The CLOTS Collaboration

CLOTS

Clots in **L**egs **O**r s**T**ockings after **S**troke

A Randomised Trial to
Establish the Effectiveness of Graduated
Compression Stockings to Prevent Post Stroke
Deep Vein Thrombosis (DVT).

Protocol

Version 1.1 26th June 2006 (incorporating revised appendices)
(Replaces Version 1.0 12th November 2003)

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The Importance of Post Stroke DVT

Several studies reported over the last 30 years have shown that deep venous thrombosis (DVT) is common in patients with a recent stroke. Patients with significant weakness of the leg and who are immobile appear to be at greatest risk. Studies, which used radio-labelled fibrinogen to identify all thromboses, even those, which were not clinically obvious, showed that about 50% of hemiplegic patients had DVT (Cope et al 1973, Warlow et al 1976). More recent studies with magnetic resonance imaging demonstrated DVT in 42% of stroke patients within the first three weeks, and above knee DVT in 17% (Kelly J & Rudd A –personal communication) Studies using less sensitive screening techniques, such as Doppler ultrasound, suggest a lower frequency of perhaps 10% although the types of patients included and the duration and timing of follow up influences the estimates (Oczkowski 1992). Clinically apparent DVT confirmed on investigation is even less common but DVTs may not be recognised and may still cause important complications. Pulmonary embolism (PE) is an important cause of preventable death after stroke (Bounds et al 1981). Clinically evident PE has been variably estimated to affect one to 16% of patients in prospective trials (Gubitz et al 2000, McCarthy and Turner 1986) and three to 30% in observational studies (Davenport et al 1996). Fifty percent of patients who die following an acute stroke showed evidence of PE on autopsy (Warlow et al 1976) but it is difficult to judge how often these PEs significantly contributed to the patients' death. However, since some of these studies were published, management has changed considerably to include earlier mobilisation, more aggressive hydration and routine use of antithrombotic drugs in patients with ischaemic stroke which may have reduced the frequency of thrombosis.

Antithrombotic Drugs to Prevent Post Stroke DVT

Both low and medium dose subcutaneous heparin reduce the risk of DVT, and probably PE, in patients with acute ischaemic stroke (Gubitz et al 2000). However, evidence from the International Stroke Trial (IST 1997) shows that even low dose heparin (5,000 unit twice daily) is associated with a significant excess of symptomatic intracranial and extracranial bleeds which offset any other advantages heparin may have on recurrent ischaemic stroke and fatal PE. Trials have demonstrated that aspirin is probably effective in preventing DVT and PE after surgery (The Antiplatelet Trialists' Collaboration 1994, Pulmonary Embolus Prevention Trial 1999). The results of the IST and the Chinese Acute Stroke Trial (CAST) suggest that aspirin should be started in all patients with a proven ischaemic stroke as soon as possible since it is associated with a reduced risk of death and recurrence within the first month (Gubitz et al 2000). Therefore all patients with stroke, except those with haemorrhagic stroke or with other contraindications to aspirin, should be treated with aspirin. This might also be expected to reduce the frequency of DVT and PE. Indeed in the IST, although DVT was not an endpoint, aspirin was associated with a reduction in risk of PE in the first two weeks from 0.8% to 0.6% (2p = 0.08, odds reduction 26% (95% CI 48% reduction to 4% increase) IST 1997).

The Role of Graduated Compression Stockings

Rationale

GCS are thought to reduce the risk of DVT by:

- Compressing the leg and thus reducing the cross sectional area of the veins which in turn reduces stasis by increasing the blood flow velocity.
- Increasing flow by providing greater compression around the ankle than more proximally.
- Augmenting the effect of the calf muscle pump.
- Improving the function of venous valves and reduction of venous pooling.
- Altering levels of clotting factors.

Evidence for their effectiveness

At least three systematic reviews of randomised trials evaluating GCS have concluded that graduated compression stockings are effective in peri-operative patients (Wells et al 1994, Agu et al 1999, Roderick personal communication). In 1994, a systematic review of GCS was published (11 trials, n=1752) which demonstrated that their use is associated with a 68% (95% CI 53 - 73%) reduction in the risk of DVT after surgery. A more recent systematic review showed a 62% (95% CI 52 - 70%) reduction in the risk of DVT in 2582 patients randomised in 18 trials (Roderick personal communication). The latter review also

demonstrated a 53% (95% CI 3 – 83%) reduction in PE amongst 1466 patients entered into 12 trials. Only one of the trials included in the more recent review randomised high-risk medical (rather than surgical) patients (Kierkegaard & Norgren 1993). This contributed only 6 DVTs, which occurred in 80 patients with acute myocardial infarction.

There is only one published RCT which has evaluated GCS in stroke patients (Muir et al. 2000). This trial randomly allocated 98 patients with an acute stroke to one of three treatment groups: routine care; routine care plus Kendall TED stockings; routine care plus Brevett TX stockings. At randomisation 9/97 (9%) already had detectable popliteal thrombus on Doppler ultrasound and five additional patients had detectable DVT by Day 5 to 9. Thus 14/97 (14%) of patients had DVTs within 10 days of stroke. Of the five DVTs, which occurred after randomisation, four occurred in the non stocking group. Fifteen of 65 patients allocated full length stockings and 10 of 32 allocated to avoid stockings either died or had Doppler ultrasound detected DVTs (OR 0.66; 95% CI 0.26 - 1.70). This small single centre trial was unable to demonstrate that differences between treatment groups were statistically significant.

Therefore, almost all of the randomised evidence to support the use of GCS comes from peri-operative patients. It does not seem reasonable to extrapolate the results of the systematic review in surgical patients to those with stroke. In surgery, stockings are applied before the operation, which represents a brief insult to the veins in the legs. Paralysis only occurs during the surgery itself and immobilisation is usually only for a few days. In stroke, stockings are applied after the onset of paralysis and the patients are often immobile for weeks. They may have prolonged paralysis of the affected leg. Paralysis may reduce the effectiveness of stockings in augmenting flow. Moreover, many stroke patients develop DVT and PEs several weeks after the ictus (Cope et al 1973, Oczkowski et al 1992).

The Problems Associated With GCS In Stroke Patients

The risks of GCS are small. However, in patients with severe peripheral vascular disease and/or peripheral neuropathy, their use can cause skin necrosis and occasionally this has necessitated amputation (Kay and Martin 1986, Merrett & Hanel 1993, Warlow et al 1996). Patients with stroke are more likely than surgical patients to have diabetes and peripheral vascular disease. Perhaps more significant than this small risk is the much more common experience of patients and nursing staff that GCS, especially the full length variety, are uncomfortable and may be difficult to apply in patients with limb weakness. In addition, many stroke patients are incontinent of urine and /or faeces, which can lead to soiling of the stockings, greater discomfort and more problems with the underlying skin. If stockings are ineffective the nursing staff's time applying and monitoring them might be put to better effect.

In the UK graduated compression stockings vary in cost, from £4 to £7 for one pair of full length stockings. In some other countries the cost of stockings are much higher. A patient might need two pairs per month allowing for regular washing. In addition there are staff costs relating to training in their use and, the regular application and removal of stockings in immobile patients. Therefore, given the frequency of stroke the financial implications of routine use of GCS are important.

Variation in use

In a recent survey (Ebrahim and Redfern 1999) (with a response rate of 86.8%) of over 1,716 physicians in the UK who routinely care for stroke patients, 46% thought stockings were useful for prevention of post stroke DVT, 26% thought they were of no use and 28% were uncertain of their value. If these views are translated into everyday practice it is clear that there is considerable variation in how patients are treated. This variation must be unacceptable if stockings are effective (since perhaps as many as 50% of patients are currently denied them) or ineffective (since this represents a huge waste of resources). It is clear therefore that we need to perform a large randomised trial to establish the effectiveness (or not) of GCS in prevention of DVT and PE after stroke.

Full Length or Below Knee Stockings?

Graduated compression stockings may be full length, extending up to the mid thigh, or below knee. Most clinically important DVTs occur above the knee which provides a rationale for using full length stockings. However, below knee stockings are cheaper, easier to apply and more comfortable for patients. However, a

recent study in stroke patients indicated that patients tolerated full length stockings well (Scholten et al 2000). There are concerns that full length stockings often ruck around the knee and can produce a tourniquet effect which might restrict flow, reverse the effect of graduated compression and increase the risk of ischaemia or DVT (Williams et al 1996). There is evidence that the velocity of flow in the deep veins is similar in patients wearing below knee and full length stockings although it is unclear to what extent the maintenance of flow is responsible for any effect on prevention of DVT (Lawrence and Kakkar 1980). This indirect evidence might suggest that short stockings are likely to be at least as effective and more acceptable to staff and patients than the full length variety.

In the systematic review of RCTs (Roderick et al – personal communication) in 11 of the trials (n=1689), the investigators specified that the stockings were full length and demonstrated a 67% (95% CI 55 - 76%) reduction in DVT. In five (n=769) the investigators did not specify the length and showed a 68% (95% CI 50 - 79%) reduction. Only two trials (n=224) specifically evaluated below knee stockings and demonstrated only a 13% (95% CI 51 - 56%) reduction in DVT. Two RCTs in patients undergoing abdominal surgery compared the occurrence of DVT detected using radio-labelled fibrinogen allocated full length and short stockings (Williams and Palfrey 1988, Porteous et al 1989). In one trial, 8 (18.2%) of 44 patients fitted with short stockings and 6 (13.6%) with full length ones developed a DVT (OR 1.4; 95% CI 0.4 - 4.5) (Williams & Palfrey 1988). In the other, one DVT (clinically apparent) occurred amongst 58 patients allocated short stockings and three (only one clinically apparent) of 56 patients allocated full length stockings developed a DVT (OR 0.31; 95% CI 0.03 - 3.1). These trials, even when combined, were too small to provide reliable evidence regarding their relative effectiveness (OR 0.98; 95% CI 0.4 - 2.6).

There is wide variation in the length of stockings used which partly reflects the greater practicality and comfort of the below knee stockings despite the lack of definite evidence of benefit. There is a clear need for further studies to establish whether below knee stockings are effective in prevention of DVT and PE in all patients at risk, including those with stroke.

Detecting Deep Venous Thrombosis

The lack of recent studies of post stroke DVT and trials to evaluate preventative treatments is in part due to the absence of a sensitive, specific, safe and practical test to diagnose DVT (Anand et al 1998). Options include: venography, radio-labelled fibrinogen scanning, Doppler ultrasound, plethysmography, magnetic resonance imaging and the measurement of D-Dimers in the blood or plasma. None represents an ideal technique on which to base ones primary outcome in a randomised trial of DVT prevention.

Venography is still regarded as the gold standard with which other techniques are compared. However it is invasive, is occasionally associated with serious adverse reactions to the contrast and problems with interpretation arise where there is inadequate filling of veins. One might expect 10% of tests to be technically inadequate. In this trial where we are expecting only perhaps 10% of patients to have a DVT it is probably unreasonable to subject the other 90% to such an invasive and uncomfortable test for no gain. Its use is likely to be associated with difficulties in obtaining informed consent, low accrual and a high drop out rate especially as we plan to screen over the first month after randomisation.

Radiolabelled fibrinogen provided a very sensitive and reasonably specific test for identifying calf vein DVT although it was less specific for more proximal and more clinically relevant thromboses. Because it appeared to be reasonably safe it was used to screen asymptomatic patients in earlier studies. Unfortunately, because of concerns about the transmission of virus particles via blood products it is no longer available.

Doppler ultrasound imaging provides a very accurate and specific tool to detect above knee thrombus in symptomatic patients. There is more uncertainty concerning its sensitivity and specificity for detecting calf vein thrombus and in asymptomatic patients (Davidson 1998). Reported sensitivities in asymptomatic patients vary between 42% and 70% with positive predictive values varying between 35% and 83% depending on the operator's expertise and the prevalence of DVT in the patient group examined. However, it is rapidly becoming the investigation of choice to confirm the diagnosis of DVT since it is non invasive (Baxter 1997). It is acceptable to patients, can easily be repeated several times and uses equipment which is widely available. Thus consent, accrual and compliance in a trial are likely to be more easily achieved than with alternatives.

Plethysmography This technique is of comparable accuracy to Doppler ultrasound and is also non invasive but it is not widely available in centres which are likely to participate in this randomised trial.

Magnetic Resonance Imaging Preliminary reports suggest that this technique might offer an alternative non invasive method of detection. However it is available in very few centres and has not yet been fully evaluated (Moody 1997, Kelly et al 2001).

D-Dimers are degradation products produced when thrombus present in the circulation is lysed. Raised levels of D-Dimers have been used as a very sensitive but less specific test for diagnosis of DVT (Bounameaux et al 1997). However, its performance in detecting DVT/PE in prevention studies remains to be established. At this time it could not be used as a test to confirm DVT, but given its sensitivity it might be used as a preliminary screening test to select patients for imaging (Harvey et al 1996, Bernardi et al 1998)

Primary Research Questions

The primary research questions are:

- Does early and routine application of above knee or full length graduated compression stockings reduce the risk of above knee DVT in the weeks following an acute stroke?

- Are above knee or full length graduated compression stockings more effective than below knee graduated compression stockings in reducing the risk of DVT?

Secondary Questions

- What is the frequency of Doppler ultrasound proven DVT in immobile stroke patients treated routinely with antiplatelet agents?

- What clinical factors might predict a greater risk of post stroke DVT?

- Are GCS effective in preventing DVT in the non-paralysed leg in stroke patients which would provide data relevant to patients immobilised with other medical conditions?

Add on Studies

In addition, we would ideally aim to collect extra data in selected centres, which would allow us to answer some additional questions:

- Can haematological investigations refine the clinical prediction of which patients will develop post stroke DVT and other vascular events?
- What is the sensitivity and specificity of D-Dimers (measured using an ELISA test) in the detection of DVT after stroke?
- What is the inter-observer reliability of Doppler ultrasound scanning in the detection of above and below knee DVT after stroke?
- What is the sensitivity and specificity of MRI in the detection of DVT after stroke?
- How acceptable are graduated compression stockings to patients?
- What are the resource implications of the routine use of stockings?
- What are the genetic markers of increased risk of post stroke DVT?

Trial Design – A Family of Trials

CLOTS is a family of two multicentre randomised controlled trials with blinded assessment of primary outcomes (Dennis et al 1999). The two trials will make use of common randomisation, data collection and follow up systems. Centres will generally randomise patients into either Trial 1 or Trial 2 depending on their current practice and beliefs with respect to graduated compression stockings after stroke.

Trial 1

In centres where collaborating clinicians / nurses are uncertain about the value of graduated compression stockings in stroke patients, patients will be allocated to one of the following two treatments:

Full length graduated compression stockings in addition to routine care

Or

Routine care and avoid the use of graduated compression stockings

If allocated to full length GCSs, these should be applied to both legs as soon as possible after the randomisation phone call and should be worn until the patient is independently mobile around the ward (i.e. can get up from a chair/ out of bed and walk to the toilet without the help of another person), or until the patient is discharged from hospital or until the patient declines to wear them. In the last case, below knee stockings should be substituted if the patient will accept them.

If allocated to routine care, full length and below knee GCS should be avoided unless a clear indication for their use becomes obvious.

Trial 2

In centres where responsible clinicians / nurses are certain about the value of GCS in stroke patients but are uncertain whether to use full length or below knee stockings patients will be allocated to one of the following two treatments:

Full length graduated compression stockings in addition to routine care

Or

Below knee graduated compression stockings in addition to routine care

The appropriate length of GCS, should be applied to both legs as soon as possible after the randomisation phone call and should be worn until the patient is independently mobile around the ward (i.e. can get up from a chair/out of bed and walk to the toilet without the help of another person) or until they are discharged from hospital or until the patient declines to wear them.

Routine Care

In Trial 1 and 2, all patients should receive aspirin as soon as a haemorrhagic stroke has been excluded by CT as long as there is no other contraindication. The responsible clinician may prescribe aspirin before a CT scan where this is accepted practice in patients thought unlikely to have a haemorrhagic stroke. In some centres heparin may be used (despite the lack of evidence of overall benefit). In these centres use of heparin must be the same in both treatment groups.

Inclusion Criteria

- Any patient admitted to hospital within 7 days of a clinical stroke fulfilling the WHO criteria

and

- Who is not able to get up from a chair/ out of bed and walk to the toilet without the help of another person

and

- In whom the responsible clinician / nurse is substantially uncertain about either the value of graduated compression stockings (Trial 1) or the optimal length (Trial 2).

Patients can be randomised from Day 0 (day of admission) to Day 3 of hospital admission. If a patient has a stroke during a hospital admission they are eligible until Day 3 from the stroke onset (Day 0).

Exclusion Criteria

- Patients who, in the opinion of the responsible clinician / nurse, are unlikely to benefit from GCS.
- Patients with peripheral vascular disease, diabetic or sensory neuropathy, where the responsible clinician / nurse judges that stockings may cause tissue necrosis.

Consent

UK Multicentre Research Ethical Committee (MREC) approval has been granted. Each collaborating centre will need to confirm Local Research Ethics Committee (LREC) approval.

Patients (or their carers) are given a Patient Information Booklet which describes the aims of the trial and the potential risks and benefits of graduated compression stockings. The patients (or their carers) should be given enough time to consider the trial fully and ask any questions they may have about the implications of the trial.

Patients are asked for their written informed consent unless they are unable to do so because of reduced conscious level, cognitive or communication problems. In these cases the randomising clinician or nurse can either gain witnessed verbal consent or assent of the patient's next of kin. Randomisation without patients' consent or relatives' assent is not permitted in the UK but is allowed in other countries where randomisation without patients' or relatives' agreement is permitted by law and where this has been agreed by the local ethics committee. In such circumstances the agreement of the patient and or relative should be sought when this becomes practical.

Randomisation Procedure

The randomising clinician or nurse collects baseline data necessary to complete a randomisation form. He/she then rings a telephone randomisation service, giving the baseline data (which are then stored securely) and receives the treatment allocation at the end of the call. A minimisation program is used to achieve optimum balance for important prognostic factors i.e.

- Delay since stroke onset. (Day 0 or 1 vs. Day 2-10)
- Stroke severity (using a validated prognostic model (Counsell 1996) which includes the following factors; age, pre stroke dependency in activities of daily living, living with another person prior to stroke, able to talk and orientated in time, place and person, and able to lift both arms to horizontal position against gravity).
- Severity of leg paresis (able or not to lift leg off the bed)
- Use of heparin, warfarin or thrombolysis (rt-PA) at the time of enrolment
- Centre

By balancing randomisation within centres we should avoid problems associated with variation in accuracy of Doppler ultrasound between centres.

Follow up

Patients should have a Doppler ultrasound examination of the veins in both legs between Day 7 and Day 10 and between Day 25 and 30. This examination will document thrombus in the calf, popliteal and femoral veins separately. Centres are prompted to perform this test by fax or email sent by the trial management system.

Where the randomising person judges that it is likely to be impractical to perform a Doppler ultrasound between Days 25 and 30, they may, prior to randomisation, stipulate that a Doppler ultrasound will only be performed between Days 7 and 10. This might be the case if the patient is likely to be discharged home to

another region or transferred to a rehabilitation facility that does not have use of Doppler ultrasound facilities and is remote from the randomising centre.

Stockings should be removed before the patient leaves the ward to have the Doppler ultrasound to ensure optimal blinding of the primary outcome measure (sufficient time needs to be allowed to let indentations due to compression stockings disappear). The Doppler ultrasound operator will be asked to guess which treatment group the patient is in prior to the examination to estimate the effectiveness of blinding. Thus patients enrolled in CLOTS will benefit from non invasive screening for DVT which is likely to lead to earlier and probably more effective treatment and prevention of PE.

Discharge Form

A Discharge Form should be completed for all randomised patients on discharge from the randomising centre or in the event of earlier death. This form should be returned to the CLOTS Co-ordinating Centre in Edinburgh. The data collected includes:

- Use of thrombolysis, heparin, warfarin and antiplatelet drugs during admission
- Compliance with treatment allocation (including the use of full length or below knee stockings)
- Any clinical DVT or PE requiring treatment (diagnosis will be reviewed blind to the treatment allocation) or any further vascular event during admission.
- Any complications of treatments
- Contact details to facilitate 6 month follow up

GP Questionnaire

A questionnaire will be sent at 5½ months after randomisation to the GP of all patients who survive to discharge from hospital. This will establish that the patient is alive prior to sending out a follow-up form and ascertain whether they have had any DVT or PE since discharge.

Six Month Follow up Form

For those patients who have been discharged, outcome is assessed via a postal or telephone questionnaire. This will be sent to the patient directly from the CLOTS Co-ordinating Centre (for UK patients) or National Co-ordinating Centre (for non UK patients) after the patient's general practitioner has been contacted by post or phone to establish:

- that the patient is alive or the date and cause of death (if applicable)
- current address (to allow follow-up)

The six month questionnaire aims to establish:

- the place of residence (own home, with relatives, residential care or nursing home) [as a guide to resource use]
- their functional status - degree of functional impairment on the Modified Rankin Scale (Bamford 1989), Simple Questions (Dennis et al 1997) and Health Related Quality of Life (HRQoL) measured using EUROQoL (EUROQol Group 1990)
- The current antithrombotic medication regimen
- Presence of symptoms which might reflect **post** DVT syndrome (e.g. leg swelling, ulcers)

If the patient is still in hospital when the six month follow-up is due, the randomising clinician / nurse will be sent a six month “in hospital” follow-up form which should be completed with the patient.

Patients’ or relatives’ approval will be routinely sought for information from the follow up to be fed back to the general practitioner. This will hopefully facilitate more effective management of patient’s residual functional and emotional problems and any pain or discomfort being suffered.

Management of DVT in the Trial

A Radiology Report Form should be completed for all Doppler ultrasounds and venograms. This form, and in the case where there is evidence of DVT, the best image, still or video, should be returned to the CLOTS Co-ordinating Centre in Edinburgh.

If a popliteal or femoral vein DVT is detected during the routine Doppler ultrasound examinations, the responsible clinician will need to decide whether to confirm the presence and extent of any thrombus using venography. Although they may only perform confirmatory venography where the Doppler ultrasound is equivocal in their normal practice, compared with treating patients with a swollen leg the positive predictive value of a screening Doppler ultrasound study performed in an asymptomatic patient is likely to be lower. Put another way, the Doppler result is more likely to produce a false positive result in an asymptomatic patient. If the clinician is satisfied that the patients has a DVT (with or without a confirmatory venogram) the patient should be anticoagulated using subcutaneous heparin according to local protocols as long as there is no contraindication (SIGN Guidelines 1999).

If only calf vein thrombus is detected (by screening Doppler ultrasound and/or venography), the responsible clinician may anticoagulate the patient according to local protocols or alternatively arrange a follow up Doppler ultrasound approximately seven days later to identify any propogation into the popliteal vein. If definite popliteal or femoral vein thrombus is detected the patient should be anticoagulated unless contraindicated. If calf vein thrombus is detected during the first scheduled scan (between Day 7 to 10) a scan should also be performed between Days 25 and 30 in addition to any other scans deemed necessary.

If a patient develops symptoms or signs suggestive of DVT during their admission they should be investigated by either Doppler ultrasound and/ or venography and treated according to local protocols if the diagnosis is confirmed. Such patients should still have a Doppler ultrasound between Day 25 and 30 blinded to treatment allocation.

Analyses

All analyses will be based on intention to treat.

Primary Outcome

Presence of first symptomatic or asymptomatic DVT in the popliteal or femoral veins detected on either of two routine Doppler ultrasound scans (performed at about 7-10 days and 25 – 30 days) or contrast venography within 30 days of randomisation.

Secondary Outcomes

In hospital: symptomatic or asymptomatic DVT in the popliteal or femoral veins detected on either a Doppler ultrasound scan or contrast venography within 30 days of randomisation; death within 30 days, symptomatic or asymptomatic below knee DVT, confirmed fatal or non-fatal PE, medical complications of GCS (e.g. skin necrosis) and compliance with allocated treatment.

At six months: death from any cause, place of residence, post discharge DVT, PE, post DVT syndrome, disability (modified Rankin), and health related quality of life (EuroQol). The later effects of DVT/PE (e.g. breathlessness, leg pain or swelling, poor stroke recovery) or the complications of GCS (skin ulceration, amputation, loss of mobility) may be diverse, so it seems sensible to include a measure of overall health related quality of life.

Symptomatic DVTs, which occurred within 30 days of randomisation, would be counted in the primary endpoint. However, because the detection of such symptomatic DVTs is not blinded and hence prone to ascertainment bias, an analysis excluding these symptomatic DVTs will also be performed. Inevitably, some patients will not survive to have both routine Doppler ultrasounds and many of these will not have a detailed autopsy to establish whether they had a DVT or PE prior to death. However, it is possible that there will be an imbalance in the number of such deaths between the treatment groups especially if GCS are very effective in preventing fatal PE. Therefore, we will also perform an analysis combining our primary outcome

with death within 30 days, that is of 'death or confirmed symptomatic or asymptomatic DVT on routine Doppler ultrasound or contrast venography by Day 30'.

Preplanned Subgroup Analyses

Preplanned Subgroup Analyses include: the effect of treatment allocation on the primary outcome subdivided by key baseline variables:

- Time from stroke onset to randomisation (Day 0 or 1 vs 2 to 10)
- Use of anti thrombotic agents (use of either heparin, warfarin or thrombolytic agent vs none)
- Paralysis of leg (complete vs. incomplete)
- Unaffected leg (as model for immobile medical patient)

The proportion with a primary or secondary outcome will be compared using odds ratios with 95% confidence intervals. Results will be adjusted for any imbalance in baseline variables.

Sample Size

Ideally the trial would demonstrate the impact of graduated compression stockings on survival and functional status. However, this would require a trial of enormous sample size. We have therefore chosen a surrogate outcome as our primary outcome, i.e. presence of first symptomatic or asymptomatic DVT in the popliteal or femoral veins detected on either of two routine Doppler ultrasound scans (performed at about 7-10 days and 25 – 30 days) or contrast venography within 30 days of randomisation.

In this trial we have elected to define our sample size not in terms of the number of patients we plan to enrol but rather the number of primary outcomes we need to detect. To achieve at least 90% power in Trials 1 & 2 we need to identify about 175 and 300 patients with our primary outcome in each trial respectively. This might be achieved by enrolling 1500 and 3000 patients in Trials 1 and 2 respectively, if thrombus will be detectable in the popliteal or femoral veins within 30 days of randomisation in 15% of control patients, 9% of those wearing full length GCS and 13% of those wearing below knee stockings. If the current event rate in our pilot phase applies we may require about 2000 and 3500 in Trials 1 and 2 respectively.
The estimates of treatment effects are based on the systematic reviews and the prevalence of DVT detected on Doppler ultrasound in stroke patients estimated from a previous RCT (Muir et al 2000), an observational study (Oczkowski et al 1992) and our start up phase. A recent (Dec 2002) confidential review (by the trial statistician) of the event rates in the CLOTS start up phase(for all treatment groups combined) for the first 160 patients followed up to 30 days indicated that about 8% of patients had our primary outcome.

These sample sizes take into account: the uncertainty introduced by the 70% sensitivity and 97% specificity of Doppler ultrasound in identifying DVT in mainly asymptomatic patients; an attrition rate due to death (8% in our start up phase) and missing Doppler results (8% in our start up phase) in the first month; the anticipated low non – compliance rate.

Trial Organisation

CLOTS Trial Co-ordinating Centre Personnel

Principal Investigator:	Prof Martin Dennis
Co-investigator:	Prof Peter Sandercock
Co-investigator:	Dr John Reid
Trial Manager:	Alison Gunkel
Recruitment Co-ordinator:	Carol Williams
Trial Statistician:	Stephanie Lewis
Trial Programmer:	Vera Soosay
Trial Support Team:	Anne Fraser, Sheila Grant, Janie Hunter, Anne Williamson and Adam Young

MRC Steering Committee: Dr G Venables (Independent Chairperson), Dr A Rudd (Independent expert), Prof G Murray (Independent statistician), Dr M Roberts (MRC secretariat), Prof Martin Dennis (Principal

Investigator), Prof Peter Sandercock (Co-investigator), Ms Alison Gunkel (Trial Manager), Dr Stephanie Lewis (Trial Statistician). The Committee will be responsible for overseeing the conduct of the trial. It shall be constituted and operate as laid out in the MRC Guidelines for Good Clinical Practice.

Trial Management Group - Prof Martin Dennis (Principal Investigator), Professor Gordon Lowe (Chairman)(Haemostasis thrombosis), Dr John Reid (Radiologist - Doppler ultrasound & quality control), Professor Peter Sandercock (Neurologist and Trialist), and Professor Joanna Wardlaw (Radiologist), Elizabeth Barrie (Stroke unit nurse), Andrew Smith (Patient representative – TBC)*:* An **International Advisory Board** will also be established which will report to the MRC steering Committee and will consist of the National Co-ordinator from each participating country.

Independent DMC: Dr John Bamford (Stroke neurologist in Leeds), Jim Slattery (Statistician with Scottish HTA Board) and Colin Baigent (trialist and author of HTA systematic review of GCS from CTSU in Oxford). They will define stopping rules for the study and monitor the data on a regular basis.
During the period of recruitment into the study, interim analyses of in-hospital mortality and of any other information that is available on major outcome events (including serious adverse events believed to be due to treatment) will be supplied, in strict confidence, to the chairman of the data monitoring committee, along with any other analyses that the committee may request. In the light of these analyses, the data monitoring committee will advise the chairman of the steering committee if, in their view, the randomised comparisons in CLOTS have provided **both** (i)"proof beyond reasonable doubt" that for all, or for some, specific types of patient, one particular treatment is clearly indicated or clearly contraindicated in terms of a net difference in mortality or serious morbidity, **and** (ii) evidence that might reasonably be expected to influence materially the patient management of the many clinicians who are already aware of the results of the other main trials. The steering committee can then decide whether to modify intake to the study (or to seek extra data). Unless this happens, however, the steering committee, the collaborators, and the central administrative staff (except those who produce the confidential analyses) will remain ignorant of the interim results.

Collaborators, and all others associated with the study, may write through the CLOTS office, Edinburgh to the chairman of the data monitoring committee, drawing attention to any worries they may have about the possibility of particular side-effects, or about particular categories of patient requiring special consideration, or about any other matters that may be relevant.

Publication of the Trial Results

All full publications in peer reviewed journals will be published in the name of the collaborative group.

All publications relating to the main trial will be published in the name of the CLOTS Collaboration. No individual author will be identified, but the contribution of each individual to the planning, completion, analysis and reporting of the trial will be given.

Abstracts relating to the main study will be submitted as the CLOTS Collaboration along with the presenter's name.

Papers and abstracts relating to 'Add-on' studies will be in the name of those collaborators who took part or the groups name but recognising the input of the entire Collaboration by putting 'part' or 'member' of the CLOTS Collaboration.

Anyone wishing to use the data generated from this trial for higher degrees, PhDs etc. must first seek the permission of the Steering Committee. All papers must be approved by the Steering Committee prior to submission for publication. Anyone wishing to use the data in this way, will be asked to sign a confidentiality agreement which will prevent them from publishing the data until the results of the main trial have been published.

No group of collaborators should publish the results of any sub-study, which splits patients by treatment allocation without the agreement of the Steering Committee on behalf of the other members of the Collaboration. Studies which report any of the process or outcome data collected as part of the main study must acknowledge the collaboration as an author e.g. Smith on behalf of the CLOTS Collaboration.

References

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Patient Information Booklet (Trial 1)

Introduction to the study

You very recently had a stroke, an interruption in the blood supply to part of the brain. Sometimes a stroke can cause blood clots in the veins in the legs. These clots can be very dangerous if they travel up the vein to the heart or lungs. You may receive aspirin and possibly other blood thinning drugs which reduce the risk of clots forming. However, we believe that wearing graduated compression stockings until you are able to walk may reduce the risk further. This is why we are asking for your help (even though we know that this is a very difficult time for you).

We would like to invite you to participate in the CLOTS study, which aims to identify the best way of preventing clots forming. We need to include about 2,000 patients like yourself into this study to be certain of which treatment is best. If you agree to participate in this study, you will be randomly allocated, by computer, to either wear thigh length compression stockings or not to wear stockings. If you are allocated to wear stockings, a nurse will help you put these on. If allocated, stockings should be worn until you are able to walk around the ward or until you are discharged home. Whichever treatment you receive you will be carefully monitored throughout your hospital stay. A simple ultrasound test, called a Doppler scan, will be carried out twice during the first month to check the veins in your legs. If this scan shows a clot your doctor may organise another X-ray and you will be treated with a blood thinning or anticoagulant drug. Alternatively, if you do not wish to participate in the study, you can decide whether to wear stockings or not.

You will leave hospital when your doctor thinks that you are well enough to go home and the timing of your discharge will not be influenced by taking part in the study. In a few months, we will either send you a questionnaire to find out how you are doing or we may telephone you instead. In addition, we will telephone or write to your family doctor to see how you are getting on during the follow up period. You can of course decline to be followed up although this would reduce the power of the trial.

What are the risks and benefits?

Compression stockings reduce the risk of blood clots in the legs in patients having surgery. The benefits of stockings in patients with stroke are not established. Thigh length compression stockings can be uncomfortable, however, the risks of wearing them are very small.

Very occasionally stockings cause skin ulceration on the leg or more commonly itchy skin. If you find the stockings uncomfortable, please let your doctor know as an alternative may be available. The Doppler scan takes about 30 minutes and causes little discomfort. If you are harmed by taking part in this research project, there are no special compensation arrangements. If you are harmed due to someone's negligence, then you may have grounds for a legal action but you may have to pay for it. Regardless of this, if you wish to complain about any aspect of the way you have been approached or treated during the course of this study, the normal National Health complaints mechanisms would be available to you.

Who will be told about my illness?

Any information we collect about you will be confidential and used only for the purpose of this study. Information about you will only be available to research staff and the medical staff caring for you. The results of this study will eventually be published in a medical journal, however, no patient will be identified.

What happens now ?

We would like you to think very carefully about whether or not to join the study. It is entirely voluntary and if you decide not to join it will not influence your care in any way. You may also choose to stop wearing the stockings at any time, although we would like to continue monitoring your progress. You must be happy about any decision you make and if we can give you any additional information to make the decision easier we will be happy to do so. Your family doctor will be informed about this study if you decide to participate. Thank you for taking the time to read this leaflet. Please keep a copy of this leaflet along with the consent form for your records.

If you would like to know more, please contact _____ (or ask the nurse to contact).

This study is funded by the Medical Research Council (UK), Chief Scientist Office, Scotland and Chest, Heart & Stroke Scotland

Patient Information Booklet (Trial 2)

Introduction to the study

You very recently had a stroke, an interruption in the blood supply to part of the brain. Sometimes a stroke can cause blood clots in the veins in the legs. These clots can be very dangerous if they travel up the vein to the heart or lungs. You may receive aspirin and possibly other blood thinning drugs which reduce the risk of clots forming. However, we believe that wearing compression stockings until you are able to walk may reduce the risk further. There are two types of stockings – long ones which are thigh length and short ones. We want to find out whether they are equally effective in preventing clots. This is why we are asking for your help (even though we know that this is a very difficult time for you).

We would like to invite you to participate in the CLOTS study, which aims to identify the best way of preventing clots forming. We need to include about 2,000 patients like yourself into this study to be certain which treatment is best. If you agree to participate in this study, you will be randomly allocated, by computer, to either wear thigh length compression stockings or below knee stockings. A nurse will help you put these on. The stockings should be worn until you are able to walk around the ward or until you are discharged home. Whichever type of stocking you receive you will be carefully monitored throughout your hospital stay. A simple ultrasound test, called a Doppler scan, will be carried out twice during the first month to check the veins in your legs. If the scan shows a clot your doctor may organise another X-ray and you will be treated with a blood thinning or anticoagulant drug. Alternatively, if you do not wish to participate in the study, you can decide whether to wear stockings or not.

You will leave hospital when your doctor thinks that you are well enough to go home and the timing of your discharge will not be influenced by taking part in the study. In a few months, we will either send you a questionnaire to find out how you are doing or we may telephone you instead. In addition, we will telephone or write to your family doctor to see how you are getting on during the follow up period. You can of course decline to be followed up but this would reduce the power of the trial.

What are the risks and benefits?
Stockings are known to reduce the risk of blood clots forming in the leg in patients having surgery. The benefits of stockings in patients with stroke is not established. The risks of wearing stockings are very small. Very occasionally stockings cause ulceration of the leg and more commonly itchy skin. The Doppler scan takes about 30 minutes and causes little discomfort. If you are harmed by taking part in
this research project, there are no special compensation arrangements. If you are harmed due to someone's negligence, then you may have grounds for a legal action but you may have to pay for it. Regardless of this, if you wish to complain about any aspect of the way you have been approached or treated during the course of this study, the normal National Health complaints mechanisms would be available to you.

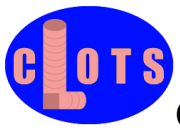
Who will be told about my illness?
Any information we collect about you will be confidential and used only for the purpose of this study. Information about you will only be available to research staff and the medical staff caring for you. The results of this study will eventually be published in a medical journal, however, no patient will be identified.

What happens now?

We would like you to think very carefully about whether or not to join the study. It is entirely voluntary and if you decide not to join it will not influence your care in any way. You may also choose to stop wearing the stockings at any time, although we would like to continue monitoring your progress. You must be happy about any decision you make and if we can give you any additional information to make the decision easier we will be happy to do so. Your family doctor will be informed about this study if you decide to participate. Thank you for taking the time to read this leaflet. Please keep a copy of this leaflet along with the consent form for your records.

If you would like to know more, please contact _____ (or ask the nurse to contact)

This study is funded by the Medical Research Council (UK), Chief Scientist Office, Scotland and Chest, Heart & Stroke Scotland



Consent Form

Patient name: _____
Address: _____
_____

I confirm that I have read and understand the Patient Information Sheet for the above study and have had the opportunity to ask questions

1. I understand that my participation is voluntary and that I am free to withdraw at any time, without giving any reason, without my medical care or legal rights being affected ☐

2. I understand that sections of any of my medical notes may be looked at by responsible individuals from the CLOTS Co-ordinating Centre or from regulatory authorities where it is relevant to my taking part in research. I give permission for these individuals to have access to my records. ☐

3. I agree to take part in CLOTS ☐

Signature: _____ Date: _____/_____/_____
day month year

Independent witness (e.g. nurse): _____

If the patient gives verbal consent to take part in the trial but is unable to sign, the responsible doctor /nurse must sign here: _____ And the signature must be witnessed above

Assent by Another Person

Name: _____ Relationship to patient: _____

Signature: _____ Date: _____/_____/_____
day month year

Address: _____

_____

Independent witness (e.g. nurse): _____

Please give a copy of this form once completed to the patient if requested. Please file this form in the patient's notes. Do NOT return it to the CLOTS Co-ordinating Centre

Randomisation Form - Trial 1

Please complete the following questions before calling the CLOTS Randomisation Service on ++ 44 (0)131 5372933. Please ensure you have supplies of appropriate stockings too!

CENTRE DETAILS

Country: _____ or code ☐☐

Centre name: _____ or code ☐☐☐

Responsible consultant: _____ or code ☐☐☐☐

Randomising person: _____

Has consent or assent been given? ☐ **(Key 1)** **(must be yes)**

Patient' s Family name:_____ **Given name:**_____

Date of birth ☐☐/☐☐/ ☐☐☐☐ **(dd/mm/yyyy)** Sex: Male ☐ (Key 1) Female ☐ (Key 2)

Date of stroke onset ☐☐/☐☐/ ☐☐☐☐ **(dd/mm/yyyy)**

Date of admission ☐☐/☐☐/ ☐☐☐☐ **(dd/mm/yyyy)**

	Yes **(Key 1)**	No **(Key 0)**	Unknown **(Key 9)**
1. Did the patient live alone before admission?	☐	☐	☐
2. Was the patient independent in everyday activities before this stroke? (i.e. walking, dressing, feeding, toileting & washing)	☐	☐	☐
The patient:			
3. Is able to walk without the help of another person?	☐	☐	
4. Is able to talk and orientated in time, place and person?	☐	☐	
5. Is able to lift both their arms off the bed?	☐	☐	
6. Is able to lift right leg off the bed?	☐	☐	
7. Has a flicker of movement or better in the right leg?	☐	☐	
8. Is able to lift left leg off the bed?	☐	☐	
9. Has a flicker of movement or better in the left leg?	☐	☐	
10. Is overweight?	☐	☐	
11. Is known to be diabetic?	☐	☐	
12. Is known to have symptoms or signs of peripheral vascular disease?	☐	☐	
13. Is known to be a current smoker?	☐	☐	
14. Is known to have a history of previous DVT or PE?	☐	☐	
15. Has taken aspirin, dipyridamole (Persantin), or clopidogrel (Plavix) in last 24hrs?	☐	☐	
16. Has been given rt-PA (not IST-3) since admission?	☐	☐	
17. Is on heparin now?	☐	☐	
18. Is on warfarin now?	☐	☐	
19. Do you think it will be practical / possible to perform a second Doppler in 25 to 30 days time (in addition to one between Day 7 and 10)?	☐	☐	

Treatment Allocation (please tick the appropriate box)

Apply full length stockings ☐ **Avoid stockings until discharge** ☐

- Stockings, if allocated, should be worn until independently mobile or discharge.
- Record the allocation on the drug chart.
- Inform all the relevant people about the allocation then file this form in the patient's medical notes.
- Book the Doppler ultrasound now so this will be done on Day 7-10.

Thank you for randomising this patient.

Randomisation Form - Trial 2

Please complete the following questions before calling the CLOTS Randomisation Service on ++ 44 (0)131 5372933. Please ensure you have supplies of appropriate stockings too!

CENTRE DETAILS

Country: _____ or code ☐☐

Centre name: _____ or code ☐☐☐

Responsible consultant: _____ or code ☐☐☐☐

Randomising person: _____

Has consent or assent been given? ☐ **(Key 1)** **(must be yes)**

Patient' s Family name:_____ **Given name:**_____

Date of birth ☐☐/☐☐/ ☐☐☐☐ **(dd/mm/yyyy)** Sex: Male ☐ (Key 1) Female ☐ (Key 2)

Date of stroke onset ☐☐/☐☐/ ☐☐☐☐ **(dd/mm/yyyy)**

Date of admission ☐☐/☐☐/ ☐☐☐☐ **(dd/mm/yyyy)**

	Yes **(Key 1)**	No **(Key 0)**	Unknown **(Key 9)**
3. Did the patient live alone before admission?	☐	☐	☐
4. Was the patient independent in everyday activities before this stroke? (i.e. walking, dressing, feeding, toileting & washing)	☐	☐	☐

The patient:

3. Is able to walk without the help of another person?	☐	☐
4. Is able to talk and orientated in time, place and person?	☐	☐
5. Is able to lift both their arms off the bed?	☐	☐
6. Is able to lift right leg off the bed?	☐	☐
7. Has a flicker of movement or better in the right leg?	☐	☐
8. Is able to lift left leg off the bed?	☐	☐
9. Has a flicker of movement or better in the left leg?	☐	☐
10. Is overweight?	☐	☐
11. Is known to be diabetic?	☐	☐
12. Is known to have symptoms or signs of peripheral vascular disease?	☐	☐
13. Is known to be a current smoker?	☐	☐
14. Is known to have a history of previous DVT or PE?	☐	☐
15. Has taken aspirin, dipyridamole (Persantin), or clopidogrel (Plavix) in last 24hrs?	☐	☐
16. Has been given rt-PA (not IST-3) since admission?	☐	☐
17. Is on heparin now?	☐	☐
18. Is on warfarin now?	☐	☐
19. Do you think it will be practical / possible to perform a second Doppler in 25 to 30 days time (in addition to one between Day 7 and 10)?	☐	☐

Treatment Allocation (please tick the appropriate box)

Apply full length stockings ☐ **Apply knee length stockings** ☐

- The allocated stockings should be worn until patient is independently mobile or discharged.
- Record the allocation on the drug chart.
- Inform all the relevant people about the allocation then file this form in the patient's medical notes.
- Book the Doppler ultrasound now so this will be done on Day 7-10.

Thank you for randomising this patient.

Appendix 6 Radiology Report Form

CLOTS/RRF/'

1.
2.
For office use

CLOTS Radiology Report Form

Please complete and return by fax to the CLOTS Co-ordinating Centre on +44 (0) 131 3325150

Hospital Number: _____ or Hospital Name _____

Patient ID: _____ Patient Initial: _____

Procedure performed today Doppler ☐ Venography ☐ Both ☐

Date(s) procedure performed Doppler ____/____/____ Venography ____/____/____

Did this patient attend wearing stockings? Yes ☐ No ☐

Results - Any D.V.T. evident? Yes ☐ No ☐

If any DVT present please send best still picture that demonstrates this to the CLOTS Co-ordinating Centre (address below).

If Yes:		**Right Leg**	**Left Leg**
Femoral:	Yes, definite	☐	☐
	Yes, probable	☐	☐
	None	☐	☐
Popliteal:	Yes, definite	☐	☐
	Yes, probable	☐	☐
	None	☐	☐
Calf:	Yes, definite	☐	☐
	Yes, probable	☐	☐
	None	☐	☐
	Veins Not Visualised	☐	☐

We need to know if you are aware of whether the patient has been wearing compression stockings – this will tell us how "blind" you are to the treatment allocation

Do you think this patient has been wearing compression stockings (Do not ask the patient!)? Yes ☐ No ☐ No Idea ☐

If yes, which length? Full length ☐ Below knee ☐

Form completed by: _____ Signature:_____

Thank you for completing this form, now please fax or post it to the

CLOTS Co-ordinating Centre, Neurosciences Trials Office
Western General Hospital, Crewe Road, Edinburgh, UK, EH4 2XU

Fax Number +44 (0) 131 3325150

Discharge Form

Please complete this form on the patient's discharge from hospital, transfer from the centre or death (whichever occurs first) as accurately as possible.

HOSPITAL DETAILS

Hospital Number: ☐☐☐ or Hospital Name: _____

Patient Details:

Patient ID: _____

Patient Initial: _____

Affix Patient Sticker Here

ABOUT THE STROKE

Was stroke diagnosis confirmed in this patient? Yes ☐ No☐

If not a stroke, please specify the diagnosis:_____ ☐☐ For office use

Was the stroke due to: **cerebral infarction?** ☐ **haemorrhage?** ☐ **uncertain?**☐

DRUGS DURING HOSPITAL STAY

Has this patient taken any of the following drugs since randomisation (Tick all appropriate)?

Aspirin ☐ Dipyridamole (Persantin) ☐ Clopidogrel (Plavix) ☐ Ticlopidine (Ticlid) ☐

Low dose heparin ☐ Full dose heparin ☐ Warfarin ☐ **None**☐

If patient was given heparin or warfarin during admission please give reason:

Atrial fibrillation (AF) ☐ Artificial heart valve ☐ To treat DVT or PE ☐

Other ☐ Please specify _____ ☐☐ For office use

STOCKING USE

Did this patient wear stockings prior to randomisation? Yes ☐ No ☐

Since randomisation, has this patient:

Worn full length stockings at any time? Yes ☐ No ☐

If **yes** on which leg(s)? Right ☐ Left ☐

Worn below knee stockings at any time? Yes ☐ No ☐

If **yes** on which leg(s)? Right ☐ Left ☐

If the allocated stocking use has not been followed, please give reasons below:

_____ ☐☐ For office use

If wore stockings at any time since randomisation

Date stockings first worn since randomisation ____/____/____

Date any stockings last worn ____/____/____

Number of days (between these dates) stockings **not** worn _____ ☐☐ For office use

---

If compression stockings were not worn each day till discharge, please tick reason(s) below:

Patient was independently mobile ☐ Concerns about skin condition on legs ☐

Patient refused to wear stockings ☐ Other difficulties encountered ☐

Patient complained of discomfort ☐ Please specify _____ ☐☐ For office use

---

MAJOR EVENTS DURING HOSPITAL STAY

Since randomisation has this patient had a:

Symptomatic or clinically apparent DVT?
(not clinically silent DVT diagnosed on screening Doppler)
Yes ☐ No ☐
If **yes** give date 1st diagnosed ___/___/___

Pulmonary Embolism?
Yes ☐ No ☐
If **yes** give date 1st diagnosed ___/___/___

Skin break on either leg
Yes ☐ No ☐
If **yes** give date 1st diagnosed ___/___/___

DETAILS OF ANY SYMPTOMATIC DVT

If Symptomatic DVT diagnosed how was it confirmed?

Doppler ultrasound ☐ Venography ☐ Other ☐ Please Specify _____ ☐☐ For office use

Please specify the location(s) of any symptomatic DVT(s)

Right leg

Vein: Calf ☐ Popliteal ☐ Femoral ☐

Left leg

Vein: Calf ☐ Popliteal ☐ Femoral ☐

DETAILS OF ANY PULMONARY EMBOLISM

If Pulmonary embolism diagnosed how was this confirmed?

V/Q Scan ☐ CT Angiography ☐ Other ☐ Please Specify _____ ☐☐ For office use

SURVIVAL & DISCHARGE

Did the patient survive to discharge from the randomising centre?

Yes ☐ No ☐

If **No, *Date of death*** (dd/mm/yyyy) ____/____/___

Primary cause of death (please tick **one** box **only)**

☐ Neurological damage from initial stroke (e.g. coning) ☐ Pneumonia

☐ Pulmonary Embolism ☐ Recurrent stroke ☐ Coronary heart disease

☐ Other vascular, *please specify*:_____ ☐☐

☐ Non-vascular, *please specify* _____ ☐☐

☐ Due to stockings, *please specify*:_____ ☐☐

☐ Uncertain, *please specify*: _____ ☐☐

For office use

Cause of death confirmed by autopsy? Yes ☐ No ☐

If **Yes, Date of discharge** (dd/mm/yyyy) ____/____/____

Has the patient been discharged to: (tick **one** box **only**)

☐ Own home, alone ☐ At home, with partner or relative

☐ Relative's home ☐ Residential home

☐ Long term care/nursing home

☐ In hospital rehabilitation

☐ Other, *please specify* _____ ☐☐

For office use

Was this patient independently mobile on discharge? Yes ☐ No ☐

CONTACT DETAILS:

Patient's full postal address on discharge _____

_____

Post Code: _____ Telephone: _____

Family Doctor's Name:_____Full postal address:_____

_____

_____Postcode:_____Telephone:_____

Please provide contact details of ***another person*** *(e.g. daughter or son) who does not live with patient:*

Name: _____ Relationship:_____

Full postal address:_____

_____Postcode:_____Telephone:_____

Please write any Additional Information overleaf:

ADDITIONAL INFORMATION

(Please use this space below for any additional information you may think relevant to the trial or to the patients treatment)

_____

_____

_____

_____

_____

_____

_____

_____ ☐☐

For office use

Form completed by: _____ Date: _____

Now please return this form by post to

The CLOTS Trial Co-ordinating Centre
Bramwell Dott Building,
Western General Hospital,
Crewe Road, Edinburgh UK
EH4 2XU

or by

FAX on +44 (0) 131 3325150

Thank you!

GP Questionnaire

Patients Name: <<Patient name >>

Date of Birth: << Date of Birth >>

Is this patient alive? ☐Yes ☐ No

If Yes please confirm that the following contact details are correct and amend if necessary

address << address >>

<<Tel No.>>

If the patient is dead or alive please tell us –

Has the patient had any of the following since hospital discharge on <<date of discharge>>?

Deep Vein Thrombosis? Yes ☐ No ☐

If **yes** give date first diagnosed ___/___/___

Pulmonary Embolism? Yes ☐ No ☐

If **yes** give date first diagnosed ___/___/___

Evidence of post-DVT leg syndrome? Yes ☐ No ☐
(i.e. swelling, pain, new ulcer)

If **yes** give date first diagnosed ___/___/___

If possible, please tell us **how any of these diagnoses were confirmed** (e.g. venography,VQ scan)

_____☐☐

If this patient has died, please confirm the date of death _____/____/_____(dd/mm/yyyy)

Cause of death: _____☐☐

Was cause of death confirmed by autopsy? Yes ☐ No ☐

Completed by _____ Date _____/____/_____

Thank you very much for your assistance.

Now please fax us this form to us at ++44 (0) 131 332 5150 or send to:

The CLOTS Trial Co-ordinating Centre, Bramwell Dott Building, Western General Hospital, Crewe Road, Edinburgh UK EH4 2XU

Follow-up Questionnaire

Dear <<patients name>>

We would like to know how you are getting on. We need to know what you are **actually managing** to do now, not what you used to do, or what you would like to do.

Please answer the following questions

Please tick ONE box on each line

	YES	NO
Has the stroke left you with any problems?	☐	☐
Do you need help **from anybody** with everyday activities?	☐	☐

How do you live now? *(please tick **ONE** box only)*

On my own	☐	☐
With my partner or relatives	☐	☐

Where do you live now? (*please tick **ONE** box only*)

In my own home	☐	☐
In the home of a relative	☐	☐
In a residential home	☐	☐
In a nursing home	☐	☐

YOUR TABLETS (Please tick ONE box on EACH Line)

Are you currently taking?	**YES**	**NO**
Aspirin	☐	☐
Dipyridamole (Persantin)	☐	☐
Clopidogrel (Plavix)	☐	☐
Warfarin	☐	☐

PROBLEM WITH YOUR LEGS?

Since discharge from hospital have you had a clot (DVT) in your legs? Yes ☐ No ☐

If Yes, which leg is affected?

My right leg ☐ My left leg ☐ Both legs☐

Do you suffer from swollen ankles or legs? Yes ☐ No ☐

If Yes, which leg is affected?

My right leg ☐ My left leg ☐ Both legs☐

Have you had a leg ulcer since your stroke? Yes ☐ No ☐

If Yes, which leg is affected?

My right leg ☐ My left leg ☐ Both legs☐

Since discharge from hospital, have you had a clot in your lungs (PE) ? Yes ☐ No ☐

In the next section we would like you to read the following descriptions from people who have similar medical problems to you and choose the one which best describes your present state.

Tick the ONE box next to the sentence which best describes your present state.

☐ I have no symptoms at all

☐ I have a few symptoms but these do not interfere with my everyday life

☐ I have symptoms which have caused some changes in my life but I am still able to look after myself

☐ I have symptoms which have significantly changed my life and I need some help in looking after myself

☐ I have quite severe symptoms which mean I need to have help from other people but I am not so bad as to need attention day and night

☐ I have major symptoms which severely handicap me and I need constant attention day and night

YOUR GENERAL HEALTH

By placing a tick in ONE box in EACH group below, please indicate which statements best describe your own health state today.

Mobility

☐ I have no problems in walking about

☐ I have some problems in walking about

☐ I am confined to bed

Self-Care

☐ I have no problems with self care

☐ I have some problems with washing or dressing myself

☐ I am unable to wash or dress myself

Usual Activities

☐ I have no problems with performing my usual activities

☐ I have some problems with performing my usual activities

☐ I am unable to perform my usual activities

Pain/discomfort

☐ I have no pain or discomfort

☐ I have moderate pain or discomfort

☐ I have extreme pain or discomfort

Anxiety/depression

☐ I am not anxious or depressed

☐ I am moderately anxious or depressed

☐ I am extremely anxious or depressed

Did you complete this form yourself? Yes ☐ No, it was completed by a relative or friend ☐

Date of form completion (today's date) _____(day)/ _____ (month) _____(year)

We usually tell your GP how you are getting on based on your answers to our questions.
Please tick this box if you would prefer us not to tell your GP ☐

Thank you very much for taking the time to complete this form
Please check that you have completed each of the THREE pages and return it using the pre-paid envelope provided.

Follow-up Questionnaire (In Hospital Version)

PATIENT DETAILS

Hospital Number: ☐☐☐ or Hospital Name: _____

Patient Details:

Family Name: _____<<family name>>_____

Given Name/s: _____<<given name>>_____

Date of Birth: _____/_____/_____ (dd/mm/yyyy)

Sex: Male ☐ Female ☐

ABOUT THE STROKE:

Was stroke diagnosis confirmed in this patient? Yes ☐ No ☐
If not a stroke, please specify the diagnosis:_____ ☐☐
For office use

Was the stroke due to: cerebral infarction? ☐ cerebral haemorrhage? ☐ uncertain? ☐

DRUGS DURING HOSPITAL STAY

Has this patient taken any of the following drugs since randomisation (Tick all appropriate)?

Aspirin ☐ Dipyridamole (Persantin) ☐ Clopidogrel (Plavix) ☐ Ticlpidine (Ticlid) ☐

Low dose heparin ☐ Full dose heparin ☐ Warfarin ☐ **None** ☐

If patient was given heparin or warfarin during admission please give reason(s):

For office use

Atrial fibrillation (AF) ☐ Artificial heart valve ☐ To treat DVT or PE ☐

Other ☐ Please specify _____ ☐☐
For office use

STOCKING USE
Since randomisation, has this patient:

Did this patient wear stockings prior to randomisation? Yes ☐ No ☐

Worn full length stockings at any time? Yes ☐ No ☐

If **yes** on which leg(s)? Right ☐ Left ☐

Worn below knee stockings at any time? Yes ☐ No ☐

If **yes** on which leg(s)? Right ☐ Left ☐

If the allocated stocking use has not been followed, please give reasons below

_____ ☐☐
For office use

If wore stockings at any time since randomisation

Date stockings first worn ____/____/____
Date stockings last worn ____/____/____
Number of days (between these dates) stockings **not** worn _____

If compression stockings were not worn each day till now, please tick the main reason below:

Patient was independently mobile ☐
Patient refused to wear stockings ☐
Patient complained of discomfort ☐
Concerns about skin condition on legs ☐
Other difficulties encountered? ☐

Please specify other difficulties _____☐☐
For office use

MAJOR EVENTS DURING HOSPITAL STAY

Since randomisation has this patient had a:

Symptomatic or clinically apparent DVT?
(not clinically silent DVT diagnosed on screening Doppler)
Yes ☐ No ☐
If **yes** give date 1st diagnosed ___/___/___

Pulmonary Embolism?
Yes ☐ No ☐
If **yes** give date 1st diagnosed ___/___/___

Skin break on either leg
Yes ☐ No ☐
If **yes** give date 1st diagnosed ___/___/___

Evidence of post-DVT leg syndrome?
(i.e. swelling, pain, new ulcer)
Yes ☐ No ☐
If **yes** give date 1st diagnosed ___/___/___

DETAILS OF ANY SYMPTOMATIC DVT

If Symptomatic DVT diagnosed how was it confirmed?

Doppler ultrasound ☐ Venography ☐ Other ☐ specify _____.☐☐
For office use

Please specify the location(s) of any symptomatic DVT(s)

Right leg
Vein: Calf ☐ Popliteal ☐ Femoral ☐

Left leg
Vein: Calf ☐ Popliteal ☐ Femoral ☐

DETAILS OF ANY PULMONARY EMBOLISM

If Pulmonary embolism diagnosed how was this confirmed?

V/Q Scan ☐ CT Angiography ☐ Other ☐ specify _____☐☐
For office use

DETAILS OF ANY POST DVT SYNDROME

If Post DVT syndrome diagnosed

Does your patients suffer from swollen ankles or legs?

Right leg ☐ Left leg ☐ Both legs ☐ None ☐

Has your patient had a leg ulcer since the stroke?

Right leg ☐ Left leg ☐ Both legs ☐ None ☐

CURRENT TREATMENT

Is your patient currently taking?

	YES	**NO**
Aspirin	☐	☐
Dypridamole (Persantin™)	☐	☐
Clopidogrel (Plavix™)	☐	☐
Warfarin	☐	☐

FUNCTIONAL STATUS

	YES	**NO**
Has the stroke left your patient with any problems?	☐	☐
Does your patient need help **from anybody** with everyday activities? (i.e. walking, dressing, washing, feeding or toileting)	☐	☐

In the next section we would like your patient to read the following descriptions and choose the one which best describes their present state. If your patient cannot complete the questionnaire, please complete it on their behalf.

Tick the ONE box next to the sentence which best describes your present state.

- ☐ I have no symptoms at all
- ☐ I have a few symptoms but these do not interfere with my everyday life
- ☐ I have symptoms which have caused some changes in my life but I am still able to look after myself
- ☐ I have symptoms which have significantly changed my life and I need some help in looking after myself
- ☐ I have quite severe symptoms which mean I need to have help from other people but I am not so bad as to need attention day and night
- ☐ I have major symptoms which severely handicap me and I need constant attention day and night

By placing a tick (✓) in ONE box in EACH group below, please indicate which statement best describe your own health state today.

Mobility

☐ I have no problems in walking about

☐ I have some problems in walking about

☐ I am confined to bed

Self-Care

☐ I have no problems with self care

☐ I have some problems with washing or dressing myself

☐ I am unable to wash or dress myself

Usual Activities

☐ I have no problems with performing my usual activities

☐ I have some problems with performing my usual activities

☐ I am unable to perform my usual activities

Pain/discomfort

☐ I have no pain or discomfort

☐ I have moderate pain or discomfort

☐ I have extreme pain or discomfort

Anxiety/depression

☐ I am not anxious or depressed

☐ I am moderately anxious or depressed

☐ I am extremely anxious or depressed

Are these responses?

The patient's ☐ The doctor's ☐

Name of person completing the form: _____Today's Date: ___/___/___(dd/mm/yyyy)

Thank you very much for taking the time to complete this form
Please FAX it to us or return it using the pre-paid envelope provided.