT

11.1 Data collection method

The Medrio Electronic Data Capture (EDC) system will be used for this trial. Instructions can be found below on how to access EDC and the eCRFs.

De-identified compression Doppler cine loops will be recorded following a Sponsor developed Work Instruction to ensure consistent application across the study sites. The Doppler cine loops will be labelled with only the participant's trial ID code and centre number.

11.2 Access to EDC and eCRFs

The EDC and eCRFs are accessed through the internet and requires the use of a personal username and password.

The following are required prior to receipt of a personal username and password:

- Current signed and dated CV
- Completed Signature and Delegation List Documented training
- Email address and telephone

A personal username and password will be provided via email. The first time EDC is accessed, the password will need to be changed. If the password is forgotten and/or lost, a new password will be provided via email by following the instructions on the webpage. Each centre must be authorised to start enrolling patients in the investigation before access privileges to EDC are made available.

Access privileges are based on the tasks assigned on the Signature and Delegation List and will be either:

- Data entry and review
- Data entry, review and sign off

11.3 Procedures for verification, validation and securing of electronic clinical data systems

The sponsor will manage and maintain the trial database throughout the investigation. At the conclusion of the investigation, the database will then be locked and data transferred for analysis. A final copy of the database will be retained by the sponsor. Where data is transferred electronically, this will be in accordance with the UK Data Protection Act 2018 as well as Trust Information Governance Policy. There will be a documented record of data transfer and measures in place for the recovery of original information after transfer. The database maintained by the sponsor, shall be validated and secured according to the sponsor's standard operating procedures. Access to the data shall be limited to sponsor representatives directly involved in the collection, analysis,

maintenance or safety monitoring of the data. Any trial data released shall be done according to the publication policy and in accordance with the UK Data Protection Act 2018.

De-identified Doppler cine loop images will be stored on an encrypted hard drive provided specifically for the purposes of this study which will be encrypted with 256-bit encryption and according to the hospital Trust's encryption policy. The hard drive will be retained on site. It will be the responsibility of the Research Nurse to provide the hard drive to the sonography department for use and then retrieve for storage and be provided upon audit or for backup. It will be the responsibility of the study site to keep the hard drive secured when not in use. The Doppler cine loops will then be transferred to a secure server hosted in the UK, by Firstkind Ltd. No identifiable data will be stored on the external hard drives: The Doppler cine loops will be labelled with only the participant's trial ID code and centre number.

11.4 Access to data

Direct access will be granted to authorised representatives from the sponsor, host institution and the regulatory authorities to permit trial-related monitoring, audits, analysis and inspections in line with participant consent. 5% of the Doppler cine loops will be analysed by an independent sonographer for quality control.

The sponsor will not have access to original data other than those relating to monitoring, adverse events or to data split by treatment group until the trial is complete, the database is locked, and the DMC and TSC have approved access. Unblinded data will be prepared for the DMC upon request by an independent statistician at Keele University. Results will be published, whatever the outcome. At the end of the trial, after database lock and publication of the primary outcomes, anonymized data will be shared with other research groups upon request to the CI for systematic reviews, meta-analyses and other appropriate and approved research studies.

11.5 Traceability of documents and recording of data

Source documents shall be created and maintained by the clinical site team throughout the trial.

The data reported on the eCRFs that is derived from these source documents must be consistent with the source documents, and any discrepancies shall be clarified following query in EDC. The CRFs shall be validated by the Principal Investigator or a delegated Investigator. In case of modifications after the validation, the eCRFs should be re-approved by the Investigator. Source documents include all original records from which the eCRFs derive their data e.g. participant's medical notes. Worksheets can also be used to aid Investigators in the capture of clinical trial data and ensure all protocol required data, which is not captured in medical records, is recorded to support data for the trial. These worksheets will not be a copy of the eCRFs but will contain entry blanks for trial required data not routinely collected by the Investigators.

The Investigator shall ensure accuracy, completeness, legibility and timeliness of the data reported to the sponsor on the eCRFs and in all required reports. Where copies of the original source document as well as print outs of original electronic source documents are retained, these shall be signed and dated by the appropriate clinical site personnel.

11.6 Review of data

The trial will be monitored by remote eCRF review.
The following activities will occur:

- All eCRFs will be reviewed for completeness and accuracy after completion in EDC by sponsor personnel.
- The Investigator (co-investigator) and / or delegate will be notified regarding any missing or unclear / inconsistent data
- Any discrepancies will be clarified in EDC

- All eCRFs must be completed in a timely manner and all data queries raised in EDC should be resolved within 10 working days.

11.7 Monitoring

On-site monitoring shall be performed during the trial to guarantee adherence to all applicable regulations, the protocol, and the signed Clinical Trial Agreement. By monitoring, the sponsor will also verify the accuracy of data collected on the accompanying eCRFs throughout the duration of the trial.

Monitoring is necessary to ensure adequate protection of the rights and safety of human participants involved in the clinical trial and the quality and integrity of the data obtained during the trial. The sponsor will at the same time assess the trial site and trial team on staffing and facilities to ensure the trial can continue in a safe and effective fashion.

During the monitoring visits, data reported on the eCRF shall be reviewed as specified in the monitoring plan.

11.7.1 Designated monitors

Only monitors qualified by education, training, and experience, which have been trained on the protocol, eCRF content, Monitoring Plan, relevant requirements, and informed consent process will be allowed to perform monitoring activities during this clinical trial. The monitor's qualifications and training will be documented by the sponsor.

11.7.2 Clinical monitoring plan

Prior to the start of the site monitoring activities for this clinical trial, a project specific Clinical Monitoring Plan (CMP) will be created and will be available upon request.
At a minimum, the Monitoring Plan will include the following:

- Required activities
- Frequency of monitoring visits
- Visit Requirements
- Procedures for securing site compliance
- Monitoring report content and timelines
- Close-out procedures

The Monitoring Plan may be updated as appropriate. All revisions will be tracked.

11.7.3 Regulatory Authority (RA) Inspections

The Investigator and / or delegate should contact the Sponsor immediately upon notification of an RA inspection at the site. A clinical monitor will assist the Investigator and / or delegate in preparing for the audit.

An Investigator who has authority to grant access shall permit authorized RA employees, at reasonable times and in reasonable manner, to enter and inspect any establishment where devices are held (including any establishment where devices are used or where records or results are kept).

An Investigator, or any person acting on behalf of such a person with respect to the trial, shall permit authorized RA employees, at reasonable times and in reasonable manner, to inspect and copy all records relating to the trial.

An Investigator shall permit authorized RA employees to inspect and copy records that identify participants, upon notice that RA has reason to suspect that adequate informed consent was not obtained, or that reports required to be submitted by the Investigator, to the sponsor or EC have not been submitted or are incomplete, inaccurate, false or misleading.

11.8 Trial termination

Suspension or premature termination of the trial
The sponsor reserves the right to stop the trial at any stage, with appropriate written notice to the Investigator.

Possible reasons for early termination of the trial by the Sponsor, either at local, national, or international level, may include, but are not limited to:

- The therapy fails to perform as intended
- Occurrence of USADE which cannot be prevented in future cases

- Sponsor's decision, e.g. based upon significant delays in enrolment
- Recommendation from Steering Committee and Sponsor
- Request from Regulatory bodies
- Request of EC

The trial will be terminated according to applicable regulations. The Investigator may also discontinue participation in the clinical trial with appropriate written notice to the Sponsor. Should either of these events occur, the Investigator shall return all documents to the Sponsor; provide a written statement as to why the premature termination has taken place and notify the EC and the RA (if applicable). Follow-up for all enrolled participants will be as per protocol requirements. Participants will be informed accordingly.

The site shall be closed appropriately by the Sponsor.

11.9 Trial conclusion

The trial will be concluded when:

- A Close-Out visit has been performed AND
- The Final report has been provided

12 ARCHIVING

All trial documentation will be archived in accordance with sponsor / funder SOPs.

The trial site will maintain all essential clinical trial documents for a minimum of 15 years (or longer if required by local legislation) after the termination of this trial.

At the completion of the trial, details of the archival process must be provided to the sponsor / funder. The trial site must contact the sponsor / funder prior to destroying or archiving off-site any records and reports pertaining to this trial to ensure that they no longer need to be retained on-site.

12.1 Trial Records

Trial records are subject to inspection by applicable health and regulatory agencies at any time.

Records to be retained by the trial site include, but are not restricted to:

- Source data and the primary records upon which they are based (e.g., participant's progress notes, adverse event data, test results, and any other diagnostic procedures required to evaluate the progress of the trial).
- Signed protocols and protocol amendments
- Product accountability records
- Trial personnel signature log
- Monitoring logs
- Correspondence to and from the Funder, designee and EC
- Principal Investigator and co-Investigator(s) Curricula Vitae (CVs)
- Signed ICFs
- Patient screening and randomisation log
- SAE reports
- EC approval letters and correspondence if applicable
- Completed QoL questionnaires
- Other documents pertaining to the conduct of the trial

These documents must be maintained and kept on file by the Trial site so that the conduct of the trial can be fully documented and monitored.

13 ETHICAL AND REGULATORY CONSIDERATIONS

This trial is to be conducted in accordance with the specifications of this protocol and in accordance with principles consistent with Declaration of Helsinki, ISO 14155:2020 and other currently applicable regulations.

No protocol changes will be implemented without the prior review and approval of the relevant EC except where it may be necessary to eliminate an immediate hazard to a research participant. Additionally, all devices used in this study are manufactured, handled and stored in accordance with applicable Good Manufacturing Practices (GMP) and the devices provided for this trial will be used only in accordance with this protocol.

13.1 Independent Ethics Committee (IEC)

This trial will need IEC review. The Principal Investigator will provide the IEC with all appropriate materials as required by their IEC, including but not limited to the clinical trial protocol, informed consent form, and any advertising materials. The trial will not be initiated until the IRB provides written approval of the aforementioned documents and until approval documents have been obtained by the Principal Investigator and Sponsor or Sponsor designee. The Investigator will not participate in the decision. If the Investigator is an IEC member, documentation must be provided indicating recusal from the approval process. Appropriate reports on the progress of this trial by the Principal Investigator will be made to the IEC as required by local and applicable government regulations and in agreement with policy established by the Sponsor. The Investigator is required to maintain an accurate and complete record of all written correspondence to and received from the IEC and must agree to share all such documents and reports with the Sponsor. No changes from the final approved protocol will be initiated without the IEC's prior written approval or favourable opinion of a written amendment, except when necessary to eliminate immediate hazards to the participants or when the change involves only logistics or administration.

13.2 Patient, Carer, Public Involvement and Engagement (PCPIE)

PCPIE representatives will be involved in the trial design, management of the research, interpretation and reporting of the results and in the dissemination of the findings.

13.3 Protocol compliance

Investigators are required to adhere to the CIP, signed Investigator's Agreement, applicable national or local laws and regulations, and any conditions required by the appropriate EC or applicable regulatory authorities.
If the Investigator deviates from the protocol requirements, the Sponsor will make the determination as to whether the participant will continue in the trial. The Sponsor also has the right to discontinue the participant for protocol deviations/violations. All protocol deviations must be documented in the eCRFs via the trial specific EDC system.

The investigator must notify the EC if appropriate, in accordance with national and/or local laws and regulations when a deviation occurs for patient's safety (e.g. eligibility) or privacy.

13.4 Data management, data protection / patient confidentiality

All data that is collected during the course of this trial will be kept strictly confidential according to the Data Protection Act 2018. Information on paper will be kept in locked filing cabinets and where possible behind locked doors. Electronic information will be kept on computers that are protected by passwords.

The electronic data in EDC will not contain patient identifiable information and any participant information that leaves the trial site will be pseudo-anonymised, anything that could identify a participant (name, date of birth, address, and hospital number) will be removed and the participant will only be identifiable by a trial ID code.

In order to help keep participant medical records and personal information confidential only certain authorised personnel will have access to these records. This will include staff in the hospital who are part of the trial, the sponsor and sponsor representatives that perform trial-related activities e.g. monitors.

The Sponsor and/or designated CRO will be responsible for the processing and quality control of the data. Data management will be carried out as described in the Sponsor's or CRO's standard operating procedures (SOPs) for clinical trials. The handling of data, including data quality control, will comply with applicable regulatory guidelines and the Sponsor's SOPs as well as provisions of a trial-specific Data Management Plan.

All public reporting of the results of the trial will eliminate identifiable references to the subjects.

Data protection contact information of the sponsor:

Dr Kieron Day
Head of Clinical Affairs
Firstkind Ltd
Hawk House
Peregrine Business Park
Gomm Road | High Wycombe
Bucks
HP13 7DL

13.5 Financial and other competing interests for the chief investigator, PIs at each site and committee members for the overall trial management

Investigators and co-investigators at each trial site will be required to sign a Financial Disclosure Form prior to the trial site being given permission to start recruitment. A new financial disclosure form will then be collected yearly during the trial.

13.6 Insurance

The sponsor of this trial has taken out insurance for all patients participating in this trial in accordance with the requirements of the local laws.

13.7 Amendments

A modification or alteration to this protocol may not be undertaken without first obtaining the concurrence of Sponsor. Both the Chief Investigator and the Sponsor representative must sign and date the amendment prior to implementation. In addition, the Chief Investigator must report all protocol amendments to, and receive all required approvals from, the Ethics Committee prior to implementation of any protocol amendment at the trial centre, with two exceptions:

- When necessary to eliminate apparent immediate hazard to the participant; or
- When the modification involves only logistics or administration.

If a protocol change is proposed for all participants, the following procedure for a protocol amendment will be followed. An amendment must be in writing, and it must be dated by both the Sponsor and the Investigator. If necessary, the Sponsor will submit protocol amendments to the appropriate regulatory authorities and notify other Investigators using this protocol.

An amendment may also require modification of the Informed Consent form, and other participant information, or other clinical trial documents. The Investigator will provide an approval letter for the amendment and revised informed consent form, if applicable, to the Sponsor.

Any protocol amendments will be listed in Appendix 2.

13.8 Post-trial care

Participants in the trial will have completed their medical device treatment for prevention of DVT before the end of the trial and will not require further treatment.

14 TRIAL REPORT and PUBLICATION POLICY

14.1 Publication policy

The trial protocol will be published and the data analysis plan approved by the DMC and TSC prior to database lock and analysis of the data. The primary outcome report shall be written by the chief investigator in consultation with the co-applicant collaborators and submitted for publication after approval by the DMC and TSC and notification of the funder.

The first publication will be a full publication of all data from all sites. Any publications of the results, either in part or in total (abstracts in journals or newspapers, oral presentations, etc.) by investigators or their representatives will require pre-submission review by the chief investigator and the funder.

The trial will be registered on www.clinicaltrials.gov and ISRCTN.

15 APPENDICIES

APPENDIX 1: Schedule of Procedures

Procedures	Screening	Baseline[#]	Day 7 (optional) * ± 3 days	Day 14* ± 3 days	Day 30 ± 3 days**	Day 90 ± 14 days
Informed consent / Declaration		x				
Medical history***	x	x				
Vital signs		x				
CT head (standard of care)		x				
Antiplatelet / anticoagulant medications		x			x	x
Eligibility assessment	x	x				
Baseline assessments		x				
Randomisation		x				
geko™ or IPC****		x	(x) If treatment still required	(x) If treatment still required	(x) Max 30-day treatment	
Compression Doppler of both legs*****			(x) Optional	X		
VTE Status		x	(x)	(x)	x	x
NIHSS		x	(x) If practical	x		
Adverse event assessment			(x) If practical	x	x	x
Device acceptability questionnaire				x		
Day 14 Data Collection				x		
Day 30 Data Collection					x	
Covid-19 status		x			x	
Final diagnosis				x		
90 d questionnaire (including DVT/PE)						x
Vital Status						x
Leg pain assessment						x
mRS		x				x
EQ-5D-5L and PROs		x[$]				x

[#]Some baseline data may be taken from source data obtained during patient admittance
*Or at hospital discharge into the community if earlier, but within the 3-day window
**Or at hospital discharge into the community if it occurs before follow up day
*** Data collected varies depending on visit
**** Depending on randomisation; applied until the patient is independently mobile, or a maximum of 30 days.
***** Also conducted within the treatment period (maximum 30 days) any time there is clinical indication of a VTE possible

$ if possible

Clinically indicated procedures as followed, when required:

- Compression Doppler of both legs
- CT scans (head)
- CTPA ***or*** Ventilation perfusion scan or other method for diagnosing PE

Note: if the participant is unable to answer the patient questions/questionnaires, this is not deemed as a protocol deviation.

APPENDIX 2: Amendment History

Amendment No.	Protocol version no.	Date issued	Author(s) of changes	Details of changes made
N/A	1.0	20 JAN 2023	WT	First version of protocol following Ethics review and required amendments. Additional typos and corrections throughout document.
1	2.0	13 MAR 2023	WT	Non-substantial: Section 3.4, Primary endpoint / outcome: included clarification that where we have referred to compression Dopplers in the text, we are referring to Compression Duplex Ultrasound procedure. Section 7.3, The randomisation scheme: amendment of randomisation method – change from minimisation to 1:1 randomisation with permuted blocks and stratification variables. Section 8.4, Storage and Supply: inclusion of Product Accountability section for geko device. 10.3.2, Primary outcome analysis; 10.3.3, Secondary outcome analysis; 10.4, Sub-group analyses; 10.5, Sensitivity analysis: Updated section to reflect updated analyses required due to change in randomisation method.
2	3.0	14 NOV 2023		Substantial Amendment designed to enhance trial recruitment through the reduction of site burden:- • Make Day 7 compression Doppler optional • Make Day 7 follow-up clinical assessments to be collected only if practical e.g. patient is still in hospital • Change timing for collecting: Device Acceptability Device questionnaire, Final diagnosis, Decompressive craniectomy, Surgery for intracranial haemorrhage, Intensive care. Amend from Day 30 to Day 14. • Only data collection to be conducted at Day 30. Removal of requirement to collect data at discharge. • Due to the above change in timing for data collection, the Trial Summary Table (page 11) and Table 1 (page 21) were updated • Additional baseline data points:

				-Treatment with tranexamic acid for haemorrhages (yes/no) -Treatment with other haemostatic agents (yes/no); if yes: octaplex, FVII, platelets, vitamin K, other (specify) -Indicate Option – whether the participant will undertake the Day 7 compression Doppler if considered practical • Additional 30-Day data points: -Patient transfer -Patient discharge • Amendment to Day 90 follow-up window • Removal of "Physical Examination" from Schedule of Procedures • Removal of 30 day/discharge NIHSS, and also remove from Schedule of Procedures • Clarification that protocol deviations do not apply if patient is unable to answer patient questions/ questionnaires • Removal on the requirement to collect Historical or ConMed data - we will only collect information on anticoagulation and antiplatelet medication at baseline, Day 30 and Day 90. Additional medication information at baseline will be related to tranexamic acid treatment and treatment with other haemostatic agents. • Updated Trial Flow Chart and Appendix 1: Schedule of Procedures to reflect the noted changes to the study data that will be collected Additional corrections and further clarifications:- • Noted that some information collected at baseline may be taken from source data obtained prior to patient consent/Consultee advice e.g. during patient admittance. • Further clarification regarding how to consent patients who regain capacity but are discharged out of hospital, using witnessed verbal consent over the phone. • Correction that Personal / Nominated Consultees will be providing advice not consent • Update Schedule of Procedures table to include Day 30 follow-up data collection questions. • Rename “30 day/discharge” visit to “Day 30” visit. • Amend protocol text on page 29: 90-DAY follow up will be completed by the

				site not by the TMG. Change text from 'trial management team,' to 'local site management team'. • Minor corrections, clarifications and formatting throughout text

APPENDIX 3: geko™ - Instructions for Use

Sent Under Separate Cover

APPENDIX 4: Intermittent pneumatic compression (IPC) – Instructions for Use

Example Sent Under Separate Cover

For alternative manufacturers, please refer to manufacturer's website.

APPENDIX 5: geko™ Fitting Positions

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APPENDIX 6: Device Acceptability Questionnaire

APPENDIX 7: 90 d questionnaire worksheet

16 REFERENCE LIST

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